Direct and Indirect Effects of Pain on Participation in Individuals with Multiple Sclerosis

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ABSTRACT

Multiple sclerosis (MS) is the most common disabling neurological disease among young adults in North America, affecting mainly women. MS has received great attention recent years due to its increased prevalence in the world and its impact on every domain of life. Pain is a frequent symptom in persons with MS and considered to be one of the major contributors to sick leave or premature work cessation and other restrictions in societal and family roles. However, the relative importance of pain to participation and social functioning, key domains affecting quality of life in MS, is under studied. Symptoms such as fatigue, pain, and impairments of physical and mental capacity, can make participation in life's roles a challenge for people with MS. However, how factors that predict variations in participation of people with MS interact with one another to influence participation is still unknown.

The objective of this study, therefore, was to estimate the extent to which pain and other MS-related symptoms, physical and mental functional factors, and individual characteristics predict participation in people with MS.

This study was a secondary analysis of data from a longitudinal study on Gender Life Impact of MS. A centre-stratified random sample of persons registered at the 3 MS clinics in Montreal was drawn, comprising 139 women and 49 men. Subjects completed a battery of self-report and performance-based measures that assessed participation and domains affecting participation. In order to understand the relationships between pain, other symptoms, physical and mental function, participation, and contextual factors we tested a conceptual framework based on the Wilson & Cleary Model that posits specific relations between different levels of these health outcomes. Specific analyses of pain and its consequences led to the development of a Structural Equation Model (SEM) aimed at identification of the predictors of the latent construct of participation within the hypothesized theoretical model.

The results of the analysis indicated that fatigue, physical function, and psychological well-being were significant direct predictors of participation. Pain and age were significant indirect predictors through fatigue and physical function, respectively. Identification of the contributors to participation is important for MS rehabilitation as a clear understanding of the path to

participation can be used to develop specific interventions aimed at their removal or reduction, ultimately, impact favorably on quality of life.

A theoretical approach to role participation would expand its clinical use as an important outcome and contribute to the development of a psychometrically sound measure. Current symptoms, functional status, and contextual factors can be used to identify individuals who are likely to have restrictions in participation now or in the future.

RESUME

La sclérose en plaques (SP) est la maladie neurologique la plus commune chez les jeunes adultes en Amérique du Nord, affectant surtout les femmes. La SP a reçu beaucoup d'attention dans les dernières années à cause de l'augmentation de la prévalence mondiale et son impact sur tous les domaines de la vie. La douleur est un symptôme fréquent chez les gens atteint de la SP et est considérée comme un des principaux contributeurs à la prise de congé de maladie ou la cessation d'emploi et autres restriction des rôles familiaux et sociaux. Cependant, l'importance relative de la douleur sur la participation et le fonctionnement sociaux, deux domaines clés affectant la qualité de vie, n'est que très peu étudié. Les symptômes tels que la fatigue, la douleur et les troubles physiques et mentaux peuvent rendre difficile la participation dans les rôles de la vie pour les gens atteints de SP. La manière dont les facteurs prédisant des variations dans la participation des gens ayant la SP interagissent les uns avec les autres pour influencer la participation n'est pourtant pas connue. L'objectif de cette étude est donc d'estimer à quel point la douleur et autres symptômes de la SP, les facteurs de la fonction physique et mentale et les caractéristiques individuelles prédisent la participation chez les gens atteints de la SP.

Cette étude était une analyse secondaire d'une étude longitudinale sur l'Impact sur la vie du Genre en SP (Gender Life Impact of MS study). Un échantillon aléatoire stratifié par centre de patients inscrits dans l'une des trois cliniques de SP de la région de Montréal a été recueilli, comprenant 139 femmes et 49 hommes. Les sujets ont complété une batterie de mesures auto-rapportées et de performance évaluant la participation et différents domaines affectant la participation. Afin de comprendre les relations entre la douleur, les autres symptômes, la fonction physique et mentale, la participation et les facteurs contextuels, nous avons testé le cadre conceptuel basé sur le modèle de Wilson et Cleary qui décrit les relations spécifiques entre les différents niveaux de ces indicateurs d'état de santé. Des analyses spécifiques de la douleur et de ses conséquences ont mené au développement d'un modèle à équations structurelles (SEM) visant à identifier les prédicteurs du construit latent de la participation à l'intérieur du cadre théorique proposé dans l'hypothèse.

Les résultats de l'analyse ont indiqué que la fatigue, la fonction physique et le bien-être psychologique sont des prédicteurs directs significatifs de la participation. La douleur et l'âge

sont des prédicteurs indirects significatifs à travers la fatigue et la fonction physique, respectivement. L'identification des contribuants à la participation est importante pour la réadaptation des gens atteints de SP puisqu'une compréhension claire des pistes causales menant à des restrictions de la participation peut-être utilisée pour développer des interventions spécifiques visant à les supprimer ou les diminuer et, ultimement avoir un impact favorable sur la qualité de vie.

Une approche théorique à la participation dans les rôles élargirait son utilisation clinique en tant qu'important indicateur de l'état de santé et pourrait contribuer au développement d'une mesure solide au niveau psychométrique. Les symptômes, état fonctionnels et facteurs contextuels actuels peuvent être utilisés pour identifier les individus qui sont à risque d'avoir des restrictions de la participation maintenant ou dans le futur.

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DEDICATION

I dedicate this dissertation

To my parents for opening my eyes to the world; for instilling in me from an early age the importance of hard work and higher education and the desire to obtain a PhD degree.

To my husband for his encouragement, patience, and understanding

PREFACE

Statement of originality

This document contains no materials that have been published elsewhere, except where specifically referenced. The main contribution of this study is to enhance the understanding of pain in people with multiple sclerosis (MS). In consultation with my supervisory committee and statistician with health outcome units, the method of structure equation modeling (SEM) was selected. The work presented in this thesis represents the first applications of the Wilson-Cleary conceptual framework and SEM to assess the direct and indirect effects of pain on participation in people with MS. The originality in the work presented in this thesis is also reflected in the creation of the latent variables for pain and participation in MS population. We further believe this study provides important information for addressing symptom clusters in MS. This is the first application of cluster analysis to gender differences using a well-designed and large epidemiological study using both analytic and conceptual approaches that has been recommended in the literature for identifying a symptom cluster.

Contribution of authors

There were many steps involved in the development of this manuscript-based thesis. This thesis builds upon work from the Gender Life Impact of Multiple Sclerosis Study. The manuscripts contained in this thesis are the work of Shahnaz Shahrbanian with extensive editing and feedback from Dr Nancy Mayo, and support from the members of the thesis supervisory committee. This entire process has been conducted under the direct supervision and guidance of Dr. Nancy Mayo.

Organization of thesis

The global aim of this thesis was to contribute to understanding of the pain experience of people with MS with the context of function, disability, and health. Several objectives were used to reach this global aim. The first was to estimate the extent to which pain impacts on work, a key aspect of participation in this group. The second was to characterize pain in an epidemiologically sampled group of community-dwelling individuals with MS. The third was to estimate the extent to which there is stability in pain type and pain severity over time. The fourth was to estimate the extent to which different MS-related symptoms, including pain, cluster. Finally, the

last objective was to contribute evidence to support a framework for understanding the direct and indirect effect of pain on participation in people with MS. Each objective is independently addressed in five separate manuscripts which will be submitted to scientific journals for publication.

Additional chapters have been included in this thesis in accordance with the regulations outlined by the Graduate and Postdoctoral Studies (GPS) Office of McGill University. GPS requires that each thesis contains a literature review and conclusion that is separate from the manuscripts. Therefore, duplication of material and repetitions in this thesis is unavoidable.

Chapter 1 includes several parts. It first provides an introduction to MS and its symptoms, prevalence, types and treatment. The second part presents an overview of prevalence, cost, management, impact, and reasons for pain in the MS population. The third part of this chapter focuses on the concept of participation in MS. The most common conceptual frameworks used in health care which are going to be used throughout the thesis and an introduction to SEM are presented in this chapter.

Chapter 2 states a general rationale for assessing pain in MS and emphasizes knowledge about the relationship between pain and participation. It also outlines the main objectives in the manuscripts.

The first manuscript is focused in Chapter 3, a systematic review and meta-analysis of relationships between pain and employment in persons with MS. This paper was published in the Journal of Pain Research and Management.

Chapter 4 links the first manuscript to the second manuscript.

The second manuscript presented in Chapter 5 includes the text, figures, tables and references. The contents of this manuscript are related to assessing in-depth content of pain and its impact and predictors in MS population.

Chapter 6 presents the link between the second and third manuscripts.

Chapter 7 contains the third manuscript along with associated text, figures, tables and references. In this manuscript we explored stability in pain type, and pain severity over time.

Chapter 8 presents the integration between the third and fourth manuscripts with regards to their objectives and the logical progression between the two.

Chapter 9 consists of the fourth manuscript. It includes the text, figures, tables and references. This manuscript is related to methods and the meaning of symptom clusters in MS.

Chapter 10 presents the connection between the fourth and fifth manuscripts.

Chapter 11 contains the fifth manuscript. This manuscript contributes evidence to support a framework for understanding the direct and indirect effect of pain on participation in people with MS.

Chapter 12 includes a summary of findings and conclusions of all manuscripts. The appendices contain additional information that is not normally included in a manuscript.

Corresponding tables, figures, and references are presented at the end of each chapter or manuscript. A complete list of appendices is presented in the table of contents. The appendices contain information that is not normally presented in a manuscript to be submitted for publication (e.g. Description of measures used in the study). The table of contents provides a list of the appendices.

Ethical approval for the studies in this thesis was obtained from the Research Ethics Board (REB) of the McGill University Health Center, and the ethics committee of each participating hospital's Research Ethics Board. Copies of the ethic forms were sent to the school of PT& OT during the initial submission.

CHAPTER 1: OVERVIEW

1.1 Overview of Multiple Sclerosis

1.1.1 Background

Multiple sclerosis (MS) is a chronic, inflammatory autoimmune demyelinating disease of the central nervous system (CNS) characterized by relapses, remissions and often progression of disability over time (Noseworthy 2008). In MS, the body's own immune system attacks the myelin tissue surrounding the nerve fibers in the brain, spinal cord and optic nerves. When myelin is destroyed, scar tissue forms, and nerve messages are not transmitted properly. The exact cause of MS is not known, but there are data suggesting that infection, viruses, genetics, a person's environment, and hormones play a role (Compston 2005; Noseworthy 2008). There are four clinical forms of MS: relapsing remitting (RR), primary progressive (PP), secondary progressive (SP) and progressive relapsing (PR). RR is the most common form of MS disease (Ramagopalan 2010a). In most patients MS begins between the ages of 20 and 40 (Beeson 1994) and the condition is seen more frequently in women (Orton 2006; Ramagopalan 2010b).

1.1.2 MS prevalence

MS is estimated to affect 2.5 million of people in the world (Rosati 2001). MS prevalence is low in African blacks, Asians and other ethnic groups with little Caucasian admixture. MS especially affects those of northern European ancestry, such as Scandinavians, English and Irish **(**Compston 1997). Individuals living in USA, New Zealand and Australia have higher risk of having MS. In North America MS is considered to be as the most common disabling neurologic disease of young adults (Noseworthy 2008). Canada has one of the highest rates of MS in the world (MS Society of Canada, 2008 Atlas of MS). MS prevalence in Canada have found to be 1/1000 people; however, it could be as high as 240 per 100,000 people (O'Connor 2009).

1.1.3 MS Symptoms

Symptoms of MS affect patients differently and, even in the same person, change from time to time. Type and severity of MS symptoms depend on which part of the CNS has been affected by MS. Symptoms interfere with daily functioning, work, and leisure activities. Fatigue is extremely

common in people with MS, with a prevalence of 78%-91% (Fisk 1994, Ford 1998). Pain is also a frequent complaint among persons with MS; appearing in almost 50% of patients at some point of their disease course (Archibald 1994, Ehde 2003, Kalia 2005, Svendsen 2003, 2005). Sleep disturbance is another common symptom, occurring in approximately 54% to 60% of the MS population (Bamer 2008, Brass 2010, Stanton 2006, Tachibana 1994). In addition, approximately 48% to 80% of people with MS report problems with balance at some stage during the course of their disease (Grytten 2006). Leg spasms have been reported by 40% to 70% of individuals with MS (Leussink 2012). The prevalence of memory and concentrated problems, other frequent symptoms in people with MS, ranges from 30% to 70% (Rao 1991, Teng 2009) and can present in patients at any time during their disease process.

Restless Leg Syndrome (RLS) is another common symptoms of MS (Auger 2005, Deriu 2009, Gómez-Choco 2007, Italian REMS Study Group 2008, Li 2012, Manconia 2007); affecting overall health-related quality of life of people with MS. RLS is a neurological disorder characterized by abnorma sensation in limbs, mostly in calves and ankles (Tarsy & Sheon 2009) that can result in nighttime insomnia, and daytime fatigue (Auger 2005, Gómez-Choco 2007, Li 2012). RLS is different than burning, numbness, and tingling sensation that is related to MS-related neuropathic pain as they cannot be relieved by movement, and they are usually present in the day, and not only at night (Auger 2005, Manconia 2007). In addition, RLS sensations are relieved by movement, but this does not work with unpleasant sensations of MS-related neuropathic pain (Tarsy & Sheon 2009).

Emotional changes are also common in individuals with MS and are thought to be related to either a normal response to having a serious health condition or the result of damage to the nervous system. The reported prevalence of depression for people with MS has ranged from 40% to 50% (Feinstein 2002). Symptoms of psychological distress such as anxiety and irritability also affect a large percentage of individuals with MS and often co-occur with depressive symptoms (Bamer 2008, Mohr 2007). Other symptoms of MS are: visual disturbances (50% to 90%), bladder dysfunction (80%), bowel dysfunction (35% to 54%) and sexual problem (75%) (Mohr 2007, Grytten 2006, Sprangers 2000, Confavreux 2000).

1.1.4 MS Cost

The annual cost of MS has been estimated at 2.5 billion dollars in the US, and $502.3 million in Canada (O'Brien 2003). Indirect costs are identified as major contributors to total costs in MS. Indirect costs refer to lost productivity, early retirement, sick leave, reduced hours of work, and changing the type of work (Gold 1996). The total annual indirect cost of MS for Canadians has been estimated at $313.7 million (Asche 1997). In the most recent study, the mean total cost per MS person per year was estimated at $37,672, of which 32% was attributable to patients' sick leave and early retirement due to MS (Karampampa 2012). Direct costs of MS include medications, physician and other health professional services, and hospital and other institutional care during relapses. Thirty percent of all people with MS need to be hospitalized at some time during the course of their disease (Buchanan 2002). Additionally, the cost per person for a relapse can be as high as $12,870 (O'Brien 2003).

1.1.5 MS treatments

Several pharmacological and non-pharmacological therapies for MS exist. One category of MS medications are called disease modifying therapies (DMT) which attack the inflammation that damages the myelin, decrease the severity and length of relapses, reduce the accumulation of lesions within the brain and spinal cord, and appear to slow down the speed of physical disability (Kieseier 2003; O'Connor 2000; Frohman 2004; Morris 2002). Some of the DMTs that have been approved for relapsing-remitting MS include Betaseron, Avonex, Copaxone, Bebif, and Novantroneand Tysabri (Frohman 2004). It has been shown that DMTs such as Interferon Beta (IFNß), Glatiramer Acetate (GA) and Copolymer (Copaxone) which are often taken on a long-term basis, can slow the natural course of MS (Kieseier 2003; Jacobs 2000). Steroids may also help to decrease the severity and duration of MS relapses by actively suppressing the inflammation. Other pharmaceutical approaches may focus on reducing the MS related symptoms e.g. baclofen or tizanidine for spasticity and pain, anticholinergics for overreacting bladder, and antidepressant for depression (Acquadro 2003).

As with any medical treatment, medications used in the management of MS may have several adverse effects. As a result, many people with MS prefer to use complementary treatments such as meditation, massage, rest, physiotherapy, occupational therapy, exercise, yoga

and swimming (White 2004). Disease coping strategies, self management techniques and education are some of the rehabilitative approaches in the management of MS to assist persons with MS in taking control over their symptoms and disability (Willke 2004).

1.1.6 Health-related Quality of Life for persons with MS

Quality of life (QOL) is defined as "the individuals' perceptions of their position in life in the context of the cultural and value system in which they live and their relationship to their goals, expectations, standards, and concerns" (WHO 2001). Based on this definition, QOL covers all aspects of well-being including social, emotional, economic and cultural facets of a person's life. Health-related quality of life (HRQL) is defined as "the value assigned to duration of life as modified by impairments, functional status, perceptions and opportunities influenced by disease, injury, treatment and policy" (World Health Organization, 2001). HRQL, therefore, is generally distinguished from QOL by those aspects of life which are most likely to be affected by health (Patrick 1990).

Given that MS is a chronic and progressive disease characterized by various neurological symptoms, physical disability and social isolation that affect many aspects of everyday life, people with MS report poorer HRQL in comparison to some of the other chronic conditions such as epilepsy, diabetes, rheumatoid arthritis, and inflammatory bowel disease, or the general population (Brunet 1996, Hopman 2009, Rudick 1992, Devins 1993, Nortvedt 1999). Aspects of HRQL such as physical function, social participation, and emotional and mental health are domains that have been shown to be greatly reduced in the MS population (Beck 2005, Devins 1993, Nortvedt 1999).

1.1.7 The New MS

Before 1995, the diagnosis of MS was based on its natural history, severity of symptoms and progression of disability. In addition, therapeutic approaches were mainly based on using the steroids to reduce inflammation and medications for symptoms management. Since 1995, advances in neuroimaging techniques such as magnetic resonance imaging (MRI), and disease modifying therapies (DMTs) have facilitated earlier diagnosis of disease, and reduced the speed of disease progression (Mayo 2008). In 2008, Dr. Nancy Mayo used the title of "New MS" for

those people with MS diagnosed after 1995 as they differed slightly from populations of people diagnosed with MS prior to 1995 (Mayo 2008). Therefore, it would be an important research purpose to find out if among people with “New MS” any change has also occurred in symptoms patterns, disease course and consequences, as well as other aspects of the disease. This would help us to gain a better understanding of the disease, and development of new therapeutic intervention.

1.2 Overview of Pain in Multiple Sclerosis

1.2.1 Prevalence

Pain is a frequent complaint among persons with MS. The reported prevalence of pain in people with MS differs in the literature, from 10% to 90%, with most reporting rates ranging from 40% to 80% (Kalia 2005, Indaco 1994, Kassirer & Osterberg 1987, Moulin 1988 & 1989, Svendsen 2003, Stenager 1991, 1995, Vermote 1986, Carter 1948). In Canada, pain in MS was reported in 41% to 71% of people with MS (Ehde 2003& 2006, Piwko 2007, Archibald 1995, Warnell 1991). This variation is partly due to methodological differences across studies related to the patient sources, method of sampling, and research design. In addition, pain measurement studies have used different time frames of pain (previous week, one month, 3 months), and different pain constructs (frequency, intensity, and duration). In addition, studies varied as to whether headache was related to MS pain (Vermote 1986, Moulin 1981). Factors related to the heterogeneity and complexity of the disease itself (disease subtype and severity of other symptoms) also varied widely across studies.

1.2.2 Cost

Considering the cost of MS pain, although there are several published studies that describe the total cost of MS (Grima 2000, Amato 2002, Whetten-Goldstein 1998, Miltenburger 2002, Grudzinski 1999), only one article provided an estimate of direct and indirect costs of MS pain (Piwko 2007). The results of this study showed that the cost of 6-months pain of MS has been estimated at about $80 million per year in Canada (Piwko 2007). The total cost for pain per MS person was $3,197±5,965 (mean ± SD) including $2,528±5,695 direct cost and $669±875 indirect cost. The estimated hospitalization and drug management of pain were the two most important contributors to the total cost (Piwko 2007). Other example of cost included visiting health care providers and physical therapists, laboratory and diagnostic tests, emergency room visits and home care visits (Piwko 2007). A positive correlation between the total cost and pain severity was also reported (Piwko 2007).

1.2.3 Reasons for pain in MS

The underlying mechanisms of pain in MS are unclear. MS pain can arise from a variety of sources. MS pain is either directly related to MS lesions or dysfunction in central nervous system (CNS) which is called neuropathic pain, or indirectly as a consequence of MS symptoms such as muscle spasms and poor posture which is called musculoskeletal pain. The most common neuropathic pain types in MS are dysesthesia, trigeminal neuralgia (TN) and Lhermitte's sign (LS). Painful tonic spasms, low back pain, and muscle spasms are the frequent types of musculoskeletal pain among the MS population (O'Connor 2007). Headache that is experienced by many people with MS is either a direct result of MS lesions, or an indirect result of adjustment to having the disease (Rolak & Brown 1990, O'Connor 2007). Table 1.1 presents the classification of MS pain as proposed by O'Connor (2008). DMT and other pharmacological treatments for MS may also contribute to the development of pain and an increase in the frequency and duration of headaches (Rizzo 2003, Solaro 2004). Flu-like symptoms, muscle aches, and sensation of tingling, and numbness are other relatively frequent side effects of DMT (Rio 2004, La Mantia 2006, Pollmann 2002).

1.2.4 Course and nature of MS pain

Persons with MS and pain usually describe their pain intensity as mild to moderate (Archibald 1994); however, thirty-two percent of the patients report that pain is one of the worst symptoms of MS (Stenager 1991). There are several risk factors reported to be associated with a greater likelihood of pain in people with MS, for example older age, female sex, longer disease duration, greater disease severity, and depression (O'Connor 2008). In most people with MS pain is commonly reported to occur in more than one site. Leg pain followed by back pain and arm pain is the most common reported sites of pain (Moulin 1988, Rizzo 2003, Solaro 2004). The majority of MS- related pain is chronic in nature. The major chronic pain syndromes are dysesthetic extremity pain and back pain (Stenager 1995, Moulin 1988). The most frequent acute type of MS pain includes trigeminal neuralgia (TN) and Lhermitte's sign (LS) (Stenager 1991).

1.2.5 Pain impact

The impact of pain on persons with MS is not well recognized (Ehde 2005); however, it has been accepted that the fear of pain associated with MS prevents them from involving themselves in physical and social activities. Individuals with pain report poorer overall mental health than those without pain (Archibald 1994). Some studies, however, found no significant differences in mental health scores between people with MS with and without pain (Stenager 1991, Stenager 1995). Moreover, Ehde (2005) found that among persons with MS, individuals reporting pain compared to those without pain were more depressed (Forbes 2006, Kalia 2005). The presence of pain is also associated with lower levels of HRQL in people with MS in comparison to those individuals without pain (Murphy 1998, Nortvedt 1999, Svendsen 2005). Several studies have examined the impact of pain on other aspects of health among persons with MS. For example, one study showed that among a large community sample of persons with MS, those with pain reported poorer general health, increased fatigue, and more interference with daily living activities and household work (Ehde 2003, Svendsen 2005, Schwid 2002). Persons with MS and pain also report more difficulty in sleep, enjoyment of life, and ability to walk or move around (Hadjimichael 2007, O'Connor 2008). Research on the relationship between pain and social functioning in MS is more limited. The results have suggested that pain can have a negative effect on social role participation (Archibald 1994), recreational activities (Hadjimichael 2007), and relationships with others (Warnell 1991).

1.2.6 Treatment of MS pain

Treatment of MS pain involves a variety of pharmacologic and non-pharmacologic approaches (Leary 2000). Given that pharmacologic treatment is the most commonly prescribed treatment for pain in MS, most research have focused on their effectiveness (Henze 2006). Pharmacologic pain treatments include the use of antidepressants, and anticonvulsant for neuropathic pain and anti-inflammatory medications for musculoskeletal pain (O'Connor 2008). Some people also use Cannabinoids in the management of their MS pain. For those people with MS for whome the long-term use of medication is either ineffective or causes side effects, complementary therapies for the management of pain and sensory complaints may be more useful (Moulin 1988). Massage, exercise, yoga, tai-chi, transcutaneous electrical nerve stimulation (TENS), heat therapy, hydrotherapy, herbal remedies, acupuncture, chiropractic manipulation, reflexology, and

cognitive behavioral therapy are examples of non-pharmacologic pain treatment approaches that have been used in MS population (White 2004, Oken 2004, Nayak 2003, Siev-Ner 2003, Rabinstein 2003, Lee 2007).

1.2.7 Concept of pain

International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (Merskey 1979, 1994, 2007). Melzack and Wall in 1965 proposed the Gate Control Theory that states a gating mechanism exists within the dorsal horn of the spinal cord that controls pain signals to the brain (Melzack & Wall 1965). Nerve impulses traveling via small nerve fibers (pain receptors A-delta and C) are allowed to pass through the gate, whereas pain signals traveling via large nerve fibers (normal receptor A-beta) are blocked. Physical, emotional, and behavioral factors may facilitate or inhibit gate opening (Melzack & Wall 1965). For instance bodily injury, anxiety, depression and concentrating on the pain may open the gate, whereas pain medications, good mood, and distraction from pain may block the gate (Melzack & Wall 1965).

The gate control theory of pain emphasizes that psychological factors play an important role in pain perception. It further explains the reason that same stimulus may provide different pain perception among different people. This is in agreement with the philosophical perspectives of pain proposed by Plato (427-347 BC), Aristotle (384-322 BC) and Descartes' (1596-1650) that suggests pain experience is not only related to nerve stimulation but also may be viewed as an emotion, feeling, and soul (Cheng 2003).

Kerns later explored in 2002 the biopsychosocial model of pain (Kerns 2002). According to this model, pain perception is affected by complex interactions between disability, affective distress, and cognitive, behavioral, and social factors (Kerns 2002). The influences of individual's attitude and social and cultural differences on pain experience have also been highlighted in other studies (Cheng 2003, Zborowski 1969).

In addition, while there is an increasing interest in the concept of pain in MS population, there are conflicting ideas in the literature about which dimension of pain can be considered as the best illustration of pain. Pain has different domains that should be clarified before its assessment (Hester 1997). Pain is perceived in intensity, quality, type, duration, frequency, location, or distribution (Von Korff 2000). However, most studies on pain in MS do not take into account all aspects of this construct; pain intensity, which is only one aspect of the pain experience, is usually the primary focus (Jamison 1991, 2002, Litcher-Kelly 2004, Peters 2000, Vendrig 1997). Therefore how pain is defined and measured varies considerably across studies, with some focusing on a specific pain construct such as duration or severity, and others not specifying the criteria used to determine the presence of pain (Turk & Dworkin 2004). Because of these differences, it is often difficult to compare findings across studies.

The definition of pain and the proposed models of pain emphasize that pain is a complex health outcome (Von Korff 2000, Merskey 1979, 1994, 2007) with a multidimensional nature across a range of different physical, psychological and social factors (McWilliams 2003, Parker 2005). This further means that the relationship between and among pain and other health-related outcomes such as social participation or disability may be not only directly related to the tissue damage but may be mediated by many other factors (Fernandez & Milburn 1994) – for example, individuals with MS who experience other symptoms such as fatigue, cognitive impairment, anxiety and depression (O'Connor 2005) that may affect their pain perception (Kerns 2002). The complexity of pain also emphasizes a multidimensional assessment. To reach this goal, pain should be studied within a comprehensive and multidimensional model that includes all factors that contribute to its perception.

1.3 Overview of participation

1.3.1 Participation definition

The International Classification of Function, Disability, and Health (ICF) define participation as "involvement in life situations" (World Health Organization, 2001). Participation indeed represents the societal perspective of functioning. As illustrated in Figure 1.2, major components of role participation are personal and household management, leisure or recreations activities, community involvement, relationships, and work (Johnson 2004, Salter 2005). Participation restriction refers to problems an individual may experience in involvement in social and occupational activities (World Health Organization 2001). Social participation has been defined as "optimal accomplishment of daily activities and social roles valued by the person or socio-cultural environment which ensure survival and development in society throughout life" (Fougeyrollas 1998). Optimal social participation refers to "absence of interruption in the achievement of life situations" (Desrosiers 2002). Occupational participation is defined as "engaging in work, play or activities of daily living that are part of one's socio-cultural context and that are desired and/or necessary to one's well-being" (Kielhofner 2004).

1.3.2 Participation and HRQL

Improving HRQL of individuals with disabilities is the ultimate aim in rehabilitation and clinical practice (Renwick 1996). Participation is one of the most important domains affecting HRQL (Barclay-Goddard 2012); thus, it has been receiving increased interest in rehabilitation research in the past few years (Noreau 2004, Salter 2005). A clear understanding of role participation and its barriers and facilitators can improve HRQL in individuals with disabling conditions such as MS.

1.3.3 MS and participation

Participation has been studied extensively in traumatic brain injury (Johnston 2005), spinal cord injury (Whiteneck 2004), and stroke (Barclay-Goddard 2012, Mayo 2002, Desrosiers 2002). For individuals with MS, role participation has been defined as "taking part in valued activities, such as meaningful social, recreational, and work activities, despite the many barriers that may arise,

including pain, fatigue, cognitive-communication changes, limited mobility, and depression" (Yorkston 2005).

Fatigue is a common symptom of MS and can be considered as one of the major reasons for participation restriction in MS population (Bergamaschi 1997). The important role of fatigue for work (Ng 2012), illness intrusiveness (Bouchard 2012), and communicative participation (Baylor 2010) has been shown. Cognitive dysfunction has also been shown to negatively affect employment status, activities of daily living, ability to drive, as well as social relationships of people with MS (Rao 1992). Other ongoing symptoms such as vision and speech problems, as well as problems thinking may interact to further reduce social functioning in this population (Baylor 2010).

In addition, in persons with MS, muscle weakness, spasm, and stiffness in the legs may produce unsteady gait, difficulty with walking, and difficulty with keeping balance and coordination. Fear of falling and poor balance could make someone who experiences them avoid to participating in social activities. Spasticity can also significantly affect motor performance and daily living activities and so restrict the social participation among people with MS. In addition, disability, different symptoms, and mobility difficulties that individuals with MS experience could significantly impact their ability to remain in the workforce (Busche 2003, Noseworthy 2000), which is one of the important domains of participation. Moreover, results of a study on community participation and social and home participation among adults with complex medical, lower-extremity orthopedic, and major neurologic impairments indicated that activity limitations and physical functions were the dominant factors that explained much of the variance in the extent of community participation achieved by patients (Jette 2005).

A study on barriers and facilitators related to participation in aquafitness programs for people with MS has shown that barriers to participation can be related to inadequate transportation, lack of one-on-one support, environmental inaccessibility, and fears associated with participation in the programs (Brown 2012). Facilitators of participation included a knowledgeable instructor and experiencing physical and psychosocial benefits from the program (Brown 2012). In 2010, Tyszka examined the relation of health-promoting behaviors to participation in life roles and

HRQL in women with multiple sclerosis. They found a positive correlation among specific health-promoting behaviors (e.g., nutrition, stress management, physical activity, positive interpersonal relations, and spiritual growth), role participation, and HRQL (Tyszka 2010). He suggested that involvement in health-promoting behaviors is associated with greater participation in life roles and HRQL for women with MS.

1.3.4 MS-related pain and participation

Pain can also be considered as one of the important symptoms of MS that may contribute to problems with social functioning as in the presence of pain a person may seem more anxious about engaging in active recreational pursuits. However, there is little awareness of the role of pain in the restriction participation of people with MS. In a large study, recreational activities, work, and walking ability were the three highest-rated areas reported to interfere in the social life of MS people with pain (Hadjimichael 2007). Similar results have been reported by other studies. Warnell indicated that nearly one third of MS persons report that pain has negative effects on their relationships with others (Warnell 1991). In another study, over a third of persons with MS and pain reported more social role restriction than those without pain (Archibald 1994). Additionally, O'Connor (2008) found that individuals with MS pain report less recreational activity in comparison to MS people without pain.

Later, in 2009, Turner estimated exercise frequency and its association with QOL, including participation restriction, in a national sample of veterans with MS and found that older age, lower education, and pain provided lower rates of exercise (Turner 2009). In addition, persons with MS and pain report more depressive symptoms (Ehde 2005), greater diminished physical function (Ehde 2003), and poorer mental health (Archibald 1994) than people with MS who do not have pain. Given the relative role of pain in physical and psychological distress, it is assumed that pain can catalyze the social isolation of MS population.

1.3.5 The complexity of participation

Participation is a multidimensional global construct including a number of aspects that are more likely to be performed with others (World Health Organization, 2001). As illustrated in Figure 1.3, participation, as a complex health outcome, has a biopsychosocial nature, in that the person

is physically, emotionally, or mentally engaged (Yorkston 2005). For instance, there are several personal and disease-related factors that may affect participation including age, level of education, comorbidity, psychological distress, disease severity and duration, and severity of symptoms. The environmental factors also play an importance role for creating, or preventing, opportunities for participation (Barclay-Goddard 2012). For example, technology, social support, relationships with others, and health policy makers in interaction with the individual factors such as mood, attitude and physical health may promote or restrict participation. Similarly, to improve participation, focusing on a single factor may not be enough and it would be necessary to minimize the impairment, increase activities, reduce social and environmental barriers, and enhance personal coping strategies (Yorkston 2005, Sorensen 2002). The complexity of the nature of participation poses a measurement challenge, emphasizing that it should be studied within a multidimensional approach targeting all contributing factors.

1.3.6 Measure of participation

A number of measures have been developed to assess participation (Cardol 1999, Ostir 2006, Perenboom 2003). A few of them have been reported to assess participation widely (Perenboom 2003), however, there is no single universally accepted scale for its measurement (Heinemann 2005). There is certainly no specific measure related to the MS population. Role-Physical, Role-Emotional, and Social Functioning of RAND-36 (Hays 1993, 2001), Reintegration to Normal Living Index (RNLI) (Wood-Dauphinée 1988, Stark 2005), and Community Integration Questionnaire (Willer 1993) are examples of tools that have been reported in literature to assess participation. Using multiple measures of participation makes it difficult to interpret and compare the results across studies.

There is also no agreement in the literature about which dimension of participation should be measured (Salter 2005, Yorkston 2008). Most studies on participation do not take into account all aspects of this construct; different scales focus on different aspects of life situations and social roles (Seekins 2012). In many of the scales, participation has often been measured by the time spent or frequency of engaging in a variety of social activities (Yorkston 2005). In rehabilitation, participation is considered to be both objective and a patient-reported health outcome (Barclay-Goddard 2012, Mayo 2002). The self-perceived perspective of participation refers to the

patients' perception about their experiences, access, values, beliefs, engagement, satisfaction, and enjoyment (Barclay-Goddard 2012, Brown 2010, Hammel 2006, Yorkston 2005).

As enhancing participation is important in the rehabilitation of individuals living with MS, an accurate, reliable, and valid measure of participation would be necessary for selecting and prioritizing appropriate interventions (Yorkston 2005). Therefore, to have a valid and reliable measure of participation, using several corresponding representative measures of participation, we will create a latent component for participation that covers different aspects of the construct such as role limitations, social functioning, work, relationship with others, exercise, and leisure. This topic will be the focus of Manuscript 5.

1.4 Choosing a conceptual framework

Pain and participation are both complex constructs. Therefore, studies of relationship between pain and participation require an interactive framework to simultaneously evaluate the complex interrelationships among the variables of interest and other mediating factors. There are two commonly used theoretical frameworks that have been developed to explain the relationship among health outcomes: the International Classification of Functioning Disability and Health (ICF) and the Wilson Cleary model (WCM).

1.4.1 The International Classification of Functioning Disability and Health (ICF)

In 2001 the World Health Organization created a framework called International Classification of Functioning, Disability and Health (ICF) which is used for describing and measuring health and disability (World Health Organization, 2001). As illustrated in Figure 1.4 the ICF is a biopsychosocial model that consists of two components. The first component is Functioning and Disability, which includes: body function, body structure, and activity and participation. The term FUNCTION is an umbrella term that covers the positive aspects of health (body structure and function, activities and participation), while the umbrella term DISABILITY covers the negative aspects of health (impairment of body structure and function, activity limitation and participation restriction). Body functions and structures are assessed in terms of change in physiological function and anatomical structure (World Health Organization, 2008). Activity is the execution of a task or action, and participation is defined as involvement in life situations (World Health Organization, 2001).

The second component of ICF, Contextual Factors, includes personal and environmental factors. Contextual Factors represent the complete background of an individual's life, and can be referred to as those factors that define the person as a unique individual (World Health Organization, 2008). Within the contextual factors, the environmental factors put together the physical, psychological, and social environment in which people live, and personal factors comprise features that are not part of a health condition, i.e., gender, age, race, and lifestyle (World Health Organization, 2008). The model suggests that these factors are bi-directionally associated with each other.

The ICF model has been under multiple thorough revisions by an international assembly of experts around the world. In addition, it has been translated into multiple languages; thus cultural and linguistic differences in these components have been taken into consideration (Benito-Leon 2003, Cieza 2005, Keeney 2001). ICF can establish a common language to develop a systemic coding scheme for health information systems, permit comparison of data across countries, health care disciplines, and research fields, improve the planning of functioning-oriented rehabilitation services, and facilitate the description and evaluation of individuals' functioning (Godges & Irrgang 2008, Jette 1998, Irrgang & Godges 2006, World Health Organization 2001, Grimby & Stucki 2004).

1.4.2 Wilson and Cleary Model (WCM)

The Wilson-Cleary Model (WCM) is another commonly applied conceptual frame of reference. The WCM is considered to be an interactive, comprehensive, and biopsychosocial framework to present consequences of health conditions in a meaningful, interrelated, and easily accessible way (Wilson & Cleary 1995). As illustrated in Figure 1.5, Wilson and Cleary have conceptualized HRQL as a multidimensional directional model that explains the linear relationship between and among biological & physiological, symptoms status, functional status, general health perception and overall QOL (Wilson & Cleary 1995). The model also acknowledges that each of these components can be affected by individual and environment characteristics.

Wilson and Cleary's (1995) model of HRQL has been applied to several diseases including HIV/AIDS, heart failure, gastrointestinal bleeding, diabetes, and Hodgkin's lymphoma (Sousa & Kwok 2006). Yet, the performance of the model determining the impact of pain on participation in persons living with MS has not been evaluated (Bakas 2012).

The combination of WCM and ICF can also be used as a conceptual framework as there is considerable overlap between the components of two models. As demonstrated in Figure 1.6 biological and physiological variables and symptoms of the WCM are equivalent to impairments of body function and structure in the ICF. In addition, activity and participation of the ICF correspond to the functional status of WCM. Moreover, both models consider the important roles

of environmental and personal factors. However, WCM and ICF differ from one another in several ways. First, the overall construct covered in the ICF is functioning and disability – which is a component of HRQL, but WCM includes general health perception and QOL. Second, while the Wilson-Cleary model is a medical model focusing more on the physiological aspect of health, the ICF puts more emphasis on functioning and disability. Finally, the ICF framework expresses the relationship between health components in a dynamic way, where all items are related and influence one another. On the other hand, the WCM is a more linear model than ICF. By combining these two models together, the effectiveness of interventions can be achieved from both medical and rehabilitative perspectives.

For the last part of this thesis, by using the WCM as a conceptual framework, we will be evaluating the relationship between pain as a symptom status and participation as functional status in people with MS. Having a common conceptual framework would significantly help researchers and health care providers to measure health outcomes in the same way with considering their mediating factors, provide a guide for clinical assessment, and help evaluate the effectiveness of intervention approaches (Sousa 2006).

1.5 Choosing a statistical method

To be able to study multidimensional health outcomes, such as pain and participation, in a hypothesized conceptual framework with complex interrelationships between multiple variables, a more advanced or complex statistical method is needed.

1.5.1 Regression

Regression is the most common statistical test for researchers and clinicians to analyze simple relationships between different variables (Kupek 2006); however, it has several challenges that limit its application as an appropriate statistical analysis in multidimensional health outcomes. Multiple regression analysis estimates the effect that certain predictor variables have on a single outcome (Wall & Li 2003), so it would not be an appropriate method for determining a model that contains more than a single outcome variable (Kupek 2006). A larger concern is that the variables in a regression models cannot be used both as independent and dependent variables.

In addition, regression analysis only proposes a fixed model to evaluate the relationship among variables at one point of time (Wall & Li 2003), so the selection of the variables that will shape the model is a challenge (Kupek 2006). With regression it is not possible to develop and evaluate alternative theoretical frameworks representing the different relationships between and among all related variables.

Another challenge with regression occurs when a variable is latent or unobserved (unmeasured). Regression only deals with observed variables, which is are variables that can directly be measured, such as height or weight. In contrast, a latent variable, such as pain, cannot directly be measured, so it is implied by the covariances among ≥2 indicator variables (Hoyle 1995). A latent variable can also be created while there is a global outcome with no agreement in literature about which dimension of that construct should be measured. Latent variables can further be helpful when there is no widely accepted valid, reliable, and accurate measure to assess different aspects of a construct. The created latent variable would then help verify how well the different measures that build the different dimensions of the construct hold together. There are several possible analytical methods of creating latent variables such as factor analysis, principal component analysis, and Rasch analysis (Bartholomew 2002).

Additional challenge with regression would be related to the fact that multiple linear regression only estimates the direct effects, not indirect effects (Plummer & Clayton, 1993). Indirect effect is where the effect of an exposure on an outcome is mediated through one or more intervening variables such that after removing it, there is no longer a relation between the outcome and exposure (Hooper 2007, Kenny 1979).

1.5.2 Structural equation modeling (SEM)

In contrast to what has been said about regression analysis, SEM, a combination of factor analysis and path analysis, is a powerful and advanced statistical approach that has the ability to simultaneously evaluate both direct and indirect relationships between observed and latent variables within multiple alternative theoretical models (Duncan 1999, Hays 2005, Kline 2005, MacCallum 1995, 2000, Suhr 2000).

SEM begins with a hypothesized model or diagram that consists of a number of variables connected together based on a theoretical knowledge background (Hays 2005) or some pre analyses. To establish the model, the researcher should consider all possible relationships among variables. Each model of SEM has two components: a measurement model and a structural model (Hoyle 1994). The measurement model is a multivariate regression model which examines the relationship between a common component or latent variable and a set of its related indicators or observed variables. Measurement error from each indicator is evolved into the latent component estimate, which increases the reliability of the estimates. This further will increase the validity of the latent component as each indicator may capture the underlying construct in a different way. The second component of the SEM model called structural model that permits the estimation of direct and indirect relationships among latent variables, and if any other observed variables that are not factor indicators**,** in the model (Kline 1998) (Figure 1.7).

SEM tests the hypothesized model against the data and modifying the model based on the theory or fit indices (Kline 2005). The goodness of fit of the model is examined using several fit indices including the Chi-square statistic, Comparative Fit Index (CFI), Tucker- Lewis Index (TLI), Root Mean Square Error of Approximation (RMSEA), and the Standardized Root Mean Squared Residual (SRMR) (Hu & Bentler 1999). A p value smaller than .05 for Chi square test, a cutoff

value .95 or larger for CFI and TLI; a p value smaller than .06 with a cutoff value .90 for RMSEA; and a p value below .08 for SRMR suggest an adequate fitting model (Hu & Bentler 1999). If the model did not fit the data well, the model will be modified several times to determine whether a better model could be developed with an acceptable fit index (Kline 2005, 2011, Martens 2005). Evaluation of the alternative models is based on the theoretical knowledge, along with the statistical criteria for adding or removing paths. The amount and direction of the relationships between and among variables are represented by path coefficients, which are interpreted similar to the regression coefficients.

It is important to note that SEM has several imitations that should be considered while using this statistical method in research and clinical settings (Tomarken 2005). As with any statistical modeling technique, interpreting results of SEM depends on the sample size, generalizability of the sample, measurement instruments, quality of the measured data, multivariate normality, parameter identification, outliers, missing data, and interpretation of model fit indices (MacCallum & Browne 1996, Schumacker & Lomax 1996). In addition, although according to Tomarken and Waller (2005) SEM provides valuable information about variance of one variable due to change of other variables, the fit of a model of SEM does not prove any causal inference among variables (Kline 1998, Suhr 2000). Finally, SEM requires a large sample size. In general, 10 to 20 subjects per parameter estimated or an optimal sample size of greater than 200 subjects is recommended (Kline 2011, Hoyle 1995). The parameters of the model are the number of path coefficients, variances, covariances, and disturbance terms (Hatcher 1994). If the sample size is small, the model will be low power.

The last manuscript of this thesis will use SEM to evaluate the direct and indirect effects of pain and other MS- related symptoms, physical and mental functional factors, and individual characteristics predict participation in people with MS.

References List

Acquadro C, Berzon R, Dubois D et al. Incorporating the patient's perspective into drug development and communication: an ad hoc task force report of the Patient-Reported Outcomes (PRO). Harmonization Group meeting at the Food and Drug Administration, Health 2003; 6:522-31.

Amato M, Battaglia M, Caputo D, et al. The costs of multiple sclerosis: A cross-sectional, multicenter cost-of-illness study in Italy. J Neurol 2002; 249:152-63.

Archibald CJ, McGrath PJ, Ritvo PG. Pain prevalence, severity and impact in a clinic sample of multiple sclerosis patients, Pain. 1994; 58: 89–93.

Asche CV, Ho E, Chan B. Economic consequences of multiple sclerosis for Canadians. Acta Neurol Scand 1997; 95:268-274.

Auger C, Montplaisir J, Duquette P. Increased frequency of restless legs syndrome in a French-Canadian population with multiple sclerosis. Neurology 2005; 65(10):1652.

Bakas T, McLennon S.M, Carpenter J.S, Buelow J.M. Systematic review of health-related quality of life Models. Health and Quality of Life Outcomes 2012, 10:134.

Bamer AM, Johnson KL, Amtmann D, Kraft GH. Prevalence of sleep problems in individuals with multiple sclerosis. Mult Scler. 2008; 14(8): 1127–1130.

Barclay-Goddard R, Ripat J, Mayo N. Developing a model of participation post-stroke: a mixed-methods approach. Qual Life Res 2012; 21:417–426.

Baylor C, Yorkston K, Bamer A, Britton D, Amtmann D. Variables Associated with Communicative Participation in People With Multiple Sclerosis: A Regression Analysis. American Journal of Speech-Language Pathology 2010, (19): 143–153.

Beck CA, Metz LM, Svenson LW et al. Regional variation of multiple sclerosis prevalence in Canada. Mult Scler. 2005; 11:516-9.

Beeson PB. Age and sex associations of 40 autoimmune diseases. Am J Med 1994; 96(5):457-9.

Benito-Leon J, Morales JM, Rivera-Navarro J et al. A review about the impact of multiple sclerosis on health-related quality of life. Disabil Rehabil 2003; 25:1291-303.

Brass SD, Duquette P, Proulx-Therrien J, Auerbach S. Sleep disorders in patients with multiple sclerosis. Sleep Medicine Reviews 14 (2010) 121–129

Brown M. Participation: The insider's perspective. Archives of Physical Medicine and Rehabilitation, 2010 (91): S34–S37.

Buchanan RJ, Wang S, Ju H. Analyses of the minimum data set: comparisons of nursing home residents with multiple sclerosis to other nursing home residents. Mult Scler 2002; 8:512–22.

Cara Brown, Kaitlyn Kitchen, and Kaley Nicoll (2012) Barriers and Facilitators Related to Participation in Aquafitness Programs for People with Multiple Sclerosis. International Journal of MS Care 2012; 14 (3):132-141.

Cardol M, de Haan RJ, van den Bos GAM, de Jong BA, de Groot IJM. The development of a handicap assessment questionnaire: The Impact on Participation and Autonomy (IPA). Clinical Rehabil 1999; 13: 411- 419.

Cheng S.F, Foster R.L, Huang C.Y. Concept Analysis of Pain. Tzu Chi Nursing Journal 2003; 2:3, 20-30.

Cieza A, Geyh S, Chatterji S et al. ICF linking rules: an update based on lessons learned. J Rehabil Med 2005; 37: 212-8.

Compston A, Confavreux C, Lassmann H. McAlpine's Multiple Sclerosis. Philadelphia: Elsevier, 2005.

Compston, Alastair Journal of Neurology, Neurosurgery & Psychiatry. 62(6):553-561, June 1997.

Confavreux C, Vukusic S, Moreau T et al. Relapses and progression of disability in multiple sclerosis. N.Engl.J.Med. 2000; 343:1430-8.

Deriu M, Cossu G, Molari A, Murgia D, Mereu A, Ferrigno P, Manca D, Contu P, Melis M. Restless legs syndrome in multiple sclerosis: a case-control study. Mov Disord 2009; 24 (5):697.

Devins GM, Edworthy SM, Seland TP et al. Differences in illness intrusiveness across rheumatoid arthritis, end-stage renal disease, and multiple sclerosis. J.Nerv.Ment.Dis. 1993; 181:377-81.

Ehde DM, Gibbons LE, Chwastiak L, Bombardier CH, Sullivan MD, Kraft GH. Chronic pain in a large community sample of persons with multiple sclerosis. Mult Scler. 2003; 9:605–11.

Ehde DM, Osborne TL, Jensen MP. Chronic Pain in Persons with Multiple Sclerosis. Physical Medicine and Rehabilitation Clinics of North America 2005; 16: 503-512.

Feinstein A. An examination of suicidal intent in patients with multiple sclerosis. Neurology 2002; 59:674-8.

Fernandez E, & Milburn TW. Sensory and affective predictors of overall pain and emotions associated with affective pain. Clinical Journal of Pain 1994; 10:3-9.

Fisk JD, Pontefract A, Ritvo PG, Archibald CJ, Murray TJ. The impact of fatigue on patients with multiple sclerosis. Can J Neurol Sci 1994; 21:9-14.

Forbes A, While A, Mathes L, Griffiths P. Health problems and health-related quality of life in people with multiple sclerosis. Clin Rehabil 2006; 20:67–78.

Ford H, Trigwell P, Johnson M. The nature of fatigue in multiple sclerosis. J Psychosom Res 1998; 45:33–8.

Fougeyrollas P, Noreau L, Bergeron H, Cloutier R, Dion SA, St-Michel G. Social consequences of long term impairments and disabilities: conceptual approach and assessment of handicap. International Journal of Rehabilitation Research 1998; 21:127-141.

Frohman EM, Brannon K, Alexander S et al. Disease modifying agent related skin reactions in multiple sclerosis: prevention, assessment, and management. Mult Scler 2004; 10:302-7.

Gold MR. Cost-effectiveness in health and medicine. New York: Oxford University Press. 1996.

Gómez-Choco MJ, Iranzo A, Blanco Y, Graus F, Santamaria J, Saiz A. Prevalence of restless legs syndrome and REM sleep behavior disorder in multiple sclerosis. Mult Scler 2007; 13(6):805.

Grima D, Torrance G, Francis G, Rice G, Rosner A, Lafortune L. Cost and health-related quality of life consequences of multiple sclerosis. Mult Scler 2000; 6:91-8.

Grudzinski A, Hakim Z, Cox E, Bootman J. The economics of multiple sclerosis: Distribution of costs and relationship to disease severity. Pharmacoeconomics 1999; 15:229-40.

Grytten N, Maseide P. 'When I am together with them I feel more ill.' The stigma of multiple sclerosis experienced in social relationships. Chronic Illn 2006; 2:195-208.

Hadjimichael O, Kerns RD, Rizzo MA, Cutter G, Vollmer T. Persistent pain and uncomfortable sensations in persons with multiple sclerosis. Pain 2007; 127:35–41.

Hammel J, Jones R, Gossett A & Morgan E. Examining barriers and supports to community living and par-ticipation after a stroke from a participatory action research approach.Topics in Stroke Rehabilitation 2006, 13, 43–58.

Hawkes CH, Fawcett D, Cooke ED, et al. Dorsal column stimulation in multiple sclerosis: effects on bladder, leg blood flow and peptides. Appl Neurophysiol 1981; 44(1–3): 62–70.

Heinemann, A. (2005). Putting outcome measurement in con-text: A rehabilitation psychology perspective. Rehabilitation Psychology, 50(1), 6–14. doi:10.1037/0090-5550.50.1.6

Italian REMS Study Group. Multicenter case-control study on restless legs syndrome in multiple sclerosis: the REMS study. Sleep. 2008; 31(7): 944.

Jacobs LD, Beck RW, Simon JH, Kinkel RP. Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. CHAMPS Study Group. N Engl J Med 2000; 343 (13):898-904.

Kalia LV, O'Connor PW. Severity of chronic pain and its relationship to quality of life in multiple sclerosis. Mult Scler2005; 11:322–7.

Karampampa K, Gustavsson A, Miltenburger C, Kindundu CM, Selchen DH. Treatment experience, burden, and unmet needs (tribune) in multiple sclerosis study: The costs and utilities of MS patients in Canada. J Popul Ther Clin Pharmacol 2012; 19:11-25.

Keeney S, Hasson F, McKenna HP. A critical review of the Delphi technique as a research methodology for nursing. Int.J.Nurs.Stud. 2001; 38: 195-200.

Kerns R, Kassirer M, Otis J. Pain in multiple sclerosis: a biopsychosocial perspective. J Rehabil Res Dev 2002; 39:225–32.

Khan F, Pallant J. Chronic Pain in Multiple Sclerosis: Prevalence, Characteristics, and Impact on Quality of Life in an Australian Community Cohort. The Journal of Pain 2007; 8 (8): 614-623.

Kielhofner G. Conceptual Foundations of Occupational Therapy. Philadelphia, PA: F.A. Davis Company; 2004.

Kieseier BC, Hartung HP. Current disease: modifying therapies in multiple sclerosis. Semin eurol 2003 June; 23(2):133:46.

Kuspinar A, Andersen R, Mayo NE. Predicting Exercise Capacity through SubMaximal Fitness Testing in Persons with Multiple Sclerosis. Arch Phys Med Rehabil 2010; 91: 1410-7.

La Mantia L, D'Amico D, Rigamonti, A. Interferon treatment may trigger primary headaches in multiple sclerosis patients. Mult Scler 2006; 12: 476-480.

Lee H, Park HJ, Park J, et al. Acupuncture application for neurological disorders. Neurol Res 2007; 29 Suppl 1: S49–54.

Leussink VI, Husseini L, Warnke C, Broussalis E, Hartung HP, Kieseier BC. Symptomatic therapy in multiple sclerosis: the role of cannabinoids in treating spasticity. Ther Adv Neurol Disord. 2012 Sep; 5(5):255-66.

Li Y, Munger KL, Batool-Anwar S, De Vito K, Ascherio A, Gao X. Association of multiple sclerosis with restless legs syndrome and other sleep disorders in women. Neurology 2012; 78(19):1500-6.

Manconia M, Fabbrinib M, Bonannib E, Filippic M, Roccac M, Murrib L and Ferini-Strambia L. High prevalence of restless legs syndrome in multiple sclerosis. European Journal of Neurology 2007, 14: 534–539.

Massimo Filippi, Rohit Bakshi, Marco Rovaris, Giancarlo Comi. MRI and Multiple Sclerosis: What Happened in the Last 10 Years? Journal of Neuroimagaing 2007; 17:1S:2S.

Mayo N. Setting the agenda for multiple sclerosis rehabilitation research. Mult Scler 2008; 14(9):1154:6.

Melzack R, Wall PD. Pain mechanisms: a new theory. Science 1965; 150 (699): 971–9.

Merskey H, Albe-Fessard DG, Bonica JJ et al. Pain terms: a list with definitions and notes on usage. Recommended by the IASP Subcommittee on Taxonomy. Pain 1979; 6(3):249–52.

Merskey H and Bogduk N, Eds. International Association for the Study of Pain (IASP), Part III: Pain Terms, A Current List with Definitions and Notes on Usage, in Classification of Chronic Pain: IASP Press: Seattle; 1994: 209-14.

Merskey H. The taxonomy of pain. The Medical clinics of North America 2007 91(1): 13–20.

Miltenburger C, Kobelt G. Quality of life and cost of multiple sclerosis. Clin Neurol Neurosurg 2002; 104:272-5.

Mohr DC. Stress and multiple sclerosis. J Neurol. 2007; 254 Suppl 2:II65-II68.

Morris LA, Miller DW. The regulation of patient-reported outcome claims: need for a flexible standard. Value Health 2002; 5:372-81.

Nayak S, Matheis RJ, Schoenberger NE, et al. use of unconventional therapies by individuals with multiple sclerosis. Clin Rehabil 2003; 17(2): 181–91.

Nortvedt MW, Riise T, Myhr KM et al. Quality of life in multiple sclerosis: measuring the disease effects more broadly. Neurology 1999; 53:1098-103.

Noseworthy John H., Claudia Lucchinetti, Moses Rodriguez, Brian G.Weinshenker. Multiple Sclerosis. The New England Journal of Medicine 2008 September 28; 343(13):938-52.

O'Brien JA, Ward AJ, Patrick AR, Caro J. Cost of managing an episode of relapse in multiple sclerosis in the United States. BMC Health Serv Res. 2003 Sep 2; 3(1):17.

O'Connor A, Schwid S, Herrmann D, Markman D, Dworkin R. Pain associated with multiple sclerosis: Systematic review and proposed classification. Pain 137 (2008) 96–111

O'Connor P. Key issues in the diagnosis and treatment of multiple sclerosis: An overview. Neurology 2009; 59: S1-33.

Oken BS, Kishiyama S, Zajdel D, et al. randomized controlled trial of yoga and exercise in multiple sclerosis. Neurology 2004; 62(11): 2058–64.

Orton SM, Herrera BM, Yee IM et al. Sex ratio of multiple sclerosis in Canada: a longitudinal study. Lancet Neurol 2006; 5(11):932-936.

Ostir GV, Granger CV, Black DA, et al. Preliminary results for the PAR-PRO: A measure of home and community participation. Arch Phys Medicine Rehabil 2006; 87: 1043-1053).

Patrick DL, Bergner M. Measurement of health status in the 1990s. Annu Rev Public Health 1990; 11:165-83.

Patrick DL, Erickson P. Health status and health policy. New York: Oxford Univ Pr; 1993.

Perenboom RJM, Chorus AMJ, Measuring participation according to the International Classification of Functioning, Disability and Health (ICF) Disabil Rehabil. 2003; 25 (11–12):577–585.

Plummer MT, Clayton DG: Measurement error in dietary assessment, an investigation using covariance structure models. Stat Med 1993, 12:925-948.

Pollmann W, erasmus L, Feneberg W et al., Interferon beta but not glatiramer acetate therapy aggravates headaches in MS Neurol 2002. 59(4): 636–9.

Poser CM, Brinar VV. Diagnostic criteria for multiple sclerosis. Clin. Neurol. Neurosurg; 2001; 103:1-11.

Rabinstein A, Shulman LM. Acupuncture in clinical neurology. Neurologist 2003; 9(3): 137–48.

Ramagopalan S. Genes and Environmental Factors in Multiple Sclerosis 2010a, 16: 259-259.

Ramagopalan S, Byrnes JK, Orton S-M. Sex ratio of multiple sclerosis and clinical phenotype. European Journal of Neurology, 2010b (17), 10.1111/j.1468-1331.2009.02850.x

Rao SM, Leo GJ, Bernardin L, Unverzagt F. Cognitive dysfunction in multiple sclerosis. Frequency, patterns, and prediction. Neurology 1991 May; 41(5):685-91.

Renwick R & Friefeld S. Quality of life and rehabili-tation. In R. Renwick, I. Brown, & M. Nagler (Eds.), Quality of life in health promotion and rehabilitation 1996, pp: 26–37. Thousand Oaks: SAGE Publications.

Rio J, Nos C, Bonaventura I, et al. Corticosteroids, ibuprofen, and acetaminophen for IFNbeta-1a flu symptoms in MS: a randomized trial. Neurology 2004; 63(3): 525–8.

Rosati G. The prevalence of MS in the world: an update. Neurol.Sci 2001; 22:117-39.

Rudick RA, Miller D, Clough JD et al. Quality of life in multiple sclerosis. Comparison with inflammatory bowel disease and rheumatoid arthritis. Arch.Neurol 1992; 49:1237-42.

Salter K, Jutai JW, Teasell R, Foley NC, Bitensky J, Bayley M. Issues for selection of outcome measures in stroke rehabi-litation: ICF Participation. Disabil Rehabil 2005; 27(9):507- 528.

Seekins T, Shunkamolah W, Bertsche M, Cowart C, Summers JA, Reichard A, White G.A systematic scoping review of measures of participation in disability and rehabilitationresear ch: a preliminary report of findings. Disabil Health J 2012; 5(4):224-32.

Siev-Ner I, Gamus D, Lerner-Geva L, et al. Reflexology treatment relieves symptoms of multiple sclerosis: a randomized controlled study. Mult Scler 2003; 9 (4): 356–61.

Sousa KH, Kwok OM. Putting Wilson and Cleary to the test: analysis of a HRQOL conceptual model using structural equation modeling. Qual Life Res 2006; 15(4):725-37.

Sprangers MA, de Regt EB, Andries F et al. Which chronic conditions are associated with better or poorer quality of life? J.Clin.Epidemiol. 2000; 53:895-907.

Stanton BR, Barnes F, Silber E. Sleep and fatigue in multiple sclerosis. Mult Scler 2006; 12 (4):4 81–6.

Svendsen KB, Jensen TS, Hansen HJ, Bach FW. Sensory function and quality of life in patients with multiple sclerosis and pain. Pain 2005; 114:473–8.

Svendsen KB, Jensen TS, Overvad K, Hansen HJ, KochHenriksen N, Bach FW (2003). Pain in patients with multiple sclerosis. Arch Neurol 60:1089–1094.

Tachibana N, Howard RS, Hirsch NP, Miller DH, Moseley IF, Fish D. Sleep problems in multiple sclerosis. Eur Neurol 1994; 34 (6):320–3.

Tarsy D & Sheon R.P. Restless legs syndrome. Up To Date. Accessed: March 2009. Available at http://www.uptodate.com/contents/restless-legs-syndrome.

Teng SY, Bartlett S, Koski L, Chamelian L, Duquette P, Grand'Maison F, Lapierre Y, Mayo NE. Self-perceived and tested cognition in multiple sclerosis: Differences across gender. Journal of Multiple Sclerosis Clinical and Laboratory research, 2009; 15 (2).

Tyszka AC, Farber RS. Exploring the relation of health-promoting behaviors to role participation and health-related quality of life in women with multiple sclerosis: a pilot study. Am J Occup Ther. 2010 Jul-Aug; 64 (4):650-9.

Whetten-Goldstein K, Sloan F, Goldstein L, Kulas E. A comprehensive assessment of the cost of multiple sclerosis in the United States. Mult Scler 1998; 4:419-25.

White LJ, Dressendorfer RH. Exercise and multiple sclerosis. Sports Med 2004; 34(15):1077:100.

Willer B, Rosenthal M, Kreutzer JS, Gordon WA, Rempel P. Assessment of community integration following rehabilitation for traumatic brain injury. J Head Trauma Rehabil 1993; 8(2):75- 87.

Willke RJ, Burke LB, Erickson P. Measuring treatment impact: a review of patient-reported outcomes and other efficacy endpoints in approved product labels. Control Clin.Trials 2004; 25:535-52.

Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. JAMA 1995; 273(1):59-65.

World Health Organization. ICIDH-2: international classification of functioning and disability. Beta-2 draft. Geneva: WHO; 1999.

World Health Organization. International classification of functioning, disability and health. Geneva: WHO, 2001.

World Health Organization. International classification of impairments, disabilities, and handicaps: a manual of classification relating to the consequences of disease. Geneva: WHO; 1980.

Yorkston K, Johnson K, Klasner E. Taking Part in Life: Enhancing Participation in Multiple Sclerosis. Phys Med Rehabil Clin N Am 2005 (16): 583–594.

Yorkston K, Kuehn C. M, Johnson K, EHDE D. M, Jensen M. Measuring participation in people living with multiple sclerosis: A comparison of self-reported frequency, importance and self-efficacy. Disability and Rehabilitation, 2008; 30(2): 88 – 97.

Table 1.1 Proposed classification of MS pain

Pain classification	Examples
Continuous CNP	Dysaesthetic extremity pain
Intermittent CNP	Lhermitte's sign Trigeminal neuralgia
Musculoskeletal pain	Painful tonic spasms Low back pain Muscle spasms
Mixed neuropathic and non-neuropathic pain	Headache

Taken from: O'Connor A, Schwid S, Herrmann D, Markman D, Dworkin R. Pain associated with multiple sclerosis: Systematic review and proposed classification. *Pain* 137 (2008) 96–111.

Table 1.2 WCM Terminologies

Term	Definition	Example
Biological & Physiological Variables	Changes that happen at the level of cells, organs and organs systems	Laboratory values, e.g. serum haemoglobin
Symptom Status	Patients' perspectives of their health conditions	Pain Shortness of breath
Functional Status	Capacity of the individual to perform functional, social or psychological tasks	Bathing Shopping
General Health Perception	Persons' global perceptions of their health, and it integrates the components of biological factors, symptoms and functional status	Rating of health status
Overall Quality of Life	Integration all of the pervious concepts; subjective well-being and satisfaction with life as a whole	Rating of satisfaction with quality of life

Taken from: Alaa Mohammad Arafah. What Constructs Are Represented in Multiple Sclerosis Specific Health-Related Quality of Life Measures? Master of Science thesis in Rehabilitation Science, McGill University 2009, pp: 17

Table 1.3 Comparison between SEM and multiple regressions

Multiple regression analysis	***Structural equation modeling (SEM)***
Deals only with one dependent variable.	SEM has the ability to test models with several dependent variables.
Deals only with observed variables.	SEM allows the estimation of latent variables rather than only observed or measured variables.
Deals only with direct effects.	SEM has the capacity to assess both direct and indirect effects of one variable on another.
Simultaneous assessment of complex relationships between multidimensional constructs is not possible.	SEM permits the simultaneous assessment of multiple dependents and independent variables.
It only proposes a fixed model for relationships to be assessed.	SEM has the desirability of testing alternative models using indices of overall fit of hypothesized models to the data.
Cannot detect measurement error and, therefore, may yield biased results.	Using confirmatory factor analysis, SEM estimates the relationship between each latent variable and its corresponding indicators thus eliminates or reduces measurement error.
Less powerful	SEM is more powerful alternative to multiple regression because it takes into account the modeling of interactions, nonlinearities, measurement error, etc.
Cannot detect response shift	SEM has the ability to detect response shift at the group level.

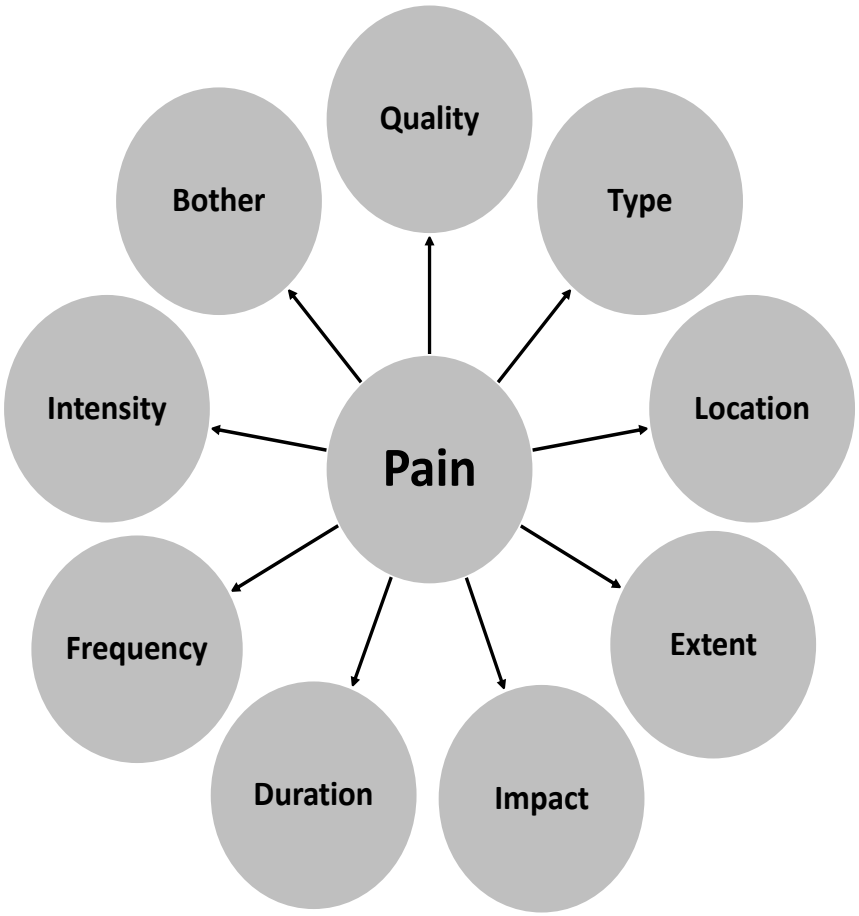

Figure 1.1 Conceptual model of pain

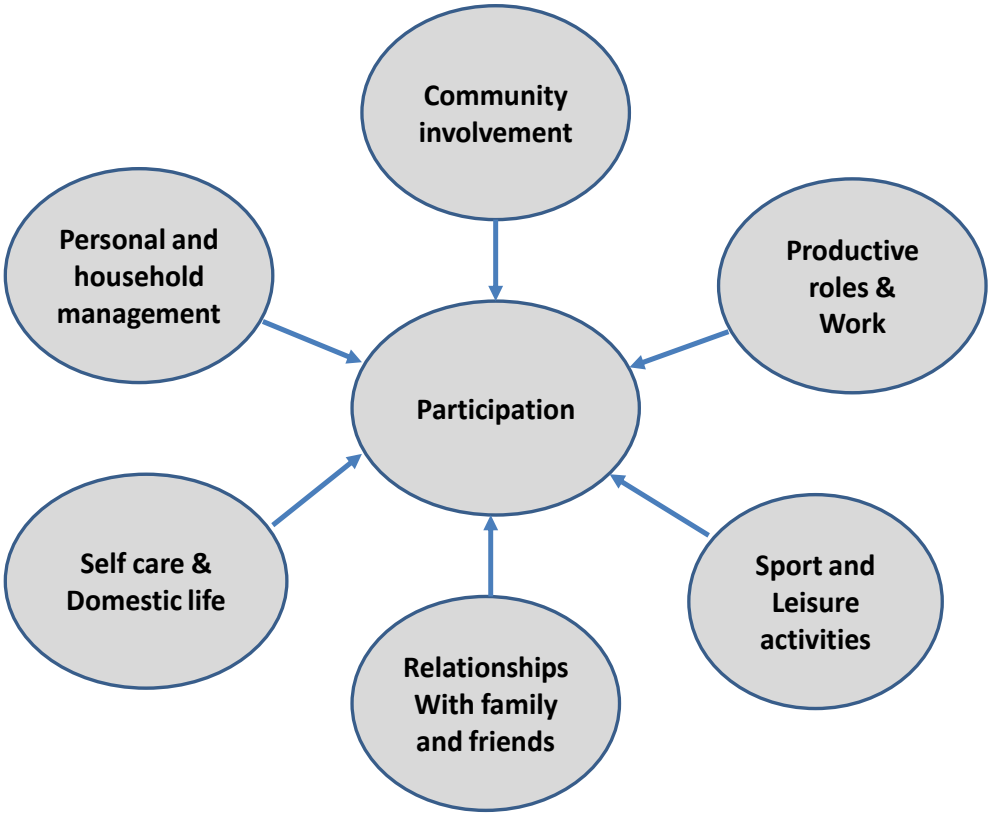

Figure 1.2 Conceptual model of participation

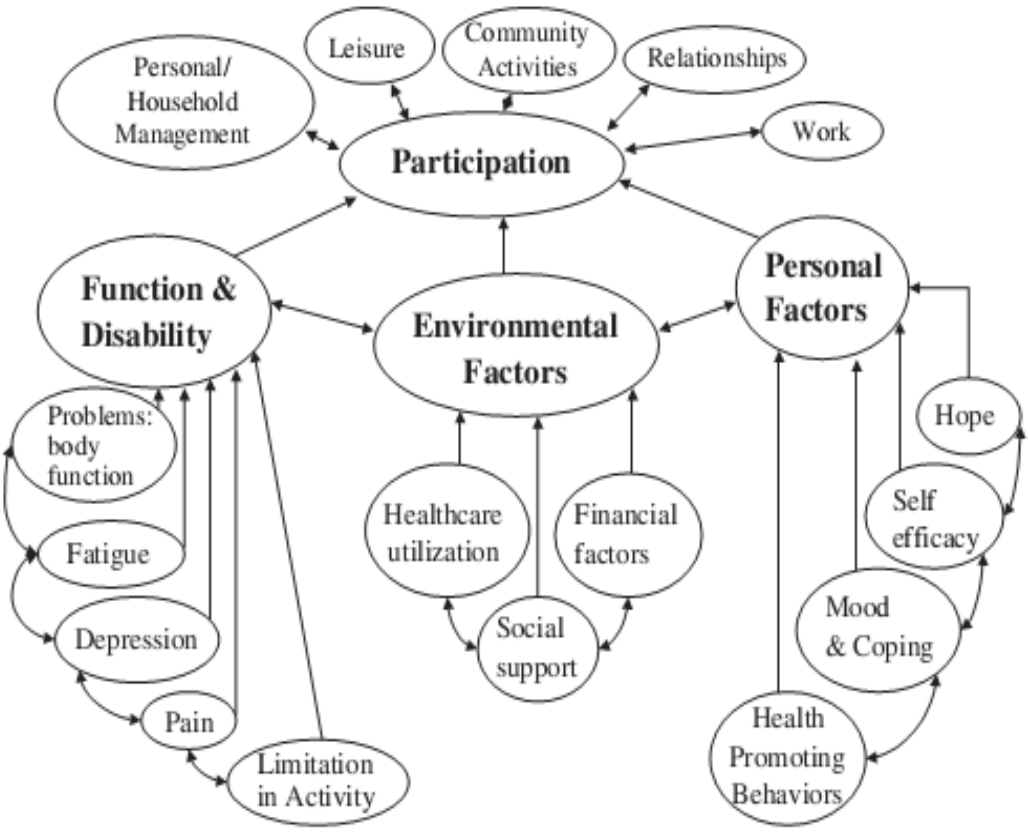

Figure 1.3 A model hypothesizing factors related to participation

Taken from: Yorkston K, Johnson K, Klasner E. Taking Part in Life: Enhancing Participation in Multiple Sclerosis. Phys Med Rehabil Clin N Am 2005 (16): 583–594.

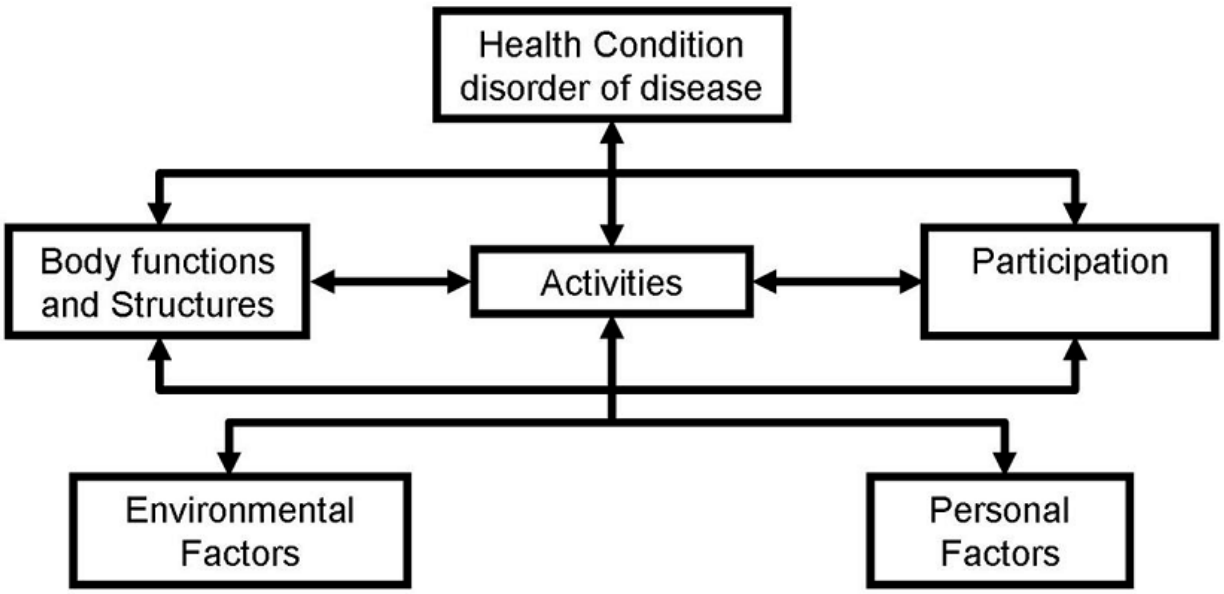

Figure 1.4 The International Classification of Functioning, Disability and Health conceptual Framework (ICF)

Taken from: World Health Organization (WHO). International Classification of Functioning, Disability and Health. Geneva, Switzerland: WHO; 2001.

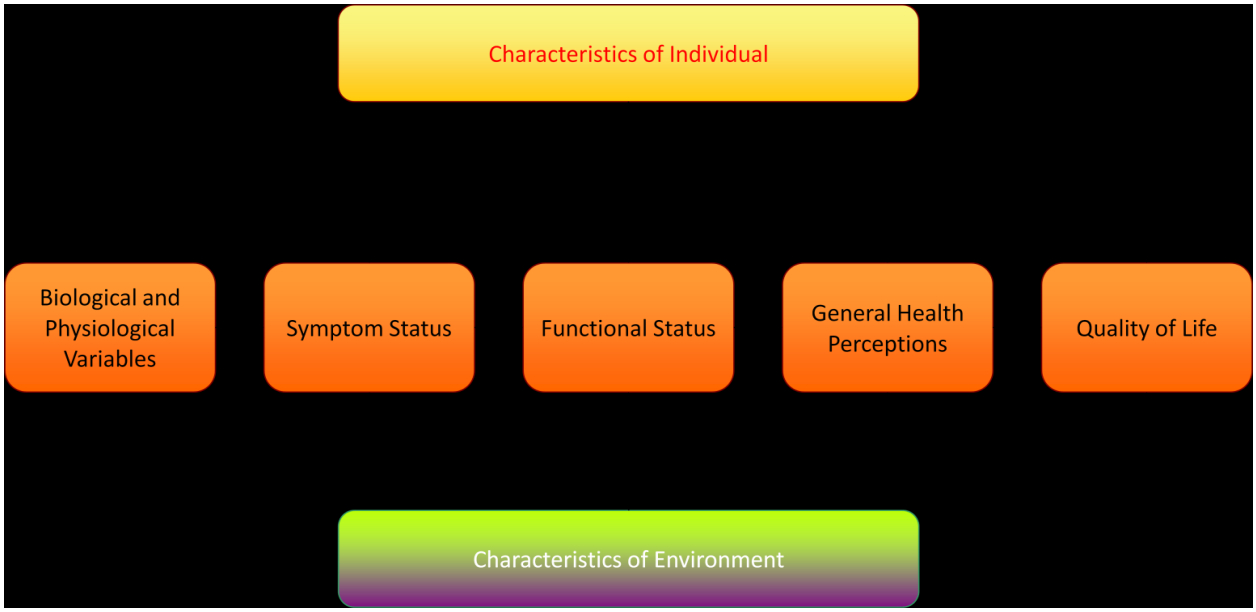

Figure 1.5 The Wilson-Cleary health-related quality of life conceptual framework

Taken from: Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. JAMA 1995; 273(1):59-65.

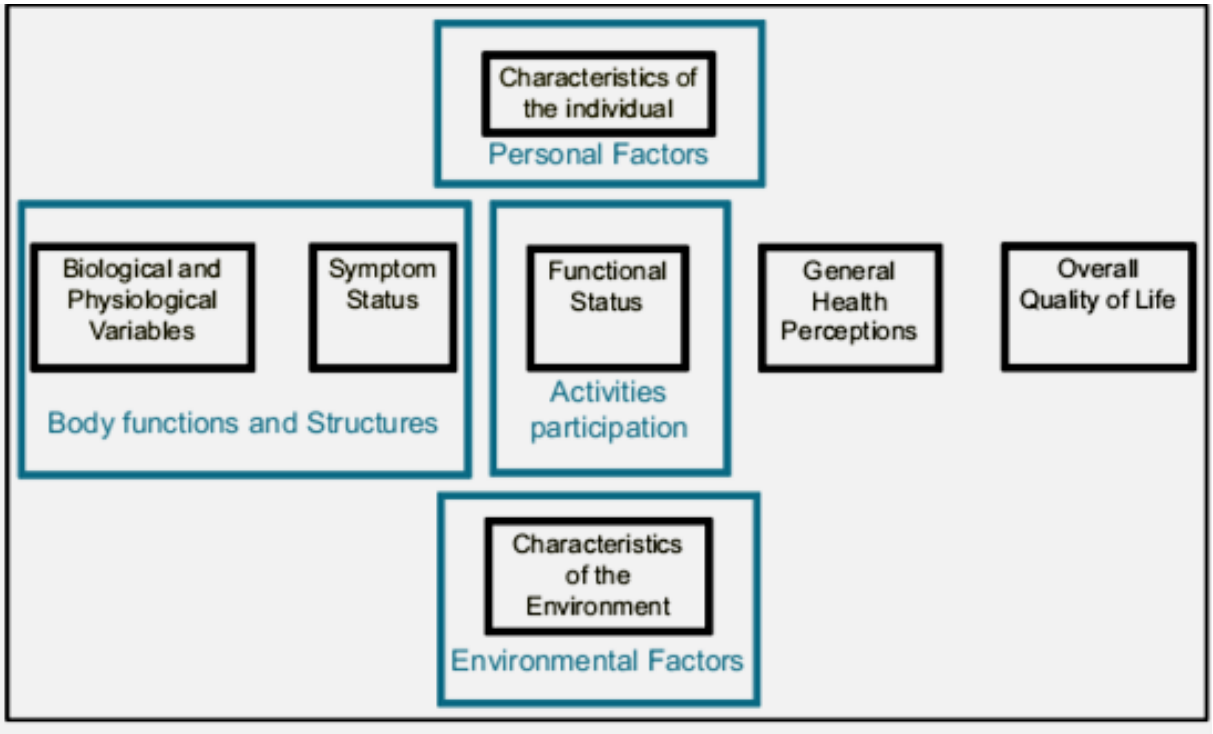

Figure 1.6 WCM and ICF

Taken from: Ayse Kuspinar. Predictors and health impact of exercise capacity in multiple sclerosis. Master of Science thesis in Rehabilitation Science, McGill University, 2009, pp: 68

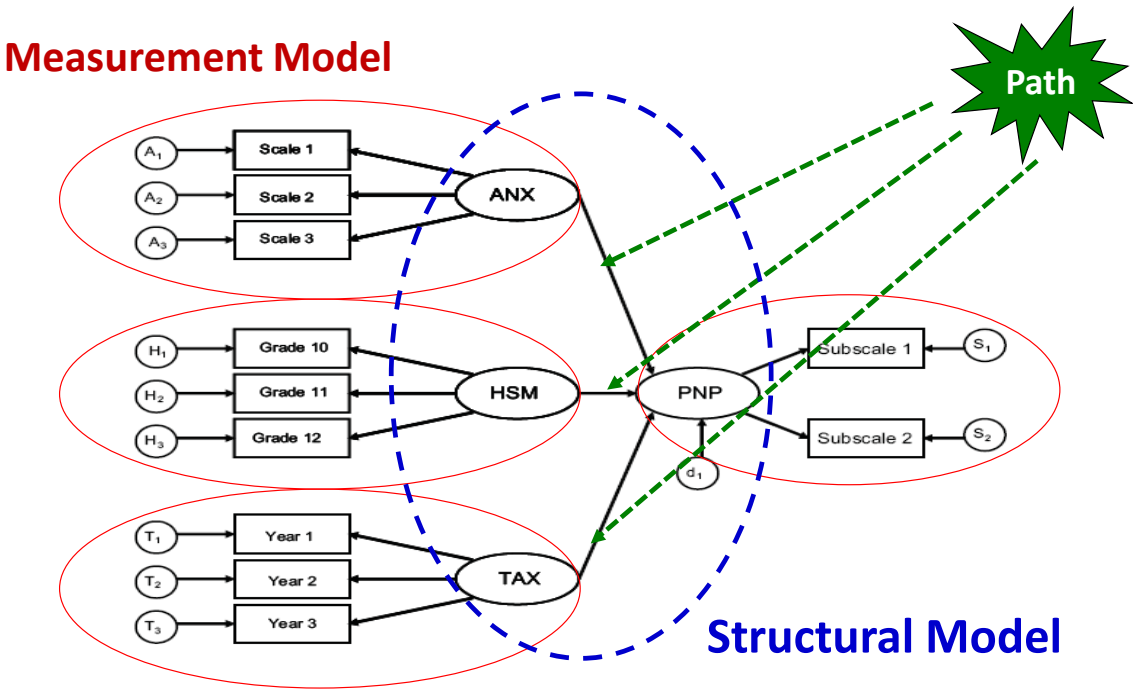

Figure 1.7 A schematic model of SEM component

CHAPTER 2: Rationale and Objectives

2.1 Rationale of the study

Pain is common among people with Multiple Sclerosis (MS); appearing in almost 50% of people with MS at some point of their disease course. Moreover, the cost of MS pain has been estimated to be high in Canada. Pain in persons with MS has an impact on work, social interactions, daily activities, and other important aspects of a person's functioning and so health-related quality of life (HRQL). This encourages clinicians and researchers to pay more attention to MS pain.

The focus in MS is often directed to therapies altering the disease course, and secondary health problems such as pain often take a back seat to primary neurological deficits. Therefore, despite the importance of pain to MS, there are still substantial gaps and unanswered questions in the literature on pain in MS. In addition, methodological and analytical problems limit obtaining clear conclusions about the MS related pain. Therefore, as research in this area moves forward, it will be important to run a large-scale and well-described epidemiologic investigation to permit the investigation of pain using valid and reliable measures that help to better characterize the experience of pain among people with MS.

Previous studies have generally looked at pain and participation as unidimensional health outcomes, and have focused on a single dimension of them in their analyses. However, it is important to understand that both pain and participation are multidimensional concepts and hence the content of measures of them should cover all of the dimensions of those constructs. A comprehensive and detailed assessment of different aspects of pain and participation would help in understanding them better.

Another limitation of previous studies is the consideration of a relatively limited range of possible intermediate variables that might account for the relationship between pain and other health-related outcomes. To the authors' knowledge, no studies have examined the relative direct and indirect contributions of pain to the role participation with regards to other most important MS symptoms and functional status using a comprehensive conceptual framework and advanced statistical methods. Findings of this part of study will lead to provide an improved framework of

a path model for measuring pain and participation and will serve as a starting point for more focused research on pain and participation in people with MS.

Considering that increasing participation in life situations and social activity is important in rehabilitation of individuals with MS and affect their HRQL, examination of the strength of the contributors to participation is critically important as a target for investigation in MS. Pain is considered to be as contributor to activity limitations and restrictions in societal and family roles. So, determination of the contribution of pain to MS-related disability and restriction in social participation is essential for selecting the appropriate interventions.

Considering the "New MS", understanding the characteristics of MS pain and other MS related consequences, results in a better understanding of the New MS thereby designing more appropriate interventions that might be effective in reducing symptoms and increasing the physical and psychological functioning in individuals with MS.

2.2 Objectives

The global aim of the current study is to contribute to understanding of the pain experience of people with MS with the context of function, disability, and health. To operationalize this main objective, a series of specific objectives/questions were developed towards the manuscripts that form this thesis.

1) Does pain impact on work, a key aspect of participation in this group?
   Manuscript 1: *Does Pain in Individuals with Multiple Sclerosis Affect Employment? A Systematic Review and Meta-analysis*

2) What characterizes pain in an epidemiologically sampled group of community dwelling individuals with MS?
   Manuscript 2: *Looking at pain in multiple sclerosis: prevalence, severity, frequency, duration, quality, location, distribution, type, treatment, impact and predictors*

3) The extent to which there is stability in pain type and pain severity over time.
   Manuscript 3: *Long-term stability of pain type and severity among people with multiple sclerosis*

4) To what extents do different MS related symptoms, including pain, cluster?
   Manuscript 4: *Contribution of symptom clusters to MS consequences*

5) To estimate the extent to which pain and other MS- related symptoms, physical and mental functional factors, and individual characteristics predict participation in people with MS.
   Manuscript 5: *Pain acts through fatigue to affect participation in individuals with MS*

CHAPTER 3 (MANUSCRIPT 1)

Does Pain in Individuals with Multiple Sclerosis Affect Employment? A Systematic Review and Meta-analysis

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ABSTRACT

Background: People with MS experience some of the highest unemployment rates among all groups of chronic illnesses. Pain has been found to be a common reason for sick leave or early retirement in healthy populations or other groups with chronic illness, however, there is little awareness about the effect of pain on the work status of people with MS. The objective of this review was to estimate among people with MS the extent to which people with pain differ in employment status as compared to people without pain.

Methods: An extensive review of the scientific literature was performed in a systematic way within the framework of the Cochrane Collaboration to identify studies focusing on the effect of pain on employment in individuals with MS. The following databases were searched: PubMed, EMBASE, PsychInfo, Web of Science, MD consult & Elsevier, and Science Direct. The methodological quality of studies was examined using the McMaster Critical Review Form.

Results: Ten articles met the inclusion criteria and were included in the systematic review. Five of the sourced studies, which had clinical, methodological, and statistical homogeneity, were included in the meta-analysis. The between groups (pain + vs. pain -) pooled random odds ratio of being employed was 0.7 (strong), and was significantly different from unity with 95% confidence interval of 0.5 to 0.9 (p-value= 0.001).

Conclusions: The results of the present study indicated that persons with MS who have pain were significantly more likely to report decreased employment rate than those people with MS who were pain-free.

Key terms: pain; multiple sclerosis; employment; productivity; review; work

3.1 INTRODUCTION

Multiple sclerosis (MS) is recognized as the most common neurologic cause of disability among young adults in North America (Busche 2003, Compston 2005, Noseworthy 2000). MS occurs in individuals during peak years of their productive life, significantly impacting their ability to remain in the work force (Busche 2003). People with MS often have difficulty continuing to work due to the disability, different symptoms, mobility difficulties, and other aspects of the disease (Busche 2003, Noseworthy 2000). Unemployment is defined by the International Labor Organization as being without a paying job for four weeks or more (International Labour Organization 2007). Unemployment is common in people with MS (Busche 2003). The overall rate of unemployment in the MS population varies from 22% to 80% (O'Connor 2005, Solaro 2004, Stenager 1995). This variation may be due to differences in patients, disease and work-related characteristics as well as definition of employment (Fraser 2002). It has been found that at the time of diagnosis 60% of persons with MS are in full-time employment; however, after 5 years, 70% to 80% of patients become unemployed (Kornblith 1985, LaRocca 1995, Minden 1993, Rumrill 1996).

The total cost of MS for Canadians was measured at $502.3 million in 1994, with indirect costs estimated at $313.7 million (Asche 1997). Indirect costs refer to lost productivity, early retirement, sick leave, reduced hours of work, and changing the type of work, whereas direct costs of a disease relate to diagnosis and treatment (Gold 1996). In the most recent study, the mean total cost per MS person per year was estimated at $37,672, of which 32% was attributable to patients' sick leave and retirement due to MS (Karampampa 2012). These results confirm that indirect costs are identified as major contributors to total costs in MS population.

Previous research has demonstrated that unemployed persons generally report more depression, anxiety, and social isolation than employed individuals (Banks 1995). Research has also shown that being employed helps people with MS focus on their work activity rather than on their disease and its related symptoms and disability (Johnson 2004). Moreover, while work contributes to adult identity, financial security, life satisfaction, and quality of life (QOL), the loss of ability to work is associated with decreased QOL due to the fear of decreased income and increased distress (Aronson 1997, Dyck 2000). Thus, considering the importance of being

employed, a clear understanding of the employment barriers faced by individuals with MS will aid in the identification of appropriate interventions for removing barriers to work.

There are many factors associated with unemployment in MS population. Socio-demographic variables frequently associated with unemployment include older age and lower level of education (Busche 2003, Dyck 2000, Grima 2000). In addition, the results of previous studies have revealed conflicting results regarding gender difference in the percentage of patients who are still working (Beatty 1995, LaRocca 1982, Rotstein 2006). Disease-related factors consistently associated with unemployment include longer disease duration and having relapsing-remitting MS (Jacobs 1999, Richards 2002, Verdier-Taillefer 1995). The impact of MS on employment also varies significantly depending on the nature of the occupation itself. For example, physically demanding jobs are more affected by symptoms such as fatigue, while jobs that require thinking are more affected by cognitive impairments (Noyes 2005). Complex interactions of environmental and social factors contribute to the employment status as well. For instance, a work environment with flexible work schedules may positively influence a person's work status (Beatty 1995, Dyck 2000).

In many studies, however, people with MS attribute their unemployment primarily to the symptoms they are experiencing. For example, half of the unemployed individuals with MS report physical disability as the reason for leaving their jobs (Scheinberg 1980) that individuals with higher EDSS scores are more likely to not be employed (LaRocca 1982, Verdier-Taillefer 1995). Fatigue (Hammond 1996, Smith 2005), cognitive difficulties (Beatty 1995, Edgley 1991) and depression (LaRocca 1985, Johnson 2004) have also been found influencing unemployment, early retirement, and cutting back of work time.

Pain is a prevalent symptom among individuals with MS (Beiske 2004, O'Connor 2005, Svendsen 2005). Persons with MS and pain report more depressive symptoms (Ehde 2005), greater diminished physical function (Ehde 2003), poorer mental and general health (Archibald 1994), and health-related QOL (Ehde 2006) than people with MS who do not have pain. In addition, pain has been found to be a common reason for sick leave or early retirement in healthy populations or in other groups with chronic illness; however, there is little awareness of the role

of pain in the work status of people with MS. The focus in MS is mostly on therapies to alter the disease course, and secondary health problems take a back seat to primary neurological deficits. Given the relative role of pain on decreased QOL and increased potential for psychological distress, and social isolation of MS population, it is important to understand the association between pain and work status. Therefore, the aim of this review was to estimate among people with MS the extent to which people with pain differ in employment status as compared to people without pain.

3.2 METHODS

3.2.1 Search strategy

First, the Cochrane Library and the Database of Abstracts of Reviews of Effectiveness were searched to determine whether a systematic review on this topic had been completed and none was found. Subsequently, an extensive review of the scientific literature was performed by the two investigators (SS, MA). The search period covered years from inception to March 2012 in the following databases: PubMed/ Medline, EMBASE, PsychInfo, Web of Science, MD consult & Elsevier, and Science Direct. These electronic databases were searched using the following key terms: multiple sclerosis, transverse mellitus, pain, discomfort, job, work, and employment. Searches were undertaken using MeSH headings and text words as suitable; no language restriction was applied. To identify other pertinent articles, the reference lists contained in all retrieved articles along with pain and MS-relevant conference proceedings were searched.

3.2.2 Study selection

An initial screening of titles and abstracts was completed followed by a full-text screening of all articles for inclusion or exclusion based on the following criteria:

1. *Type of publication:* Only full publications in peer-reviewed journals were considered. Unpublished data and abstracts were not sought.
2. *Study design:* All types of studies were included (randomized controlled trails, cross-sectional studies, pre- post studies, case- control studies, cohort, and case studies).
3. *Study population*: Studies were included if the participants were older than 18 years and were diagnosed with possible, probable, or definite MS. If the study population was a

mixture of MS and other underlying diseases, the MS population had to represent the majority of the total study population, or results for MS had to be reported separately.

4. *Pain (exposure):* Study participants had to experience any type of pain as an unpleasant sensory and emotional experience arising from their MS.
5. *Employment* (outcome)*:* The study had to include information on employment rate and status among people with MS who experienced pain. People were considered as employed if they were regularly scheduled to work several hours per week and were paid at the time of evaluation. People not participating in paid work were defined as not employed.

3.2.3 Data extraction

Two reviewers (SS and MA) read all potentially relevant abstracts to identify publications that appeared to be eligible for this review. From the chosen abstracts, they read the full texts, and selected studies for the review according to the inclusion and exclusion criteria. All discrepancies between the two reviewers were discussed and if a consensus wasn't reached, a co-author (NM) was approached to decide. To ease the comparison of findings across studies, the following information was extracted from each study: researcher (s) name (s) and date of publication, study design and quality assessment of the study, participants' characteristics (e.g. sample size, age range, and gender), measures (pain and work-related variables and tools to measure variables of interest), and results, such as mean, standard deviations (SD), and confidence intervals (CI) if data were provided.

3.2.4 Quality assessment of studies

The quality of all retrieved articles was evaluated using the Critical Review Form for Quantitative Studies developed by the McMaster University Occupational Therapy Evidence-Based Practice Research Group (Law 2008). Two reviewers (SS and MA) independently assessed methodological quality of all relevant studies. Disagreements were resolved by consensus. Crude agreement and Cohen's Kappa coefficient was used to assess the inter-rater agreement between the two reviewers at the major steps of the review from study selection to quality assessment (Landis 1977).

In addition, as research has shown that quality evaluation with numeric scores are arbitrary and unreliable (Juni 2001), and such scores when used to differentiate between high- and low-quality studies can be inaccurate, methodological quality of each criterion was reported as met, partially met, or not met. Moreover, considering that employment rate was our main outcome of interest, and that in all included studies employment was not the main outcome but rather a socio-demographic variable, wherever data was gathered without a reliable and valid measurement tool, we modified the criteria for the quality assessment tool. So if the data on employment rate in both pain and pain-free groups were provided, the reviewers considered it as met.

3.2.5 Quantitative synthesis of studies (Meta analysis)

In an effort to obtain a quantitative statistical summary showing how much pain affects employment status, we combined the results of comparable study findings using Meta analysis. Included studies may represent the clinical and methodological diversity, for example inconsistency in clinical settings, exposures, and research questions. This inconsistency is called heterogeneity, which is defined as the variability between studies and gives an indication of how comparable studies in the Meta analysis are (Ried 2006). Statistical heterogeneity of this study was tested by Q test (χ^2) and reported with the I^2 statistic in which higher values indicate higher heterogeneity. A significant Q-test indicates only the presence of heterogeneity among the data included, whereas the I^2 quantifies the magnitude of the heterogeneity (Higgins 2003). I^2 ranges between 0 and 100% and the magnitude of the heterogeneity is defined as low ($I^2 \leq 33\%$), moderate ($34\% \leq I^2 < 67\%$), or high ($I^2 \geq 67\%$) (Higgins 2003). To adjust for heterogeneity when combining studies, researchers chose a random effect model to determine if results were robust – as it is more conservative, especially for small samples and it assumes that these studies are a sample from all possible similar studies (Fleiss 1993, Ried 2006). Using a random effect also helps to better generalize the results to the general population (Fleiss 1993). Data of comparable studies were then compared using a forest plot, a graphical display of Meta-analysis results, of the relative odd ratios (OR) with 95% CI between individuals with MS, with and without pain (Lalkhen 2008).

Publication bias was checked using both funnel plots and quantitative methods (Classic fail-safe N tests, Begg and Mazumdar Rank Correlation test, Egger's test of the Intercept, and Trim and

Fill test) (Begg 1994). As each one of these methods has its limitations, several methods were used together (Egger 1997, Sterne 2000)**.** The Classic fail-safe N tests calculate the number of 'null' studies would need to be included in order for the combined p-value to exceed significance level (0.05). The Rank-Correlation test (Kendall's tau-b), as suggested by Begg and Mazumdar (1994), tests the significance of the inverse correlation between study size and effect size (Begg 1994)**.** A significant correlation would suggest that bias exists. Similarly, a significant value of the intercept in the Egger's Test suggests that bias exists. Finally, the Trim and Fill method was used, which basically determines where the missing studies (if any) are likely to fall, adds them to the analysis, and then re-computes the combined effect (Egger 1997, Sterne 2000)**.**

Evidence classification for this study came from the Canadian Medical Association Journal (CMAJ) as it covers all types of study designs (Law 2008)**.** This rating system consists of 4 levels of evidence based on the design and quality of the included studies. Comprehensive Meta Analysis Version 2.0 was used for statistical analysis.

3.3 RESULTS

3.3.1 Number of papers sourced

Tabular display of study selection process is presented in Figure 1. A total of 175 abstracts were screened. They were identified through PubMed/ Medline (31), EMBASE (12), PsychInfo (8), Web of Science (20), MD consult & Elsevier Inc (54), and Science Direct (50). No new citations were retrieved from the other databases, and proceedings of the related congresses. After removal of 112 articles that were sourced from more than one database, 63 papers were screened for titles and abstracts. Of these, 29 abstracts were excluded. The primary reasons for exclusion were irrelevant, unpublished data; mixed study population where data for MS were not presented separately; or MS was not the main population of interest. The remaining articles were then assessed for eligibility to see if they met inclusion criteria. 25 studies did not meet inclusion upon full review of study. The reference lists of the retrieved studies later revealed one more additional article. Finally, 10 articles met the inclusion criteria and were included in the systematic review (Figure 1). Five of the sourced studies, which had clinical, methodological, and statistical homogeneity, were included in the Meta analysis (Figure 2). A short description of each included study is presented in Table 1.

3.3.2 Descriptive results

Pain prevalence varied from 44% to 82%. The variability in the percentage of pain in MS may be due to methodological challenges and differences across the studies related to the patient sources, method of sampling, research methods for collecting the data, definition of pain and the focus on different pain constructs (e.g. frequency, intensity, and duration). Disease subtypes and severity of symptoms also varied across studies. Pain prevalence, severity, and location were the most commonly used pain-related outcomes. The Numerical Rating Scale (NRS), and bodily pain subscale of SF-36 (BPS) were the most common measures used to assess pain across studies.

Rate of employment was from 28% to 57%. Besides the employment rate and status, other work-related outcomes included number of days off work, ability to work outside and inside home, type of occupation and hours of paid employment per week. The main cause of employment loss was unknown from these studies.

Pain interfered mostly with recreational activities, work, and ability to walk. 47% to 66% of MS subjects with pain reported that pain interfered with their work. The effects of MS pain on employment results varied. Some of the studies found that persons with pain reported that pain reduced their ability to work, while other studies could not find a significant difference; however, they mostly indicated an increasing proportion of patients not being employed in the presence of pain.

MS disability measured by EDSS, MS sub types, and duration of illness were the most common disease related outcomes across studies. The study populations were recruited variously from community-dwelling, regional referral clinics, neurology treatment centers, newspaper, Internet, neurologists' offices, and NARCOMS (North American Research Committee on Multiple Sclerosis) longitudinal database (Vollmer 1999). A community-dwelling based sample was the most common study population included. Research strategies were varied and included structured survey questionnaires, postal surveys, in-person interviews, telephone interviews, and databases.

3.3.3 Methodological quality

The quality of each paper was assessed by two authors to determine the studies' inherent bias (Table 2). One Longitudinal study using NARCOMS database, two cohort studies and seven cross- sectional studies are included in this review. The main purpose of most studies was to estimate pain prevalence using a cross-sectional study design. Range of sample size was from 38 (Michalski 2011) to 8867 (Julian 2008). Only three papers provided a statistical justification of the sample size used (Julian 2008, Douglas 2008, Piwko 2007). Response rate was relatively high in most of the studies; however, most of the studies suffered from non- response bias, inadequate sampling, losses to follow-up, and lack of drop-outs recording. None of the studies examined whether having flexible work schedules would make it possible for people with MS to continue working. Further, only one of the included studies presented a clear definition of employment and/or unemployment (Glad 2011). Four studies (Ehde 2003, 2006, Glad 2010, 2011) gave a clear definition for pain experience based on the duration of pain. The time frame for pain-related variables varied from one month to six months, which could provide recall bias due to memory distortion.

Inter-rater agreement for all stages of the studies selection and quality assessment generally was moderate to perfect (Crude agreement ranged from 75-100%; kappa's coefficient from 0.7 – 1).

3.3.4 Quantitative synthesis of abstracted data, and evidence

Figure 2 shows the forest plot of the OR of employment rates between individuals with MS, with and without pain across the studies. On this plot, an odd ratio of 1 represents no difference, while the odds ratio falls below 1 indicating that people with pain were less likely to be employed. From the plot it is clear that there is variability in the results of the individual studies. This may be due to methodological challenges related to patient self-reporting, small sample size, heterogeneity and complexity of the disease, different study populations, lack or different definition of pain and employment, and different research strategies. The pooled random odds ratio of employment status between groups was 0.7 (strong), and was significantly different from unity with 95% confidence interval of 0.5 to 0.9, and p-value= 0.001. This means that persons with MS who reported pain were about 70% at risk of unemployment.

The results of both funnel plots and quantitative bias assessment methods revealed no clear sign of publication bias. A symmetrical inverted funnel as shown in Figure 3 implies no publication bias. The dashed vertical line represents the pooled estimate of the pain effect of all included studies. In addition, as determined by Classic fail-safe N tests, the number of 'null' studies that would need to be identified and included in order for the combined 2-tailed p-value to exceed significance threshold (0.05) and turn to non-significant, is 12 studies. Put another way, there would be need to be 2.4 missing studies for every existent study in order for the effect to be nullified. Additionally, using the Rank-Correlation test, the 2-tailed p-values were insignificant (Tau= -5.0, p=0.2). A significant negative correlation would suggest that bias exists. Two-tailed p-value for Egger's Test of the Intercept was insignificant too (Intercept= -4.2, p= 0.2), with similar interpretation. Finally, using the Trim and Fill method, effect size remained unchanged under both models (fixed and random). Overall, all tests concur on the absence of evidence for publication bias.

Considering the heterogeneity test, some evidence for heterogeneity was found but was not statistically significant (Q-value= 7.1, p=0.1; I^2=44). Finally, from CMAJ, a level of evidence of III is given to the study question indicating conflicting findings of several observational studies.

3.4 DISCUSSION

This was the first systematic review and Meta analysis about the impact of pain on employment status in MS population. Although the results of the reviewed studies were conflicting, they mostly suggest that pain can contribute to problems with employment in people with MS. Thus, early identification and treatment of pain can keep people with MS employed for a longer time. However, the findings also imply that keeping a job depends on a number of factors other than specific symptoms or MS progression.

This study has several strengths. First, this review was not restricted to time, specific language, type of pain, occupation or study design. Second, data for the study were collected in a systematic way within the framework of the Cochrane Collaboration. This reduces the likelihood of omitting evidence by searching a large number of databases, and suggests that this comprehensive search strategy represents the current state of the literature. Third, as the studies

might differ widely in quality from low to high, to obtain a more precise result the methodological quality and potential sources of bias of the reviewed articles was examined using a standardized tool (Law 2008). However, it is acknowledged that different quality assessment results may have been found if a different appraisal tool had been used. Fourth, as it is necessary to determine whether included studies are sufficiently similar to reasonably to do a Meta analysis, heterogeneity was tested by standard statistical tests and reported in the results. Finally, treating the studies as a random effect model and presenting a funnel plot for publication bias may aid in reducing the selection bias of this study and may simply increase the generalisability of the results to the general population. However, interpretation and accuracy of the funnel plot is limited by the small number of total studies included in this review.

The relationship between pain and employment is affected by the quality of the studies included. First, most of the included studies were cross sectional. Therefore, the assessment of pain during enrollment in the study failed to establish the timing between pain and inability to work. Conducting longitudinal studies or case–control studies, with cases (individuals with MS who are no longer employed) and controls (individuals with MS who are still employed) compared on pain as one of the predictors of unemployment would be needed to show whether the association between pain and unemployment reveals a causal association. Second, some of the reviewed studies used small samples mostly recruited conveniently or consecutively from community-based settings. This potentially introduces underestimation of pain and other symptoms into the results. Third, some participants were volunteers and they may differ from participants who did not volunteer. Individuals who have severe pain may not be inclined to participate. This factor further introduces selection bias into the results. Finally, due to heterogeneity across the included studies, it was not possible to include all the sourced studies into a Meta analysis. As research in this area moves forward, more studies with sufficiently large samples are needed to permit the investigation of the impact of MS-related pain and other MS consequences upon employment.

A further challenge is that pain can only be measured using self-reporting. These measures vary in term of what is measured (including duration, severity, and location), and are affected by ability to concentrate, memory impairments, anxiety, mood, and emotional status at the time of evaluation as well as the timeframe in which the pain is reported. In addition, the complexity of

pain as a multidimensional construct necessitates a comprehensive multidimensional assessment and emphasizes that pain should be studied within an interactive framework targeting all contributing factors including different aspects of health from biological, functional, individual and social perspectives. Another challenge is that perception of pain on self-report measures can change over time and this may introduce response shift (Ahmed 2007). Response shift can occur with the subject's misunderstanding of questions or redefinition of the construct or change in their conception of pain (Ahmed 2007). In longitudinal designs, the issue of attrition bias and response shift may adequately address this, using a mix of modern statistical – such as structure equation modeling (SEM) – and qualitative approaches.

While there is an increasing interest in the concept of work in MS population, there are also conflicting ideas in the literature as to what exactly "work" is as a concept. Similar to pain, work is also a multidimensional construct, in that worker is physically, emotionally, or cognitively engaged (LaRocca 1995). Indeed, employment is a combination of job satisfaction, nature of occupation, work schedule, desire to work, and work productivity (Roessler 2003). Most studies on work in MS do not take into account all aspects of this construct (Solaro 2004). Results of this study showed that most of the studies assessed employment as a secondary, demographic variable (Forbes 2006, Warnell 1991) and only a few studies had employment as the primary outcome. The exact reason of unemployment was not determined in most studies to see whether persons were unemployed for reasons related to their pain, disability, other MS symptoms, an accident or pregnancy. The studies did not also include any indicative of the physical, emotional, and mental demands of the participants' occupations. Stratification of participants based on their initial level of pain and according to whether they are in acute or chronic pain as well as the duration of pain could also clarify better the role of pain. The effect of pain related treatments such as pain analgesics and muscle relaxants on work status should also be considered as they can further impair cognitive function and enhance fatigue and so limit return to work.

Considering the complexities of employment, further research is needed to determine the interrelationship between and among employment and physical, psychological, personal, and environmental factors under a well defined and interactive framework. The analysis of this complex relationship again needs a complex analysis such as path analysis and SEM.

Furthermore, studies should also examine the factors associated with returning to alternative or reduced duties at work versus those associated with complete unemployment. In addition, research should examine if having flexible work schedules and ability to change the type of job would make it possible for people with MS to continue working. Accurate information is also needed to help health professionals guide people with MS regarding the likelihood of work cessation or initiation based on their specific MS symptoms and clinical profile.

In conclusion, the results of this paper indicate that research examining the relationship between pain and employment status in MS is very limited and inconsistent. Results are sufficiently encouraging to justify more high quality research efforts in this area. Large samples sizes (over 200), use of path analysis, and SEM will optimize the estimation of direct and indirect effects of pain on employment.

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Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest upon submitting this article.

3.5 REFRENCES

Ahmed S, Mayo N. Using structural equation modeling to evaluate response shift. Journal of Clinical Epidemiology 2007**;** 60: 427-428.

Archibald CJ, McGrath PJ, Ritvo PG. Pain prevalence, severity and impact in a clinic sample of multiple sclerosis patients, *Pain* 1994; **58**: 89–93.

Aronson KJ. Quality of life among persons with multiple sclerosis and their caregivers. *Neurology* 1997; 48:74-80.

Asche CV, Ho E, Chan B. Economic consequences of multiple sclerosis for Canadians. *Acta Neurol Scand.* 1997; 95:268-274.

Banks MH. Psychological effects of prolonged unemployment: relevance to models of work re-entry following injury. *J Occup Rehabil* 1995; 5:37–53.

Beatty W, Blanco C, Wilbanks S, Paul R, Hames K. Demographic, clinical and cognitive characteristics of multi-ple sclerosis patients who continue to work. *J Neurol Rehabil* 1995; 9:167–173.

Begg, CB and Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994; 50:1088–1101.

Beiske AG, Pedersen ED, Czujko B, Myhr KM. Pain and sensory complaints in multiple sclerosis. *Eur J Neurol* 2004; 11:479–82.

Busche KD, Fisk JD, Murray TJ, Metz LM. Short term predictors of unemployment in multiple sclerosis patients. Can J Neurol Sci. 2003; 30:137- 42.

Compston A, Confavreux C, Lassmann H. *McAlpine's Multiple Sclerosis*. Philadelphia: Elsevier, 2005.

Douglas C, Wollin JA, Windsor C. Illness and demographic correlates of chronic pain among a community-based sample of people with multiple sclerosis. *Arch Phys Med Rehabil* 2008; 89:1923-32.

Dyck I and Jongbloed L. Women with multiple sclerosis and employment issues: A focus on social and institutional environments. *Can J Occup Therapy* 2000; 67: 337–346.

Edgley K, Sullivan M, Dehoux E. A survey of multiple sclerosis: determinants of employment status. *Can J Rehabil* 1991; 4:127–132.

Egger M , Smith GD , Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; 315: 629–624.

Ehde DM, Gibbons LE, Chwastiak L, Bombardier CH, Sullivan MD, Kraft GH. Chronic pain in a large community sample of persons with multiple sclerosis. *Mult Scler* 2003; 9:605–11.

Ehde DM, Osborne TL, Hanley MA, Jensen MP, Kraft GH. The scope and nature of pain in persons with multiple sclerosis. *Mult Scler* 2006; 12:629–38.

Ehde DM, Osborne TL, Jensen MP. Chronic Pain in Persons with Multiple Sclerosis. *Physical Medicine and Rehabilitation Clinics of North America* 2005; 16: 503-512.

Fleiss JL. The statistical basis of meta-analysis. *Statistical Methods in Medical Research* 1993; 2:121–45.

Forbes Angus, While Alison, Mathes Lucia& Griffiths Peter. Health problems and health-related quality of life in people with multiple sclerosis. *Clinical Rehabilitation* 2006; 20: 67-78.

Fraser RT, Clemmons DC, Bennett F. Multiple sclerosis: psychosocial and vocational interventions. New York: *Demos Medical Publishing* Inc, 2002, p. 45–82.

Glad SB, Aarseth JH, Nyland H, Riise T, Myhr K-M. Benign multiple sclerosis: a need for a consensus. *Acta Neurol Scand* 2010; 122: 44–50.

Glad SB, Nyland H, Aarseth JH. How long can you keep working with benign multiple sclerosis? *J Neurol Neurosurg Psychiatry* 2011; 82: 78-82.

Gold MR. *Cost-effectiveness in health and medicine.* New York: Oxford University Press. 1996.

Grima DT, Torrance GW, Francis G. Cost and health related quality of life consequences of multiple sclerosis. *Mult Scler* 2000; 6: 91–98.

Hadjimichael O, Kerns RD, Rizzo MA, Cutter G, Vollmer T. Persistent pain and uncomfortable sensations in persons with multiple sclerosis. Pain 2007; 127:35–41.

Hammond SR, McLeod JG, Macaskill P. Multiple sclerosis in Australia: socioeconomic factors. *J Neurol Neurosurg Psych* 1996; 61: 311–313.

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-560.

International Labour Organization: Resolution concerning statistics of the economically active population, employment, unemployment and underemployment, adopted by the 13th International Conference of Labour Statisticians. http://www.ilo.org/public/english/ bureau/stat/download/res/ecacpop.pdf (2007).

Jacobs LD, Wende KE, Brownscheidle CM. A profile of multiple sclerosis: The New York State Multiple Sclerosis Consortium. *Mult Scler* 1999; 5: 369–376.

Johnson KL, Amtmann D, Yorkston KM, Klasner ER, Kuehn CM. Medical, psychological, social and programmatic barriers to employment for people with multiple sclerosis: A review of the literature. *J Rehab* 2004; 70: 38-49.

Julian LJ, Vella L, Vollmer T, Hadjimichael O, Mohr DC. Employment in multiple sclerosis. Exiting and re-entering the work force. *J Neurol* 2008; 255:1354-60.

Juni P, Altman DG, Egger M. Systematic reviews in health care: assessing the quality of controlled clinical trials. *BMJ* 2001; 323:42–46.

Karampampa K, Gustavsson A, Miltenburger C, Kindundu CM, Selchen DH. Treatment experience, burden, and unmet needs (tribune) in multiple sclerosis study: The costs and utilities of MS patients in Canada. *J Popul Ther Clin Pharmacol.* 2012; 19:11-25.

Kornblith AB, La Rocca NG, Baum HM. Employment in individuals with multiple sclerosis. *International Journal of Rehabilitation.* 1985; 9: 155–165.

Lalkhen AG and McCluskey A. Statistics V: Introduction to clinical trials and systematic reviews. *Continuing Education in Anaesthesia, Critical Care & Pain* 2008; 8: 143-6.

Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977; 33: 159-74.

LaRocca N, Kalb R, Kendall P, et al. The role of disease and demographic factors in the employment of patients with multiple sclerosis. *Arch Neurol* 1982; 39: 25-6.

LaRocca N, Kalb R, Scheinberg L, Kendall P. Factors associated with unemployment of patients with multiple sclerosis. *Journal of Chronic Disabilities* 1985; 38: 203–210.

LaRocca N. *Employment and multiple sclerosis*. New York: National Multiple Sclerosis Society, 1995.

Law MC and MacDermid J. *Evidence-based rehabilitation: a guide to practice.* Second edition. USA: SLACK Incorporated 2008, p. 127.

Michalski D, Liebig S, Thomae E, Hinz A, Bergh FT. Pain in patients with multiple sclerosis: a complex assessment including quantitative and qualitative measurements provides for a disease-related biopsychosocial pain model. *J Pain Res* 2011; 4:219-25.

Minden SL, Marder WD, Harrold LN, Dor A. Multiple Sclerosis: a statistical portrait. New York: National Multiple Sclerosis Society, 1993.
Moher D, Liberati A, Tetzlaff J, Altman DG, the PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Annals of Internal Medicine* 2009; 151: 65-94.

Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG. Multiple sclerosis. *N Engl J Med.* 2000; 343: 938–52.

Noyes B. Maximize your options. National Multiple Sclerosis Society. 2005, http://www.nationalmssociety.org/Brochures-Workforce-Max.asp.

O'Connor RJ, Cano SJ, Ramió TL, Thompson A J, Playford ED. Factors influencing work retention for people with multiple sclerosis Cross-sectional studies using qualitative and quantitative methods. *J Neurol.* 2005; 252: 892–896.

Piwko C, Desjardins OB, Bereza BG, et al. Pain due to multiple sclerosis: Analysis of the prevalence and economic burden in Canada. *Pain Res Manage* 2007; 12:259-265.

Richards RG, Sampson FC, Beard SM. A review of the natural history and epidemiology of multiple sclerosis: Implications for resource allocation and health economic models. *Health Technol Assess* 2002; 6: 1–73.

Ried K. Interpreting and understanding meta-analysis graphs: A practical guide. *Australian Family Physician* 2006; 35: 635-8.

Roessler R, Rumrill P, Hennessey ML, Courtney V, Pugsley E, Pittman A. Perceived strengths and weaknesses in employment policies and services among people with multiple sclerosis: Results of a national survey. *Work: A Journal of Prevention, Assessment and Rehabilitation* 2003; 21: 25-36.

Rotstein Z, Hazan R, Barak Y, Achiron A. Perspectives in multiple sclerosis health care: Special focus on the costs of multiple sclerosis. *Autoimmunity Reviews* 2006; 5 511–516.

Rumrill, P. Employment and multiple sclerosis. New York: Demos,1996

Scheinberg L, Holland N, Larocca N. Multiple sclerosis; earning a living. *NY State J Med* 1980; 80: 1395–1400.

Smith MM, Arnett AP. Factors related to employment status changes in individuals with multiple sclerosis. *Mult Scler* 2005; 11, 602-9.

Solaro C, Brichetto G, Amato MP, Cocco E, Colombo B, D'Aleo A. The prevalence of pain in multiple sclerosis: a multicenter cross-sectional study. *Neurology.* 2004; 63:919–21.

Stenager E, Knudsen L, Jensen K. Acute and chronic pain syndromes in multiple sclerosis: a 5-year follow-up study. *Ital J Neurol Sci.* 1995; 16:629–32.
Sterne JA, Gavaghan D, Egger M. Publication and related bias in meta-analysis: Power of statistical tests and prevalence in the literature. *J Clin Epidemiol* 2000; 53:1119-1129.

Svendsen KB, Jensen TS, Hansen HJ, Bach FW. Sensory function and quality of life in patients with multiple sclerosis and pain. *Pain* 2005; 114: 473–81.

Verdier-Taillefer MH, Sazdovitch V, Borgel F, Cesaro P, Kurtz A, Millet MF, Roullet E, Marteau R. Occupational environment as risk factor for unemployment in multiple sclerosis. *Acta Neurol Scand* 1995; 92:59–62.

Vollmer T, Ni W, Stanton S, Hadjimichael O. The NARCOMS Patient Registry: a resource for investigators. *Int J Mult Scler Care* 1999; 1:12–15.

Warnell P. The pain experience of a multiple sclerosis population: a descriptive study. *Axon* 1991; 13: 26–8.

Table 3.1 Characteristics of the retrieved studies

Author / Year	Study Design	Participants	Measures/ Variables	Main Results
Julian 2008	Longitudinal/ NARCOMS	N= 8867 (W: 74%) Age: 48± 9 years PDDS: 3 Disease duration: 18± 11 years	0 - 5 Performance Scale to measure pain Interference with employment loss and employment initiation over 6 months. Employment status / employment loss and initiation	There was a significant difference between employed and unemployed people with their pain. But pain was not significantly predictive of employment loss (OR= 1; p value 0.9) and employment initiation (OR= 1; p value 0.8).
Glad 2010	Cohort	N= 188 (W: 64%) Age: 54± 9 years Disease duration: 22± 3 years; EDSS: 5± 2	Impact of non-motor symptoms on employment Chronic pain: present or not Employment status (full- or part-time) and type of occupation (light or heavy physical work) were registered.	Prevalence of pain was 54%. Pain was not associated with unemployment. The estimated OR for chronic pain as a prognostic factor for unemployment was 4 (p value =0.1) for EDSS <2 and 2 for the two other corresponding analyses (p value 0.3 and 0.1 respectively).
Glad 2011	Cohort	N= 188 (W: 64%) Age: 54± 9 years Disease duration: 22± 3 years; EDSS: 5± 2	clinical examination/ interview/ questionnaires Pain: present or not Employment status and type of occupation	63% of the non-benign and 45% benign patients reported pain. 32% of the cohort was employed. There were an increasing proportion of patients not being employed in the presence of pain (OR=2; CI=1 - 6, p value= 0.3).
Douglas 2008	Cross sectional	N= 219 (W: 82%) Age: 24–82 years (51±12) Median MS duration: 9 years (range, 0.5–60)	Mailed self-administered questionnaire/ structured interview Pain intensity (NRS), pain quality (MPQ), location, duration, and management. 0-5 GNDS scale to measure disability in domains due to pain. Hours of paid employment per week	67% reported pain. 66% were not in paid work. Comparisons between participants with and without pain did not reveal any significant associations between the presence of pain and employment status (rate of employment in pain group (31%), and in pain free group (37%), p- value= 0.5
Ehde 2003	Cross sectional	N=442 (W: 75%) Age 50 ± 11 years Duration of MS: 13 ± 10 years	Mail survey questionnaires 0-10 NRS: average pain intensity and pain interference on activity and work / SF-36 Employment status: employed or not	44% reported pain. 39% were employed. 20% reported severe interference in activities as a result of pain. Rate of employment in pain group (35%), pain free group (42%), p- value= 0.1, no sig difference on employment rate.
Ehde 2006	Cross sectional	N= 180 (W: 78%) Age (pain = 50± 11; No pain= 50 ±12) Duration of MS: 13 ± 10 years	Postal survey / 0-10 NRS: pain/ SF-36 Brief Pain Inventory Scale: Pain interference with normal work. CIQ: lack of handicap, and productive activity Employment status: : employed or not	Pain prevalence was 66%. Overall pain interference was 3 out of 10. Persons with pain were less employed (employment rate: with pain 25%, without pain 50%, p < 0.001). Productive activity was significantly different between two groups (pain group reported less productivity).

Author / Year	Study Design	Participants	Measures/ Variables	Main Results
Forbes 2006	Cross sectional	N= 929 (W: 69%) Age: 17–81 years (48±11) Duration of MS: 16 ± 10 years	Postal survey using a piloted questionnaire. Presence of pain 0-5 ordinal scales to measure severity of pain and problem with employment due to MS symptoms Multiple Sclerosis Impact Scale-29: disease impact / SF-36	Pain affected 73% of the sample. Mean bodily pain: 56 ± 26 (0-100). 28% of sample was employed. Those with less pain (68 on BPS) had no problem with employment, while those with more pain (56 on BPS) reported severe problem with employment.
Michalski 2011	Cross sectional	N= 38 (W: 82%) Age: 42 ±11 years Disease duration: 9± 7 years (1–26); EDSS: 4±2	Pain intensity (NRS), quality (PSS), Pain-related behavior (FSR), health care utilization, and bodily complaints (GBB-24) Employment status and number of days off work	82% reported pain. Mean pain intensity was 4.0 (range 0–10). Participants with pain had increased days off work, though with no statistical significance (patients with pain: 70 days off per year; free pain patients: 3 days)
Piwko 2007	Cross sectional	N=297(W: 77%) Age: 49±11 years	Standardized questionnaires / telephone interview Pain type and severity; treatment and resource utilization for the management of MS pain; Box Score-11 scale/ Health Utilities Index Mark 3: pain Employment status: employed or not	Pain prevalence was71%. Only 13% of participants with pain were employed full time, while 80% were unemployed. In patients without pain these rates were 23% and 70% respectively. There was no significant difference (P=0.1) in employment status between participants with pain and without pain.
Warnell 1991	Cross sectional	N= 364 (W: 68%) Age: 19- 74 years (mean 43)	An author developed questionnaire. Pain prevalence, intensity, frequency, quality and location. 0-10 VAS: pain intensity/ QOL and Employment status	64% reported pain. Mean pain intensity was 5 on VAS) Pain compromised the ability to work in 49% of subjects. Participants in two groups were similar on employment rate (56% vs. 57%).

BPS, Bodily pain subscale of SF-36; CIQ, The Community Integration Questionnaire; EDSS, expanded disability status scale; FSR, Questionnaire on Pain Regulation; GBB-24, Giessen-subjective complaints list; GNDS, Guy's Neurological Disability Scale; MPQ, McGill Pain Questionnaire; NARCOMS, North American Research Committee on Multiple Sclerosis; N, number of participants; NRS, numeric rating scale; OR, odd ration; PDDS, Patient Determined Disease Steps; PSS, Pain Sensation Scale; QOL, quality of life; SF-36, The Short Form Health Survey; VAS, visual analogue scale; W, women.

Table 3.2 Quality assessment of papers sourced

Author	Year	Study purpose	literature	Design/ Bias	Sample	Outcome*	Exposure	Results	Conclusion implication	Quality**
Douglas	2008	PM	M	M	M	M	M	M	M	M
Ehde	2003	M	M	PM	PM	M	M	M	M	M
Ehde	2006	M	M	PM	PM	M	M	M	M	M
Forbes	2006	PM	PM	PM	PM	M	M	M	M	PM
Glad	2010	M	PM	PM	PM	M	PM	M	M	PM
Glad	2011	M	PM	PM	PM	M	PM	M	M	PM
Julian	2008	M	M	M	M	M	M	PM	M	M
Michalski	2011	PM	PM	PM	PM	M	M	M	M	PM
Piwko	2007	M	M	PM	M	M	M	M	M	M
Warnell	1991	PM	PM	PM	PM	M	M	M	M	PM

Note: From The Critical Review Form for Quantitative Studies developed by the McMaster University Occupational Therapy Evidence-Based Practice Research Group (39). Criteria for quality assessment included: purpose clearly stated; literature review was relevant; research design was appropriate to answer aims and no bias introduced into study; sample size justified, study sample described in detail, and informed consent gained; used reliable and validated outcome measures; exposure described in detail; results reported in terms of significance; analysis was appropriate, and clinical importance reported; conclusions and acknowledgement of limitations of the study were appropriate, and clinical implications reported.

* Considering that employment status was our outcome of interest, and that in most studies employment was a socio- demographic variable, where was gathered without a reliable and valid measurement tool, we modified the criteria for the quality assessment tool. So if the data on employment status in both pain and pain free groups were provided, the reviewers considered it as met.

** Quality: Less than 4 criteria met = not met (NM); 4 and 5 criteria met = partially met (PM); More than 5 criteria met = met (M).

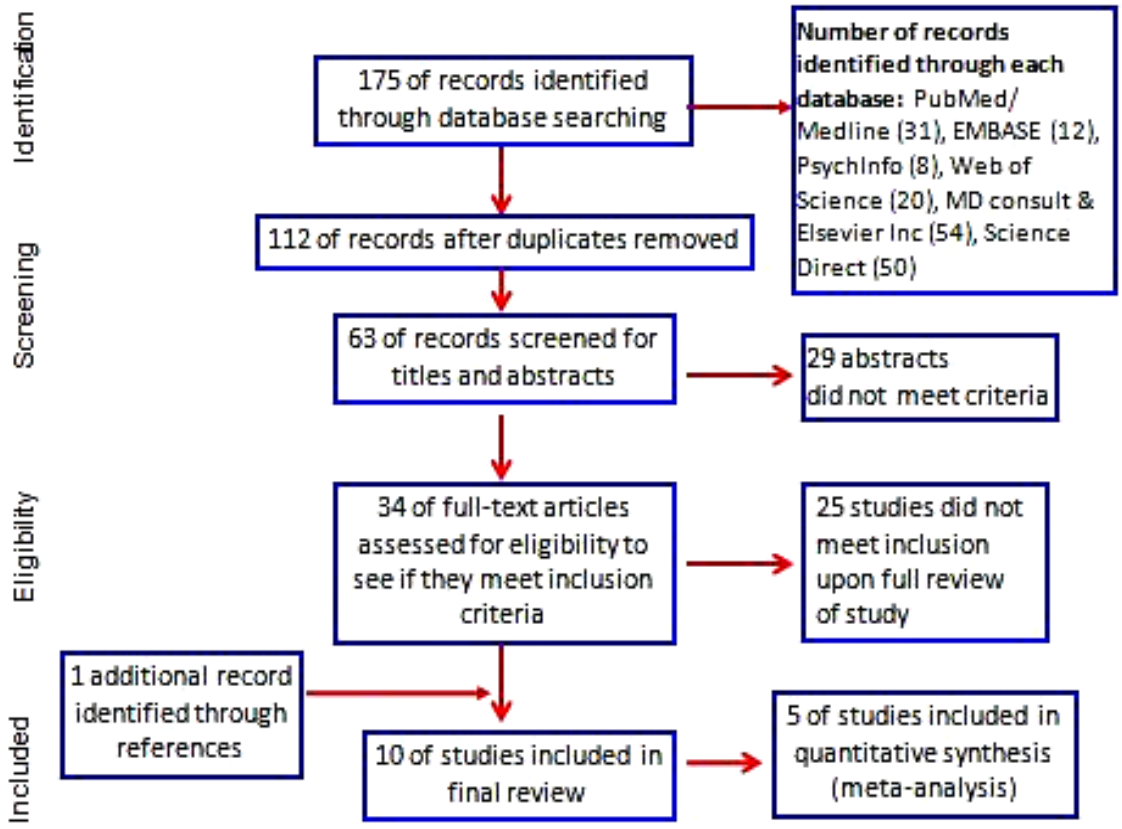

Figure 3.1 Graphic or tabular display of study selection process

Moher D, Liberati A, Tetzlaff J, Altman DG, the PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Annals of Internal Medicine* 2009; 151: 65-94.

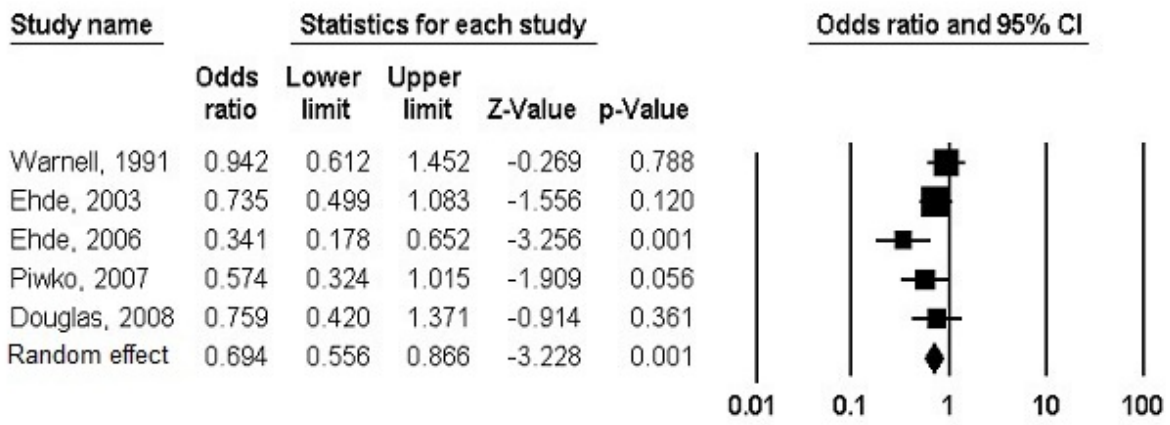

Figure 3.2 Forest plot of the effect of pain on employment status

The left-hand column lists the names of the studies, in chronological order, and the right-hand column is a plot of comparison. For each study, OR is shown as a square, with area proportional to the sample size. The 95% CI is represented by the horizontal line around each square. The vertical line in the middle is called 'the line of no effect', which visually displays the study overall results (42). The bottom line on this plot is marked "Random" and shows the combined effect or difference for the studies (44). The overall OR and 95% CI are plotted by the diamond in the last row of the graph. As the diamond doesn't cross the 'line of no effect', the calculated difference between groups can be considered as statistically significant (42). The OR falls below 1 indicating that people with MS pain were less likely to be employed than those persons with MS without pain.

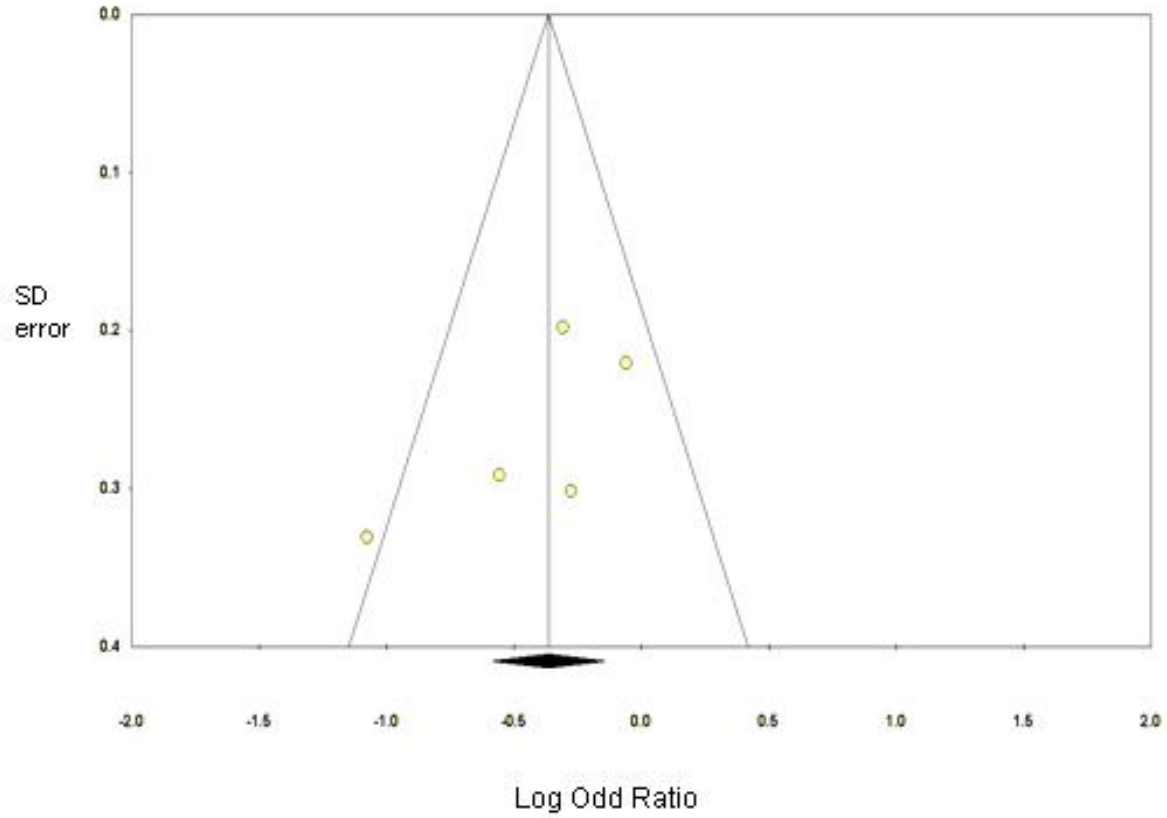

Figure 3.3 Funnel plot of the study to assess the presence of possible publication bias.

A symmetrical inverted funnel as shown implies no publication bias. The dashed vertical line represents the pooled estimate of the pain effect of all included studies.

CHAPTER 4: Integration of manuscripts 1 and 2

4.1 Research questions of manuscript 1 and 2

Manuscript 1:

Does Pain in Individuals with Multiple Sclerosis Affect Employment? A Systematic Review and Meta analysis.

Manuscript 2:

Looking at Pain in Multiple Sclerosis: Prevalence, severity, frequency, duration, quality, location, distribution, type, treatment, impact and predictors.

4.2 Integration of manuscript 1 and 2

Improving HRQL has become an important goal of all health care interventions. Participation and social functioning is one of the important domains affecting HRQL. To optimize treatment and rehabilitation efforts in MS, identifying and understanding factors that influence the level of participation and so HRQL is necessary.

The previous chapter was a systematic review and meta analysis of selected studies estimating impact of pain on employment in persons with MS. Work was chosen to be the domain of interest in the first manuscript, because work is one of the key aspects of participation and one of the most distressing challenges of MS. MS occurs in individuals during peak years of normal productivity, significantly impacting their ability to remain in the work force.

Pain is a common symptom in persons with MS and has been found to be a reason for sick leave or early retirement in healthy populations and in other groups with chronic illness. Thus, it is assumed that pain can catalyze the social isolation of MS population and increase the risk of being unemployed.

The primary aim of this thesis was to ascertain the extent to which pain affects participation in persons with MS. To have a deep and better insight about the role of pain on involvement in life roles, naturally the next step is to understand the target population, specifically, their pain

characteristics. The second manuscript, therefore, will provide an overall picture of pain in an epidemiologically sampled group of community dwelling individuals with MS.

Assessing pain is an essential component to rehabilitation as it has been widely accepted that a first step in improving the treatment of pain is its adequate assessment. A comprehensive assessment of pain, along with its impact and predictors, as well as interpretation of results using appropriate statistical methods help to understand different aspects of pain and has the potential to enhance pain management.

CHAPTER 5 (MANUSCRIPT 2)

Looking at pain in multiple sclerosis: prevalence, severity, frequency, duration, quality, location, distribution, type, treatment, impact and predictors

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Running Title: What characterizes pain in individuals with MS?

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ABSTRACT

Objective: To identify pain prevalence, severity, frequency, duration, quality, location, distribution, type, treatment, impact and predictors in a large, well-designed sample of community dwelling individuals with multiple sclerosis (MS).

Methods: This was a cross-sectional study. A centre-stratified random sample including 188 persons with MS were recruited from three major MS clinics in the Greater Montreal region, Canada. Main outcomes included pain prevalence, severity, frequency, duration, quality, location, distribution, type, treatment, interference, depression, anxiety, physical function, perceived health status, fatigue, sleep problems, and cognitive deficits. Participants completed three questionnaires: the first asked about the socio-demographic and clinical information of subjects, the second assessed the pain characteristics of subjects, and the third covered the explanatory variables.

Results: Prevalence of pain in our sample was 42%. Pain differed among participants in severity, type, location, duration, frequency, and quality. The majority of participants used pharmacological techniques for pain relief. Pain presence was predicted by fatigue and MS-related disability, while pain severity was only predicted by MS-related disability. The results of this study also showed that pain was associated with higher levels of depression, anxiety, fatigue, sleep problems, and cognitive deficits, and diminished perceived health status, ability to work, and physical functioning.

Conclusion: The considerable differences between participants with pain and those without pain on physical and psychological functions highlight the importance of accurate assessment and adequate treatment of pain in people with MS.

Key words: pain, multiple sclerosis, physical function, depression, anxiety, perceived health status, cognitive impairment, fatigue, sleep disorders, work, and disability.

5.1 INTRODUCTION

Multiple sclerosis (MS) is a chronic, inflammatory autoimmune demyelinating disease of the central nervous system (CNS) (Noseworthy 2000). The exact cause of MS is not known, but it is believed that infection, viruses, genetics, environment, and hormones play a role (Compston 2005, Noseworthy 2000, Ramagopalan 2010a). In most people, MS begins between the ages of 20 and 40 (Beeson 1994) and the condition is seen more frequently in women than in men (Orton 2006, Ramagopalan 2010b). Canada has one of the highest prevalence rates of MS in the world, affecting as many as 240 people per 100,000 (O'Connor 2009). The annual cost of MS has been estimated at 2.5 billion dollars in the US, and $502.3 million in Canada (O'Brien 2003).

Pain is a frequent complaint among individuals with MS (Svendsen 2003). Persons with MS usually describe their pain as intermittent with mild to moderate intensity (Archibald 1994). The reported prevalence of pain in MS differs in the literature, ranging from 11% to 90% (Archibald 1994, Ehde 2003, Indaco 1994, Kalia 2005, Kassirer & Osterberg 1987, Moulin 1988, 1989, Svendsen 2003, Stenager 1991, 1995, Vermote 1986, Warnell 1991). In Canada, pain was reported in 41% to 71% of persons with MS (Archibald 1994, Ehde 2006, Piwko 2007, Warnell 1991). This variation is partly due to methodological differences across studies in regards to the patient source, method of sampling, research design, and pain measurement. Studies have used different time frames ascertain pain (e.g. previous week, one month, 3 months), and different constructs of pain were measured (e.g. frequency, intensity, duration). Also, studies varied as to whether headache was related to MS pain (Vermote 1986). Factors related to the heterogeneity and complexity of the disease itself (e.g. disease subtype, duration and severity of symptoms) also varied across studies. The high prevalence of pain among persons with MS and the cost of MS pain would indicate that this is an important area of research in clinical management.

MS pain is either directly related to lesions in the nervous system (neuropathic pain), or indirectly as a consequence of symptoms such as muscle spasms and poor posture (musculoskeletal pain). Leg pain followed by back pain is the most common reported sites of pain (Moulin 1988, Rizzo 2003, Solaro 2004). There are several risk factors found to be associated with pain in people with MS such as older age, female sex, longer disease duration, and greater disease severity. However, there is still inconsistency with respect to the important of

various clinical and personal factors (O' Connor 2008). Identifying the predictors of pain is important for both health professional and researchers, because pain has repeatedly found to be a strong predictor of activity limitations and participation restrictions.

Pain management often starts after pain has established itself. Treatment of MS pain involves a variety of pharmacologic and non pharmacologic approaches (Leary 2000). Pharmacologic pain treatments include the use of antidepressants, and anticonvulsant for neuropathic pain and anti-inflammatory medications for non neuropathic pain. In order to avoid potential long-term side effects of medication, some patients have preferred alternative options for treatment of their pain, such as massage, exercise, acupuncture, and yoga (Moulin 1988, White 2004).

Pain impacts on several aspects of individuals' life. In comparison to MS people without pain and the general population, persons with MS pain report poorer health-related quality of life (HRQL), poorer overall mental and general health, more social role limitation (Archibald 1994, Murphy 1988, Nortvedt 1999, Svendsen 2005), and more depressive symptoms (Ehde 2005). Moreover, nearly half of persons with MS and pain report that pain interferes with their daily activities, household work (Ehde 2003), sleep, and enjoyment of life (Hadjimichael 2007).

There are substantial gaps in the literature on pain in MS. Nevertheless, pain is very disabling in MS population and is considered to be a major contributor to activity limitations and restrictions in societal and family roles. In addition, most of the studies in MS pain are prevalence and descriptive studies. Available information of MS related pain often is limited by value because of methodological and analytical problems. For the most part, previous studies have looked at pain as a unidimensional health outcome or have focused on only few dimensions of pain (e.g. intensity and duration) in their analyses. A comprehensive and detailed assessment of pain would help in better understanding of MS pain and result in more targeted treatment approaches for people with MS.

The main objective of the current study, therefore, was to identify pain prevalence, severity, frequency, duration, quality, location, distribution, treatment, type, and interference in a large,

well-designed sample of community dwelling individuals with MS. A secondary objective was to determine MS pain predictors.

5.2 METHODS

5.2. 1 Participants

Target population was all people with MS, diagnosed since 1995. Available population was all men and women registered at the three major MS clinics in greater Montreal including, Montreal Neurological Hospital (MNH), Centre Hospitalier de l'Université de Montréal (CHUM), and Clinique Neuro Rive-Sud (CNRS). The time frame was stratified into 3 eras: 1995 to 1999, 2000 to 2004 and 2005 to 2006 to ensure that people from each era are included. The number of people diagnosed with MS since 1995 at the 3 clinics was 1950. A centre-stratified random sample of 550 individuals with MS was drawn, of which 364 were contacted. From those who were contacted, the first 188 who responded (139 women and 49 men) shaped the study sample population. Eligibility was based on diagnosis of MS or Clinically Isolated Syndrome (CIS). In addition, participants who had a relapse in the preceding month, participants younger than 18 years old, people with severe cognitive impairments, and those with pre-existing health conditions affecting functioning were excluded from participating in the study. Further, participants were not eligible if they were unable to understand either English or French.

5.2. 2 Measures

This was a secondary analysis of data; previously described (Kuspinar 2010). Study protocol, measures and procedures were approved by the ethics committee of each participating hospital; informed consent was obtained**.** All measures chosen for the purpose of this study adequately represent the components of the underlying construct; and their validity and reliability have been determined.

5.2. 2.1 Socio-demographics characteristics

Socio- demographic factors of gender, age, smoking status, education level, and employment status were recorded on the day of testing using the socio-demographic questionnaire.

5.2. 2.2 Disease-related characteristics

The clinical records and medical charts of each participant were consulted to obtain data on MS type, years since MS diagnosis and symptoms onset. Clinical types of MS included: relapsing remitting (RR), primary progressive (PP), secondary progressive (SP), progressive relapsing (PR), and Clinically Isolated Syndrome (CIS) (Ramagopalan 2010). Participants also were asked to report if they used disease modifying therapies (DMT). The severity of neurological impairment was assessed using the Expanded Disability Status Scale (EDSS), which has become the standard measure for classification MS related disability, ranging from 0 (no disability) to 10 (maximum disability) (Kurtzke 1983).

5.2. 2.3 Pain characteristics

Pain prevalence

Pain prevalence in persons with MS was determined by calculating the proportion of participants who answered 'yes' to this question: "Are you currently experiencing any pain regardless of intensity and localization?" Additional pain questionnaires were only administered to persons who reported pain.

Bodily pain intensity

The two-item bodily pain subscale (BPS) from RAND-36 was used as a measure of bodily pain intensity during the past 4 weeks. The first item of BPS asks about pain intensity, and the second item grades the impact of pain on work. These two items are combined into a single composite score and transformed to a 0-100 scale, with higher scores indicating lower pain severity (Hays 2001). Internal consistency and content, criterion and construct validity of RAND-36 have been reported (Brunet 1996, Brazier 1992, Freeman 2000, Katz 1992, McHorney 1993).

Pain severity

To measure average, lowest and worst pain severity over the previous week as well as pain at the time of evaluation we used 0–10 Numeric Rating Scales (NRS), with 0 indicating 'No pain' and 10 indicating 'the most painful sensation imaginable'. Reliability and validity of NRS have been documented (Sharrack 1999). NRS is also strongly associated with other measures of pain

intensity (Jensen 1986, 1991, 1999) and is responsive to changes in pain treatments (Jensen & Karoly 1991).

Pain location

To measure pain location, participants were instructed to shade areas that were painful at the time of the evaluation on a pain diagram showing the front and back of the whole body consisting of 45 anatomical areas (Figure 1) (Margolis 1986).

Pain distribution

Pain distribution was measured using the Margolis drawing rating system which has 45 anatomical areas each with a corresponding percentage value of body surface in order to compute a total weighted score, indicating body pain distribution (Figure 1) (Margolis 1986). The test-retest and inter-rater reliability of scale has been established (Margolis 1988).

Pain quality and type

To assess pain quality and type, participants were asked to choose as many as of the words from a list containing 29 adjectives of pain sensation descriptors taken from the McGill Pain Questionnaire (MPQ) (Melzack 1983, 1987). Sensations of shooting, stabbing, electric shock-like, nagging, numbness, tingling, and burning were considered as neuropathic pain descriptors, whereas non- neuropathic pain was described as a sharp, aching or throbbing (Victor 2008, Wilson 2002). Superficial pain descriptors included numbness, tingling, burning, shooting, sharp, pressure, piercing, stinging, hot, smarting, radiating, cutting, while deep pain descriptors included cramping, tenderness, aching, pulling, pounding, gnawing, soreness, boring, stabbing, troublesome, annoying, dull, nagging and throbbing.

Pain duration and frequency

Participants were asked to report their pain duration and if their pain experience was constant or not. They were also asked to rate how frequently they experienced pain.

Pain management techniques

Participants were asked to indicate their pain management techniques, either pharmacological or non-pharmacological, during the previous month of the study and to report if these techniques helped relieve their pain. They were also asked to determine which specific medications they took for their pain reduction.

Pain impact

Pain impact focused on sleep, work, daily living activity, and perceived health status. To assess sleep disturbance during the previous month, we used a specific sleep questionnaire created from Rasch modeling of the Pittsburgh Sleep Quality Index **(**PSQI) **(**Buysse 1989) containing 4 items; total score ranges from 0 to 8, with a higher score indicates worse sleep quality.

Using physical function scale of RAND-36 (PFI) we measured limitations in daily living activities due to health problems. This subscale has a final score from 0 to 100; higher scores indicating higher levels of physical activity (Hays 2001). Validity and reliability of this scale has been reported (Freeman 2000, Katz 1992, McHorney 1993, Brazier 1992).

Perceived health status was measured using the EuroQOL Visual Analogue Scale (EQ-VAS) (EuroQol Group 1990). Subjects were asked to rate their overall health on 0 to 100 VAS scale, with 0 showing the worst perceived health and 100 showing the best perceived health. VAS has been widely used in health studies and has several good qualities in terms of practicality, sensitivity, and, reliability (Nortvedt 1999).

5.2. 2.4 Explanatory variables

Fatigue

To measure fatigue we used the 4-item Vitality subscale of The RAND-36. Participants were asked to rate their level of fatigue on a 6-point Likert scale ranging from 1 ‘all of the time’ to 6 ‘None of the time’ (Hays 2001). The 4 items are combined to produce a sum value from 0 to 100; a higher score indicates greater energy/ lower fatigue. RAND-36 has been used widely in MS population and its psychometric properties have been provided (McHorney 1993).

Psychological well-being

The levels of anxiety and depression of participants were measured using the Hospital Anxiety and Depression Scale (HADS) (Herrmann 1997). HADS has 14 items, 7 of them relate to anxiety and 7 to depression, each scores from 0 (most of the time) to 3 (no t at all), and the total score ranges between 0 and 21 (Bjelland 2002); higher scores indicate worse depression/ anxiety symptoms. The HADS is a reliable and valid tool and has been used in a number of MS studies (Bjelland 2002, Da Silva 2009, Honarmand 2009).

Cognitive impairment

Cognitive impairment was assessed using the Perceived Deficits Questionnaire (PDQ) developed for persons with MS (Sullivan 1992). The PDQ items assess frequency of difficulties with attention/concentration, memory, and planning/organization during the past month on a 5-point Likert scale. PDQ contains 20 items, each from 0 (never) to 4 (almost always) with a maximum total score of 80; higher scores indicate greater cognitive impairment (Shevil 2006). The validity and reliability of PDQ in MS has been widely accepted (Marrie 2003, Sullivan 1992).

5.2. 3 Statistical Analyses

Descriptive statistics (e.g., mean, standard deviations, and frequency) were used to describe the sample and summarize data. The potential for selection bias, differences between responders and non- responders on targeted variables (e.g., socio-demographic and clinical characteristics of persons), and comparison between persons with and without pain was tested using Chi square test for categorical variables, t-test for continuous variables with homogenous variances, and U Mann-Whitney test for continuous variables with non-homogenous variances.

The main outcomes of regression analyses were pain presence and severity. As outcomes were not continuous variables, multiple logistic regressions were used to analyze data (Table 1). Logistic regression in general indicates the probability of presence of the characteristic of interest. The predictor variables were personal and clinical characteristics of participants. Explanatory variables were also included in the analysis. Associations between all variables were assessed using Spearman and Pearson correlation coefficients for categorical and continuous variables, respectively.

Those variables that showed a significant relation with outcomes were considered as potential predictors in the regression analyses. Using multiple regressions each predictor variable was entered into the model, and retained or discarded based on their contribution to the overall model (statistical significance at the 0.05, beta estimate, odd ratio, and R square). The standardized coefficient of each predictor was also calculated by multiplying the standard deviation for the variable by its unstandardized parameter estimate permitting a quantifiable way of identifying which predictor had the largest effect on pain presence and severity.

Sample size calculation was based on the rule of thumb for regression analysis that is a minimum of 10 participants per predictor variable (Wilson 2007). Considering that in our final regression equations there were 9 predictors, a sample size of 188 participants would be suitable and adequate sample size for this study. Individuals with missing information from the questionnaire were excluded from the specific analysis. Statistical significance was considered for p-values less than 0.05. Statistical analyses were performed using the Statistical Analysis Systems (SAS) Version 9.2.

5.3 RESULTS

5.3.1 Response rate

Response rate was 52%, and no significant difference was found between responders (n=188) and non-responders (n = 176) on age, sex, MS related disability, date of diagnosis, and duration of symptoms.

5.3.2 Socio- demographic and clinical characteristics of the sample

Socio- demographic and clinical characteristics of the sample are presented in Table 2. The ratio of women to men participants in our study was 3: 1. Most participants were receiving DMT at the time of the study. COPAXONE (24%) followed by REBIF (22%) and AVONEX (14%) were the most common types of DMT used by participants.

5.3.3 Pain characteristics of the sample

Pain characteristics of the sample are presented in Table 3. Of the 188 persons, 42% identified pain as a symptom, and among those, 42% reported to have clinically significant pain (severity ≥4) at the time of evaluation. Duration of pain varied. Pain could last from minutes to hours to

days. The mean values of bodily pain measured by RAND-36 was 67± 27 for the whole sample which is lower than age expected norms of Canadian general population of 76 (Hopman 2000). The mean value for rating of current pain at the time of evaluation was 3.3 ± 2.3; mean of lowest pain severity was 2.2 ± 2; worst pain severity was 6.8 ± 2; and pain average was 5.0 ± 2. The NRSs later were used to classify the participants as having no pain (score 0), mild pain (scores 1–4), moderate pain (scores 5- 6) and severe pain (scores 7–10) (Grasso 2008, Serlin 1995). Distribution of the severity of pain is presented in Figure 2. All metrics of patients' pain ratings were correlated including the calculated average of lowest and worst (Figure 5.3). In addition, they all correlated similarly with an external pain rating scale (BPS of RAND-36). Interestingly, it was indicated that of all ratings, the patients' ratings of worst pain was the most closely associated with the rating of average pain ($r = 0.8$).

The frequency of pain sites are shown in Table 5.4. Participants shaded an average of 8 out of 45 parts of body as painful. Leg pain was the most common anatomical site of pain followed by arm pain and back pain. In addition, prevalence of pain was more on the left side than on the right side and in anterior parts rather than posterior parts of the body. Additionally, the average of total percent of body surface that participants had shaded as painful was 20% (range: 2 - 48).

The frequency of the pain descriptors are detailed in Figure5. 4. The average number of words chosen by participants was 5, and 36% of participants used more than 5 words to describe their pain. Neuropathic pain was the most commonly reported type of pain. There was also a significant association between severity of pain and type of pain, suggesting that neuropathic pain is more severe than non-neuropathic (Fisher exact test, p= 0.03). In addition, we found no statistically significant differences in age and gender between participants with neuropathic and non-neuropathic pain.

Pain management techniques that have been used by participants are presented in Table 5. Overall, 95% of participants reported that the methods they used for pain management, helped with their pain reduction. In addition, there were correlations between gender, age, MS related disability, and employment status with the frequency of using pain management techniques.

Regarding pain interference, 40% of participants with pain reported that pain interfered with their sleep. In addition, participants without pain were more employed and reported higher level of fatigue, and daily living activity in comparison to participants with pain. Participants without pain also tended to show less cognitive impairments, depression, and anxiety (Table 2).

As presented in Table 2 there was no difference between 2 groups on age, education, and smoking status, DMT, and duration of symptoms onset and diagnosis. However, the pain group showed a higher women-to-men sex ratio (4:1 vs. 2:1 in pain group), and higher EDSS scores.

5.3.4 *Factors associated with presence and severity of pain in MS*

Results of correlation analyses showed a statistically significant correlation between pain presence with gender, employment status, MS type, MS disability, fatigue, depression, anxiety, perceived health status, and cognitive deficit ($r = 0.1$, $r = -0.3$, $r = 0.2$, $r = 0.2$, $r = -0.34$, $r = 0.2$, $r = 0.17$, $r = -0.35$, $r = 0.3$, $p < 0.05$, respectively). MS disability, depression, and perceived health status also showed a statistically significant correlation with pain severity (r= 0.4, r= 0.3, r= -0.34, $p < 0.05$, respectively). However, no associations were observed in our study between pain severity with anxiety and cognitive deficit. Neither pain presence, nor pain severity were associated with level of education, age, DMT, and years from symptoms onset and diagnosis.

Table 6 displays the results of logistic regression analysis for response variables. The results of dichotomous logistic regression analysis for pain presence showed that only fatigue and MS disability made a significant contribution to prediction. Additionally, R square of 19% indicated a mild relationship between prediction and grouping. Furthermore, analysis of maximum likelihood showed that for every unit increase in fatigue or decrease in vitality (RAND-36, lower score means less vitality so more fatigue), the probability of pain presence increases by 0.96 (p=0.0001). Moreover, for a unit increase in MS disability (EDSS, higher score is worse), the probability of pain presence increases by 1.2 (p=0.03).

Results of ordinal logistic regression on pain severity indicated that only MS disability had a significant effect on pain severity (p=0.001). This means that for every unit increase in MS disability, (EDSS score, higher score is worse), the probability of experiencing more severe pain

increases by 1.4. Additionally, the final regression model explained 13% of the variance in pain severity.

5.4 DISCUSSION

The purpose of the present study was to characterize MS pain, compare persons with and without pain, and find predictors of pain presence and severity in individuals with MS. The prevalence of pain at the time of evaluation was 42% which is located in the range of most reporting rates of 40% to 80% in MS population (Archibald 1994, Goodin 1999, Ehde 2003, Rae Grant 1999), overlap with 42% in a study conducted by Goodin (1999), 43% estimated by Solaro (2004), and 41% and % 44 reported by Warnell (1991) and Archibald (1994) in Canada. However, it is difficult to compare studies because of inconsistencies in measurement, definition of pain, time frame, and variety of patients' clinical and personal characteristics. One reason for low prevalence of pain can be related to the fact that our sample had mild disability levels (EDSS< 3) showing the less severely impaired individuals and so less prevalence of symptoms such as pain. However, this emphasizes the need for more attention to pain in MS as it shows that participants, even with low level of disability, had pain. Another reason can be explained by the fact that participants were diagnosed with MS since 1995 while the advances in MS accurate diagnosis e.g. magnetic resonance imaging (MRI) and treatment (e.g. DMT) has changed the clinical course of MS (Kieseier 2003, Massimo 2007). In 2008, Dr. Nancy Mayo suggested that the MS people diagnosed since 1995 will probably not follow the same symptom patterns and disease course as patients diagnosed before 1995 (Mayo 2008). She used the phrase "New MS" to describe those MS people diagnosed since 1995. Results of this study confirm this hypothesis. The fact that 85% of our participants were using DMT to manage their MS progression and to control their symptoms along with a probable earlier diagnosis of disease, confirm the lower prevalence of pain in our sample.

Mean of average pain severity of our sample was 5 out of 10 which was within the range of 4.6 to 5.8 reported by Douglas (2008), Archibald (1994), Beiske (2004), Heckman- Stone (2001), Warnell (1991), Rae Grant (1999), and Ehde (2003). Participants' ratings of their worst pain intensity showed that 60% of sample reported severe pain (7–10 out of 10), which is greater than 49% reported in another study (Hadjimichael 2007). These findings taken together show that

despite low prevalence of pain, pain severity was high in our sample, therefore reinforcing the need to identify pain reasons and look for an effective approach to treat it adequately.

Typically in research, pain severity is queried on a 0 to 10 NRS. Research indicates that a single rating of pain severity may not adequately represent the construct of pain (Spadoni 2004). Frequently, multiple pain values are obtained: current, lowest, worst, and average. All of these values are relevant both for patient management and research; but for research, having four values poses logistical and statistical difficulties as several ratings would need either multiple analyses or a different statistical method. Results of this study showed that participants' estimates of average pain were highly correlated to the calculated average of lowest and worst. Thus, we recommend not asking participants "average" their pain and for research purposes calculate the average of lowest and worst.

Consistent with previous studies, the majority of participants (97%) in this study reported pain in more than one site of their body (Archibald 1994, Beiske 2004, Douglas 2008, Ehde 2006, Rae-Grant 1999, Svendson 2003, 2005, Solaro 2004, Warnell 1991). Further agreement with other studies was related to the most common site of pain as leg pain had the highest frequency among body segments (Archibald 1994, Beiske 2004, Rae-Grant 1999). Additionally we found an association among number of pain sites with pain severity and MS disability. These findings confirm the results presented by Archibald (1994) and Piwko (2007) in Canada.

The average of total percent of body surface that the participants had shaded as painful was 20% for this sample that was lower than 26.5% reported by Douglas (2008). Results also showed that pain extent was significantly correlated to pain severity, but in contrast with Douglas (2008), it was not related to gender. In addition, 55% of participants in our sample reported their pain as intermittent, which is very close to 57% reported by Ehde (2006).

With respect to type of pain, most studies on pain characteristics in MS have neither investigated the different types of pain in MS, nor differentiated between neuropathic and non-neuropathic pain. Since each type of pain needs its specific treatment approaches according to its underlying mechanism (Moulin 1988), distinguishing whether pain is neuropathic or not has important

treatment relevance. Linked with the results of few other studies (Beiske 2004, Moulin 1988, Vermote 1986), we found that the type of pain in our sample was more often neuropathic than non-neuropathic (25% vs. 9%). Similar to the results of Kalia (2005) we also found that neuropathic pain is more severe and disabling pain than non-neuropathic pain. In addition, no statistically significant associations were observed in our study between different forms of pain with age and gender.

In accord with many other studies pain management techniques involved a variety of pharmacologic and non-pharmacologic approaches (Archibald 1994, Douglas 2008, Kalia 2005, Khan 2007, Heckman-Stone 2001, Piwko 2007); however, similar with results of Archibald (1994), Khan (2007), and Kalia (2007), the majority of participants used mostly medication. In accord with several other studies such as Khan (2007), Kalia (2005), Heckman-Stone (2001), Piwko (2007), Douglas (2008), and Archibald (1994) participants reported that their pain subsided significantly following the use of pain management techniques. Common pain medications used by our sample included opioids and antidepressants which were similar with the findings of Pollman (2005), and in contrast with reports of Khan (2007) and Douglas (2008). Non pharmacological techniques commonly used in our sample were massage and exercise which was similar with reports of Kalia (2005) and Douglas (2008). The pain management techniques were used mainly by women, participants with more disability, severe pain, younger participants, and also those who were employed. These results were similar with Douglas (2008), who found that women and participants in paid employment reported more pain management techniques.

In accord with findings reported by Solaro (2004), Ehde (2003, 2006), and Hadjimichael (2007) results of regression analyses revealed that MS-related disability (measured by EDSS) was an important predictor for both pain presence and severity. In addition, similar to a previous study (Ehde 2003, 2006; Archibald 1994; Stenager 1991; Solaro 2004), we found that persons with pain were more likely to have greater MS disability than those without pain. In further agreement with Douglas (2008) the present study also found that the greater severity of MS positively correlated with the number of pain locations and pain distribution.

78% of respondents had a RR form of MS which was similar to other studies (Archibald 1994, Douglas 2008, Ehde 2006), and very close to the prevalence of 75% reported by the Canadian MS Society (Piwko 2007). Additionally, results of regression analysis revealed that pain presence and severity were not associated with MS related factors (except MS disability), which is similar to the results reported in other studies (Archibald 1994, Beiske 2004, Heckman-Stone 2001, Kalia 2004). These findings indicate that pain cannot be predicted solely based on the disease characteristics and personal differences play an important role.

Considering gender differences, our result showed that gender was correlated neither with pain severity nor the extent of pain, and this was similar to Douglas (2008), and was in contrast to Kalia (2005) and Moulin (1988). The ratio of of women to men in our study was 3: 1, which corresponds with the sex ratio of the MS population (Richards 2002) and differs from the 4:1 ratio reported by Douglas (2008).

The mean age at which participants were diagnosed with MS was 43 years, which corresponds with the results reported by the MS Society of Canada (Piwko 2007). Additionally, there was no significant difference in age between participants with pain and without. Regression analyses also revealed that neither pain presence, nor pain severity were associated with age. This finding was consistent with the results of Archibald (1994), Beiske (2004), Ehde (2006), Indaco (1994), Kalia (2005), Stenager (1991), and Warnell (1991), but in contrast with the results reported by Clifford (1984), Hadjimichael (2007), Moulin (1988), Solaro (2004), and Svendsen (2003).

Results of this study, in agreement with other studies such as Ehde (2003, 2006), showed that participants with pain in comparison to those without pain were considerably more likely to report lower perceived health status. In addition, consistent with the findings of Douglas (2008), our results further revealed that cognitive deficit was correlated to pain presence. As Douglas (2008) believes, this association can probably be related to the patients' inabilities in coping strategies and problem-solving skills. Moreover, similar to results reported by Kalia (2005), Archibald (1994), Ehde (2003, 2006), and Svendsen (2005), we indicated that people with pain tended to be more depressed and anxious than those without pain. Worsened physical function in participants with MS pain that was indicated in our study have also been reported by

other authors such as Svendsen (2003), Beiske (2004), Archibald (1994), Hadjimichael (2007), Ehde (2003), Warnell (1991), Ehde (2006), Svendsen (2005).

In reference to job status, consistent with other studies (Forbez 2006, Julian 2008, Ehde 2006, Shahrbanian 2013) comparisons between participants with and without pain revealed an increasing proportion of participants not being employed in presence of pain (63%). This was lower than of 77% reported by Piwko (2007), but still within the range of 50% to 80% as described by Orlewska (2005). As MS is a disease that often affects young adults during their productivity years, this emphasizes the importance of early identification and treatment of pain. There was also a negative association between pain extent and number of pain sites with job status.

The current study has several strong points. It assessed a variety of MS pain constructs using standardized measures which are often not assessed in MS pain literature. Response rate of study was 52%, very close to the 54% reported by Ehde (2003), and higher than the 34% reported by Goodin (1999). Also, the study sample was randomly selected from 3 different clinics in Montreal from populations who were culturally diverse and living in different areas of the city. The sample included the whole range of disease severity, and type, consistent with a clinical spectrum of MS, so it could be a representative of the general MS population. A further strength of this study was that the present sample also comprised of men, thus providing a unique opportunity to study MS and pain in both genders, whereas many studies on MS and pain have included only a few men participants. Moreover, in order to limit errors due to memory, the assessment of pain focused on pain experienced over different time frames e.g. current pain and the month and week preceding the assessment.

On the other hand, this study had several limitations. First, this was a cross-sectional study where subjects were assessed at one point in time. This issue is particularly important in MS because as disease progresses, variables contributing to pain could be different. The cross-sectional nature of this data also makes it difficult to accurately examine how the impact of pain changes over time. We purposely sampled individuals diagnosed after 1995, and thus the results may not generalize to all MS people who were diagnosed earlier. Additionally, people with the higher

pain values might have been reluctant to participate in this study. The EDSS scores were not recorded on the day of testing; instead, they were taken from subjects' medical charts during the last medical visit. Another limitation of this study was the self-reporting nature of pain measures, so the scores could be subject to memory distortion, recall bias, and response shift. What is more, participants may not have been able to differentiate between MS-related pain and pain resulting from other reasons.

Results of this study help us to better understand and characterize the experience of pain among people with MS. Comprehensive and accurate assessment of pain in MS would be essential to improve its treatment. Inadequate treatment of pain is an important public health problem, and can precipitate a progression to chronic pain. Additionally, as pain has repeatedly been found to be a strong predictor of activity limitation and participation restriction, the assessment of it should be performed as early as possible. Identification of the predictors of pain is also important for both health professionals and researchers. Another foreseeable contribution of this research could be related to the better understanding of the symptoms of persons with New MS.

Large and longitudinal studies are needed in order to see how the course and severity of MS pain change over time. The identification of factors that diminish or trigger pain is important for clinicians as well, since it facilitates the development of targeted rehabilitative intervention to reduce pain. Research studies that compare the effects of pain on functioning in comparison to other MS symptoms are necessary too as their results would help clinicians to choose the priorities of treating these symptoms in persons with MS.

5.5 CONCLUSION

Results of the current study indicates that pain is a common symptom among people with MS. Pain presence was predicted by MS disability and fatigue, while pain severity was mainly predicted by MS disability. The results of this study also showed that pain was associated with higher levels of depression, anxiety, sleep problems and cognitive deficit, and lower levels of general health perception, ability to work, and physical function. The considerable impact of pain on patients highlights the importance of identifying adequate intervention to manage pain in MS.

5.6 REFERENCES

Archibald CJ, McGrath PJ, Ritvo PG. Pain prevalence, severity and impact in a clinic sample of multiple sclerosis patients, Pain. 1994; 58: 89–93.

Beeson PB. Age and sex associations of 40 autoimmune diseases. Am J Med 1994; 96(5):457-9.

Beiske AG, Pedersen ED, Czujko B, Myhr KM. Pain and sensory complaints in multiple sclerosis. Eur J Neurol 2004; 11: 479 - 82.

Bjelland I, Dahl AA, Haug TT, Neckelmann D,: The validity of the Hospital Anxiety and Depression Scale; an updated review. J Psychiat Res 2002, 52:69-77

Brazier JE, Harper R, Jones NM, O'Cathain A, Thomas KJ, Usherwood T, Westlake L. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. BMJ 1992; 305:160-164.

Brunet DG, Hopman WM, Singer MA, Edgar CM, MacKenzie TA Measurement of health-related quality of life in multiple sclerosis patients. The Canadian Journal of Neurological Sciences. Le Journal Canadien des Sciences Neurologiques 1996, 23(2):99-103.

Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989; 28(2):193-213.

Clifford DB, Trotter JL. Pain in multiple sclerosis. Arch Neurol 1984; 41:1270–2.

Compston A, Confavreux C, Lassmann H. McAlpine's Multiple Sclerosis. Philadelphia: Elsevier, 2005.

Douglas C, Wollin JA, Windsor C. Illness and demographic correlates of chronic pain among a community-based sample of people with multiple sclerosis. Arch Phys Med Rehabil 2008; 89:1923-32.

Ehde DM, Gibbons LE, Chwastiak L, Bombardier CH, Sullivan MD, Kraft GH. Chronic pain in a large community sample of persons with multiple sclerosis. Mult Scler 2003; 9: 605–11.

Ehde DM, Osborne TL, Hanley MA, Jensen MP, Kraft GH. The scope and nature of pain in persons with multiple sclerosis. Mult Scler. 2006; 12: 629–38.

Ehde DM, Osborne TL, Jensen MP. Chronic Pain in Persons with Multiple Sclerosis. Physical Medicine and Rehabilitation Clinics of North America. 2005; 16: 503-512.

EuroQoL Group. EuroQoL- A new facility for the measurement of health- related quality of life. Health Policy 1990; 16: 199-208.

Forbes Angus, While Alison, Mathes Lucia& Griffiths Peter. Health problems and health-related quality of life in people with multiple sclerosis. Clinical Rehabilitation 2006; 20: 67-78.

Freeman, J.A., Hobart, J.C., Langdon, D.W., & Thompson, A.J. Clinical appropriateness: A key factor in outcome measure selection: the 36 item short form health survey in multiple sclerosis. Journal of Neurology and Neurosurgery 2000; 68, 150-156.

Goodin DS. Survey of multiple sclerosis in northern California. Northern California MS Stud y Group. Mult Scler 1999; 5: 78-88.

Grasso MG, Clemenzi A, Tonini A, Pace L. Pain in multiple sclerosis: a clinical and instrumental approach. Mult Scler 2008; 14: 506 -13.

Hadjimichael O, Kerns RD, Rizzo MA, Cutter G, Vollmer T. Persistent pain and uncomfortable sensations in persons with multiple sclerosis. Pain 2007; 127:35–41.

Hays Ron D, Morales Leo S. The RAND-36 measure of health- related quality of life. *Ann Med* 2001; 33:350-7.

Heckman-Stone C, Stone C: Pain management tech-niques used by patients with multiple sclerosis. J Pain 2:205-208, 2001.

Hermann C: International experience with the Hospital Anxiety and Depression Scale A review of validation data and clinical results. J Psychosom Res 1997, 42:17-41

Honarmand K, and Feinstein A. Validation of the Hospital Anxiety and Depression Scale for use with multiple sclerosis patients. Multiple Sclerosis; 2009 15(12): 1518–1524.

Hopman W.M, Towheed T, Anastassiades T, Tenenhouse A, Poliquin S. Canadian normative data for the SF-36 health survey. *Canadian Medicine Association Journal* 2000; 163 (3) 265- 71.

Indaco A, Iachetta C, Nappi C, Socci L, Carrieri PB: Chronic and acute pain syndromes in patients with multiple sclerosis. Acta Neurol Scand 16:97-102, 1994

Jensen MP, Karoly P, Braver S. The measurement of clinical pain intensity: a comparison of six methods. Pain 1986; 27:117-126.

Jensen MP, Karoly P, Harris P. Assessing the affective component of chronic pain: development of the Pain Discomfort Scale. J Psychosom Res 1991; 35:149-154.

Jensen MP, Turner JA, Romano JM, et al. Comparative reliability and validity of chronic pain intensity measures. Pain. 1999;83: 157–162.

Julian L, Vella L, Vollmer T, Hadjimichael O, Mohr DC. Employment in multiple sclerosis. Exiting and re-entering the work force. J Neurol. 2008; 255:1354-60.

Kalia LV, O'Connor PW. Severity of chronic pain and its relationship to quality of life in multiple sclerosis. Mult Scler 2005; 11:322–7.

Kassirer MR, Osterberg DH (1987). Pain in multiple sclerosis. Am J Nurs 87:968–969.

Katz JN, Larson MG, Phillips CB, Fossel AH, Liang MH. Comparative measurement sensitivity of short and longer health status instruments. Medical Care 1992; 30:917-925.

Khan F, Pallant J. Chronic Pain in Multiple Sclerosis: Prevalence, Characteristics, and Impact on Quality of Life in an Australian Community Cohort. The Journal of Pain 2007; 8 (8): 614-623.

Kieseier BC, Hartung HP. Current disease: modifying therapies in multiple sclerosis. Semin eurol 2003 June; 23(2):133:46.

Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1983; 33(11): 1444–1452.

Kuspinar A, Andersen RE, Teng SY, Asano M, Mayo NE. Predicting exercise capacity through submaximal fitness tests in persons with multiple sclerosis. *Arch Phys Med Rehabil* 2010; 91 (9):1410-7.

Leary S, Thompson A. Current management of multiple sclerosis. Int J Clin Pract. 2000;54:161–169.

Lovera J, Bagert B, Smoot KH, Wild K, Frank R, Bogardus K, Oken BS, Whitham RH, Bourdette DN. Correlations of Perceived Deficits Questionnaire of Multiple Sclerosis Quality of Life Inventory with Beck Depression Inventory and neuropsychological tests. J Rehabil Res Dev. 2006 Jan-Feb; 43(1):73-82.

Margolis RB, Chibnall JT, Tait RC. Test-retest reliability of the pain drawing instrument. Pain 1988; 33: 49- 51.

Margolis RB, Tait RC, Krause SJ. A rating system for use with patient pain drawings. Pain 1986; 24: 57-65.

Marrie RA, Miller DM, Chelune GJ, Cohen JA. Validity and reliability of the MSQLI in cognitively impaired patients with multiple sclerosis. Mult Scler 2003; 9(6):621-6.

Massimo Filippi, Rohit Bakshi, Marco Rovaris, Giancarlo Comi. MRI and Multiple Sclerosis: What Happened in the Last 10 Years? Journal of Neuroimagaing 2007; 17:1S:2S.

Mayo N. Setting the agenda for multiple sclerosis rehabilitation research. Mult Scler 2008; 14(9):1154:6.

McHorney CA, Ware JE, Jr., Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. A psychometric and clinical test of validity in measuring physical and mental health constructs. Medical Care 1993; 31:247-263.

Melzack R. The McGill Pain Questionnaire. In: Melzack R, ed. Pain measurement and assessment. New York: Raven, 1983:41-47.

Melzack R. The short-form McGill Pain Questionnaire. Pain 1987; 30:191-197.

Moulin DE, Foley KM, Ebers GC: Pain syndromes in multiple sclerosis. Neurology 38:1830-1834, 1988

Moulin DE: Pain in central and peripheral demyelinating disorders. Neurol Clin 16:889-897, 1998

Multiple Sclerosis Society of Canada. MS Information- Frequently Asked Questions. www.mssociety.ca/en/information/faq.htm? Version current at April 13, 2007.

Murphy DF, McDonald A, Power C, Unwin A, MacSullivan R. Measurement of pain: a comparison of the Visual Analogue Scale with a Nonvisual Analogue Scale. Clin J Pain 1988; 3:197-199.

Nortvedt M, Riise T, Myhr K, et al. Quality of life in multiple sclerosis: measuring the disease effects more. Neurology 1999;53:1098–103.

Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG. Multiple sclerosis. N Engl J Med. 2000; 343: 938–52.

O'Brien, 2003, online article, http : // www. Pubmedcenteral. Nih. Gov/ articlerender. Fcgi?art ID=201004.

O'Connor Alec B; Schwid Steven R; Herrmann D N. Pain associated with multiple sclerosis: Systematic review and proposed classification. Pain 137 (2008) 96–111.

O'Connor P. Key issues in the diagnosis and treatment of multiple sclerosis: An overview. Neurology 2009; 59: S1-33.

Orlewska E, Mierzejewski P, Zaborski J. A prospective study of the financial costs of multiple sclerosis at different stages of the disease. Eur J Neurol 2005; 12:31-9.
Orton SM, Herrera BM, Yee IM et al. Sex ratio of multiple sclerosis in Canada: a longitudinal study. Lancet Neurol 2006; 5(11):932-936.

Piwko C, Desjardins OB, Bereza BG, et al. Pain due to multiple sclerosis: Analysis of the prevalence and economic burden in Canada. Pain Res Manage 2007; 12:259-265.

Pollman W, Feneberg W, Steinbrecher A, Haupts M, Henze T. Therapy of pain syndromes in multiple sclerosis: An overview with evidence-based recommendations. Fortschr Neurol Psychiatr 2005; 73:268-85.

Rae-Grant AD, Eckert NJ, Bartz S, Reed JF. Sensory symptoms of multiple sclerosis: a hidden reservoir of morbidity. Mult Scler 1999; 5: 179 – 83.

Ramagopalan S (2010a). Genes and Environmental Factors in Multiple Sclerosis.vol. 16, 259-259.

Ramagopalan SV, Byrnes JK, Orton S-M et al. (2010b). Sex ratio of multiple sclerosis and clinical phenotype. EUROPEAN JOURNAL OF NEUROLOGY vol. 17, 10.1111/j.1468-1331.2009.02850.x

Richards RG, Sampson FC, Beard SM, Tappenden P. A review of the natural history and epidemiology of multiple sclerosis: implications for resource allocation and health economic models. Health Technol Assess 2002; 6:1-73.

Rizzo MA. Treatment of pain, paresthesias, and paroxysmal disorders in multiple sclerosis. In: Cohen JA,

Rudick RA, editors. Multiple sclerosis therapeutics. 2nd ed. London and New York: Martin Dunitz; 2003.

Serlin RC, Mendoza TR, Nakamura Y, Eduards KR, Cleeland CS. When is cancer pain mild, moderate or severe? Grading pain severity by its interference with function. Pain 1995; 61:277-84.

Shahrbanian Sh, Auais M; Duquette P; Anderson K; Mayo N. E. Does Pain in Individuals with Multiple Sclerosis Affect Employment? A Systematic Review and Meta-analysis. Submitted in July 2012 to the Journal of Pain Research and Management. 2013

Sharrack B, Hughes RA, Soudain S, Dunn G. The psychometric properties of clinical rating scales used in multiple sclerosis. Brain. 1999 Jan; 122 (Pt 1):141-59.

Shevil E, Finlayson M. Perceptions of persons with multiple sclerosis on cognitive changes and their impact on daily life. Disabil Rehabil 2006 June 30; 28(12):779-88.

Solaro C, Brichetto G, Amato MP, Cocco E, Colombo B, D'Aleo A. The prevalence of pain in multiple sclerosis: a multicenter cross-sectional study. Neurology 2004; 63:919–21.

Spadoni G F, Stratford P, Solomon P. E, Wishart L. The Evaluation of Change in Pain Intensity: A Comparison of the P4 and Single-Item Numeric Pain Rating Scales. J Orthop Sports Phys Ther 2004; 34 (4):187-192.

Stenager E, Knudsen L, Jensen K: Acute and chronic pain syndromes in multiple sclerosis. Acta Neurol Scand 84:197-200, 1991

Sullivan MJL, Edgley K, Mikail S, et al. Psychological correlates of health care utilization in chronic illness. Can J Rehabil 1992; 6:13–21.

Svendsen KB, Jensen TS, Hansen HJ, Bach FW. Sensory function and quality of life in patients with multiple sclerosis and pain. Pain 2005; 114:473–8.

Svendsen KB, Jensen TS, Overvad K, Hansen HJ, KochHenriksen N, Bach FW. Pain in patients with multiple sclerosis. Arch Neurol 2003, 60:1089–1094.

Van Agt HME, Essink-Bot ML, Krabbe PFM, Bonsel GJ. Test-retest reliability of health state valuations collected with the EuroQol questionnaire. Social Science Medicine. 1994; 39(11): 1537-1544.

Vermote R, Ketelaer P, Carton H. Pain in multiple sclerosis patients: a prospective study using the McGill pain questionnaire. Clin Neurol Neurosurg 1986; 88:87–93.

Warnell P. The pain experience of a multiple sclerosis population: a descriptive study. Axon 1991; 13: 26–8.

White LJ, Dressendorfer RH. Exercise and multiple sclerosis. Sports Med 2004; 34(15):1077:100.

Victor TW, Jensen MP, Gammaitoni AR, Gould EM, White RE, Galer BS. The dimensions of pain quality: factor analysis of the Pain Quality Assessment Scale. Clin J Pain 2008; 24(6):550-5.

Wilson CR, VoorhisV, Morgan BL. Understanding Power and Rules of Thumb for Determining Sample Sizes. Tutorials in Quantitative Methods for Psychology 2007, 3 (2): 43-50.

Wilson M. Overcoming the challenges of neuropathic pain. Nursing Standard 2002; 16, 33, 47-53.

Table 5.1 Classification of Statistical analyses by types of variables

Predictor Variables / **Dependent variables**		**Categorical / Continuous**	
		Sufficient numbers in each cell (>5)	Insufficient numbers in each cell (<5)
Pain presence *Categorical*	*Dichotomous* Presence=1 Absence =0	Multiple dichotomous logistic regression	Exact logistic regression
Pain severity *Categorical*	*Ordinal/nominal* 0-10 Numeric Rating Scale	Multiple ordinal logistic regression	Exact logistic regression

Table 5.2 Characteristics of study participants with a comparison of pain and pain free groups

Variables	Total sample (n=188)	Pain group (n=78)	Pain free group (n=110)	P value
Current age ($\bar{x}$± SD)	43 ± 10	44 ± 10	42 ± 10	*0.6
Gender N (%)				**0.04
Women	139(74)	66 (35)	73(39)	
Men	49(26)	15(8)	34(18)	
Education N (%)				***0.4
Primary school	2(1)	1(0.5)	1(0.5)	
High school	41(22)	22(12)	19(10)	
College	56(30)	23(12)	33(18)	
University	85(46)	32(17)	53(29)	
None	1(0.5)	0	1(0.5)	
Employment N (%)				**0.0002
Employed	119(64)	38(20)	81(44)	
No employed	64(35)	39(21)	25(14)	
Smoking status, N (%)				**0.3
Regularly	38(20)	20(11)	18(10)	
Irregularly	10(5)	5(3)	5(3)	
Non smoker	140(75)	56(30)	84(45)	
Years since diagnosis ($\bar{x}$±SD)	3±4	3 ± 5	3 ± 3.5	*0.9
Years since symptom onset ($\bar{x}$± SD)	9 ± 5	9 ± 5	9± 5	*0.9
Disability, EDSS (Median± SD)	2.4±2	3 ± 2	2 ± 2	*0.0001
DMT, N (%)				*0.6
Yes	110(85)	47(36)	63(49)	
No	20(15)	10(7.5)	(7.5)	
MS subtype, N (%)				***0.03
Relapsing-Remitting	97(78)	43(35)	54(43)	
Secondary progressive	7(5)	4(3)	3(2)	
Primary progressive	8(7)	2(2)	6(5)	
Primary relapsing	3(3)	2(2)	1(1)	
Clinically isolated syndrome	9(7)	0	9(7)	
Pain impact				
Sleep disorders (PSQI: $\bar{x}$± SD)	6.5±1.5	6.7±1.5	7.4±1.6	*0.4
Physical function (PFI- RAND-36: $\bar{x}$± SD)	68±31	57±32	76±28	*<.0001
Perceived health status (EQ-VAS: $\bar{x}$± SD)	73±17	66±19	78±13	*<.0001
Explanatory variables				
Fatigue (VIT- RAND-36: $\bar{x}$± SD)	49.5±20	41±20	56±19	*<.0001
Cognitive impairment (PDQ: $\bar{x}$± SD)	24 ± 15	29 ± 14	20 ± 14	*<.0001
Depression (HADS: $\bar{x}$± SD)	4 ± 4	5.3 ± 4	3.4 ± 4	*0.001
Anxiety (HADS: $\bar{x}$± SD)	5 ± 4	6 ± 4	4.6 ± 3.6	*0.008

$\bar{x}$± SD, mean± standard deviation; N, number; DMT, disease modifying therapy; PSQI= Pittsburgh Sleep Quality Index; PFI= physical function subscale of RAND-36; EQVAS, EuroQol Visual Analogue Scale; VITA- RAND-36= Vitality scale of RAND -36; PDQ, Perceived Deficits Questionnaire; HADS, Hospital Anxiety and Depression Scale

* T-test; ** Chi square; *** Fisher test

Table 5.3 Pain characteristics of study participants

Pain characteristics	N	%
Pain quality		
Deep	17	25
Superficial	23	34
Both	24	36
Pain type		
Neuropathic	25	37
Non neuropathic	9	13
Both	29	43
Number of pain sites		
1-5	26	39
6-10	24	36
11-15	7	10
16-20	10	15
Pain variability		
Constant	35	45
Comes and goes	43	55
Pain duration		
Minutes	7	16
Hours	25	55
Days	10	22
Weeks	3	7
Pain frequency		
At least once a day	23	50
2-3 times a week	10	22
Weekly	6	13
Monthly	1	2
Irregularly	6	13
Pain management		
Medication	40	51
Non-pharmacologic	2	2
Both	13	17
None	23	30

Table 5.4 Pain location

Location	Frequency	Location	Frequency
Leg pain			
Thigh		**Back pain**	
Anterior/ Posterior	**61 / 25**	Lower back	**28**
Left/ Right	**45/30**	Upper back	**21**
Leg			
Anterior/ Posterior	**52 / 33**	**Shoulder**	
Left/ Right	**46/39**	Left/ Right	**20/18**
Foot			
Forefoot/ Hind foot	**45 / 23**	**Head**	
Left/ Right	**36/32**	Right/ left	**21/ 14**
Arm pain		Anterior / Posterior	**13/ 12**
Hand			
Palm / Back	**35/ 15**	**Pelvic region**	**21**
Left/ Right	**24/ 26**		
Lower arm		**Neck**	**19**
Anterior/ Posterior	**26/ 15**		
Left/ Right	**21/ 20**	**Abdomen**	**14**
Upper arm			
Anterior/ Posterior	**19/ 15**	**Chest**	**3**
Left/ Right	**19/ 15**		

Table 5. 5 Pain management techniques used by participants

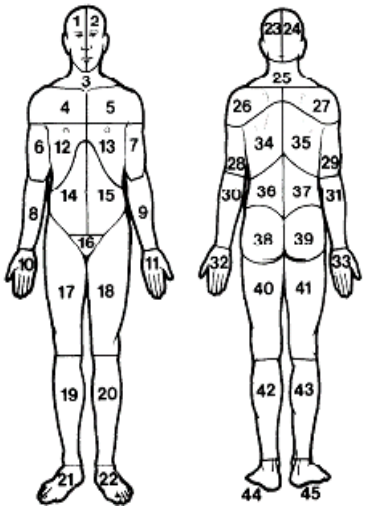
Pain management techniques	N
Medications	
Analgesics	
Opioid	30
Nonopioid	6
Antidepressants	16
Anticonvulsants	6
Anti-inflammatories	8
Spasmolytics	6
Non-pharmacological Techniques	
Massage	6
Tai-chi	4
Pilate	1
Osteopathy	1
Homeopathy	2
Physiotherapy	1
Thermotherapy (hot/ cold)	2
Relaxation	1
Whirlpool (hydrotherapy)	1

Table 5.6 Logistic regression model for pain presence and severity

Parameter	Parameter estimate	Standard coefficient*	P value	Odd ratio
Pain presence				
Fatigue (RAND-36)	-0.03	-0.6	0.0001	0.96
MS severity (EDSS)	0.2	0.4	0.03	1.2
Pain severity				
MS severity (EDSS)	0.4	0.8	0.001	1.4

*Standardized coefficient = Parameter estimate x 1 Standard Deviation of each predictor

45 anatomical areas of pain drawing



Percentage values for body areas

Area numbers	Percent
25, 26, 27	0.50
4, 5, 16	1 .00
3, 8, 9 10, 11, 30, 31, 32, 33	1.50
1, 2, 21,22, 23, 24.44, 45	1.75
6, 7, 12, 13, 28, 29, 36, 37	2.00
38, 39	2.50
14.15	3.00
19. 20.42,43	3.50
34.35	4.00
17,18,40,41	4.75

Figure 5.1 Margolis drawing rating system (Margolis 1986)

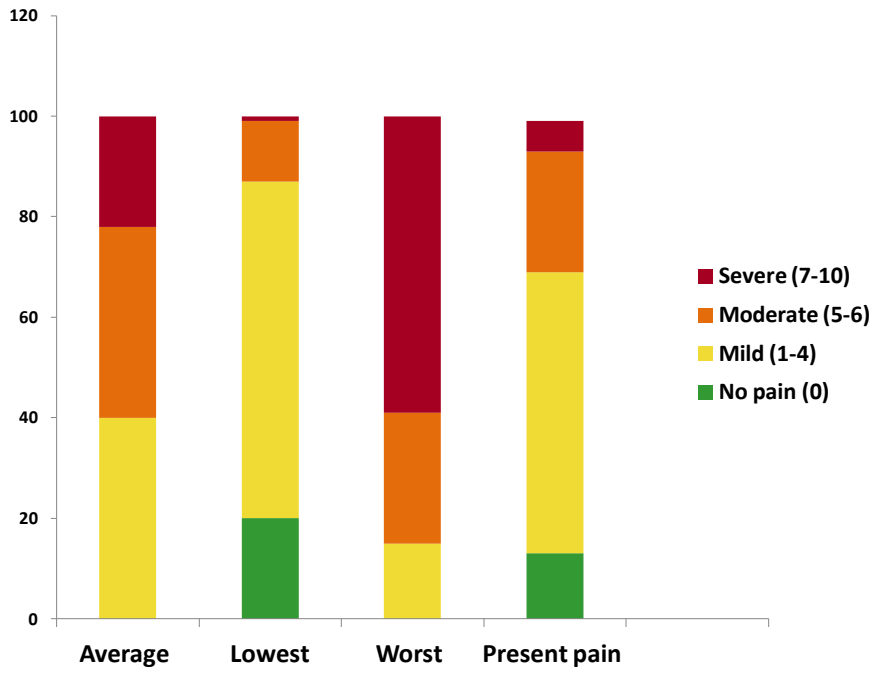


Figure 5.2 Distribution of pain severity scores within past week (0-10 NRS)

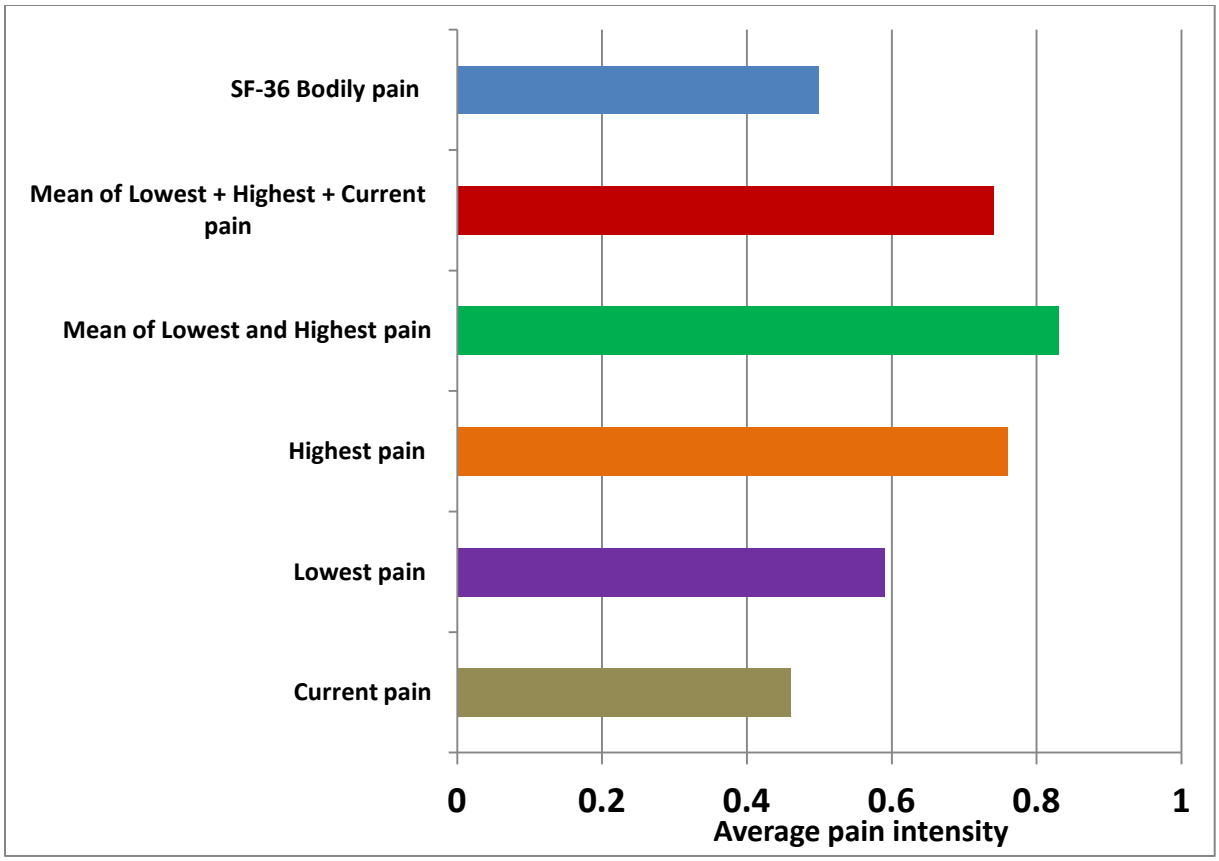


Figure 5.3 Correlation between average pain severity and pain variables

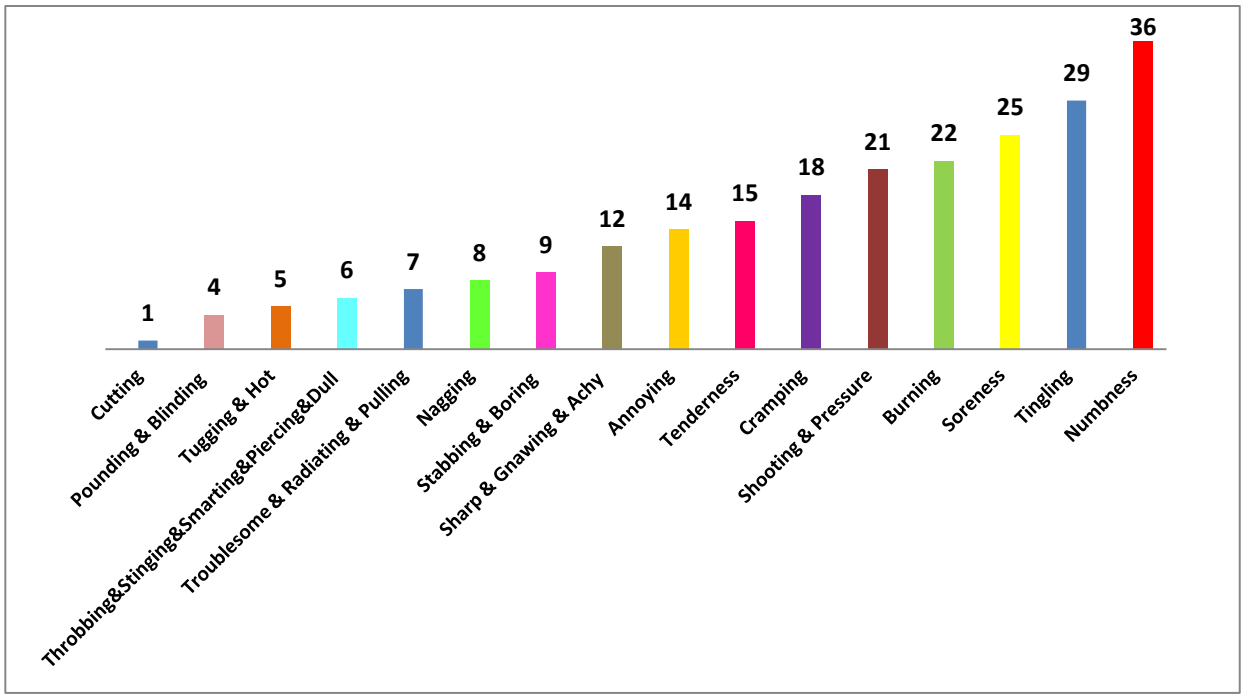


Figure 5.4 The participants' descriptions of their abnormal sensation using the words from the McGill Pain Questionnaire

CHAPTER 6: Integration of Manuscripts 2 and 3

4.1 Research questions of manuscript 2 and 3

Manuscript 2:

Looking at Pain in multiple sclerosis: Prevalence, severity, frequency, duration, quality, location, distribution, type, impact, and predictors

Manuscript 3:

Long-term stability of pain type and severity among people with multiple sclerosis

4.2 Integration of Manuscripts 2 and 3

Pain is a prevalent problem among persons with MS which may develop either as a direct result of the disease itself, characterized as neuropathic pain (NP) due to demyelination of the nerves, or it may be secondary to the protracted symptoms of MS due to abnormal posture or spasm of the spinal musculature. Pain is a major contributor to activity limitations and restrictions in societal and family roles, so the accurate and comprehensive assessment of different aspects of pain would be an essential component to rehabilitation of persons with MS.

In the second manuscript, looking at pain in MS, we characterized pain in an epidemiologically sampled group of community dwelling individuals with MS. Participants who experienced pain were asked about the most common pain dimensions targeted in clinical and research work, such as pain intensity, frequency, duration, location, distribution, and impact. Additionally, pain assessment included additional dimensions of pain such as quality and type that often are not the focus of the majority of studies on pain in MS.

While working on results of Manuscript 2, we noted that pain measures pointed to a cluster of individuals whose pain symptomatology was an indicative of NP. NP is the most common form of pain in MS. Individuals with MS may also experience abnormal sensations such as tingling, burning, itching, prickling, or shooting which are correlated to the presence of signs of neuropathy. In the clinical setting, distinguishing whether pain is neuropathic or not has therapeutic relevance as different types of pain may respond differently to certain type of

medications or treatment approaches due to the different underlying mechanism involved in pain process.

Despite advances in pain management, the accurate assessment of the NP continues to be a challenging task to both researchers and clinicians. Although several scales are currently available to assess the NP construct, the best way to assess it still remains controversial, and such tools are not routinely used in primary care settings. In the second manuscript we used the pain descriptors from McGill Pain Questionnaire (MPQ) to classify quality and type of pain. MPQ can't provide the best assessment in patients with NP as it was not primarily developed to distinguish neuropathic pain from non-neuropathic. So we postulated that a simple valid specific screening tool for a diagnosis of NP as differentiated from non NP would capture the NP experience more successfully and accurately than a generic pain scale.

To further characterize the pain profile of our sample, the third manuscript, therefore, estimated the extent to which there is stability in pain type and pain severity over time. In Manuscript 3, a short pain questionnaire specific for NP, called ID- Pain Questionnaire, was administered to those participants who reported to experience pain in the original study. Additionally, pain severity was measured.

Results of the current study help to better understanding of the natural history of chronic pain among people with MS over time. Additional knowledge on the MS pain fluctuation over time would be useful for providing prognostic information and making treatment decisions. By tracking changes of pain over an extended time period, the natural course of pain could also be examined, a feature that has been relatively ignored in the MS pain literature. This would subsequently improve the development of more effective, comprehensive treatment efforts directed toward enabling individuals with MS to maintain their active life.

CHAPTER 7 (MANUSCRIPT 3)

Long-term stability of pain type and severity among people with multiple sclerosis

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ABSTRACT

Given the impact of pain on the lives of people with Multiple Sclerosis (MS), the diagnosis and treatment of pain have received increasing attention over the past decade, but little is known about change in pain. The main purpose of this manuscript was, therefore, among individuals with MS, to estimate the extent to which pain type and severity change over time. This was a longitudinal study assessing participants' pain type and severity at first assessment and follow-up. A centre-stratified random sample comprising of 139 women and 49 men (N= 188) were recruited from three major MS clinics in Montreal. Type of pain were assessed using short form McGill pain questionnaire (MPQ) and ID-Pain questionnaire (ID-Pain) at first assessment and follow-up, respectively. To measure pain severity 0–10 Numeric Rating Scales (NRS) was used. To compare the agreement on the classification of NP based on the results of MPQ and ID-Pain administered at time 1 and time 2 McNemar test and to measure the agreement between recorded changes in pain type over time, the Cohen's un-weighted Kappa Coefficient were calculated. Paired Student T- test was used to examine if serial ratings of NRS have been stable or change over time. Generalized estimating equation (GEE) was performed to test change in pain severity between the different pain type groups at first assessment and follow up. Results showed that, on average, all ratings of pain severity increased; however, the group-based analysis showed that pain type was stable in the majority of study participants. Results of Kappa test also indicated an agreement between MPQ and ID-Pain. Results of GEE analysis suggested that pain type was a significant predictor of lowest pain severity scores over the follow-up period, while it did not emerge as significant predictors of subsequent pain ratings of worst pain severity. The findings of this study have practical applications for chronic pain management programs. We have argued that because so many factors influence responses on pain measures, a single choice of pain domain measured on a single occasion is likely to be less reliable than serial measures of different domains of pain.

Key words: Multiple Sclerosis, Neuropathic Pain, Pain Change, ID- Pain Questionnaire, Agreement

7.1 INTRODUCTION

Multiple sclerosis (MS) is a chronic, demyelinating immune-mediated disease of the central nervous system (CNS) (Noseworthy 2003, Trapp 2008). MS is recognized as the most common neurologic cause of disability among young adults in North America (Compston 2005). Canada has one of the highest prevalence rates of MS in the world, affecting as many as 240 people per 100,000 (O'Connor 2009). The annual cost of MS has been estimated at $502.3 million in Canada (O'Brien 2003). People with MS experience a variety of symptoms that affect them differently and, even in the same person, change from time to time.

Pain is one of the common symptoms in persons with MS; appearing in almost 50% of individuals at some point in their disease course (Archibald 1994, Ehde 2003, Kalia 2005, Svendsen 2003, 2005). Pain is a complex symptom (Von Korff 2000) and this complexity emphasizes the need for a multidimensional assessment. There is no consensus in the literature about which dimension of pain should be considered. Pain can be defined by intensity, quality, duration, frequency, location, and distribution (Von Korff 2000). However, most studies on pain in MS do not take into account all aspects of this construct; pain intensity, which is only one aspect of the pain experience, is usually the primary focus (Jamison 1991, 2002, Litcher-Kelly 2004, Peters 2000, Vendrig 1997). A comprehensive assessment of different aspects of pain would provide a better understanding of pain characteristics among people with MS and would lead to a more tailored treatment approach.

There are two main types of pain in MS depending on the mechanism producing pain. MS pain can be directly related to MS lesions in the CNS, termed neuropathic pain (NP), or can arise indirectly as a consequence of MS symptoms such as muscle spasms and poor posture, termed non-neuropathic pain (N-NP) (Beiske 2004, O'Connor 2008, Solaro 2006). The damaged nerves can also stimulate a range of abnormal sensations such as numbness, burning, shooting, and stabbing pain which are considered to be as indicators of NP (Boureau 1990). NP is more prevalent and disabling than N-NP in the MS population (Herr 2004, Osterberg 2005). Also there is evidence that the presence and severity of NP are associated with greater interference in a number of important health-related quality of life (HRQL) domains (Jensen 2007).

Pain impacts people both mentally and physically. In comparison to people with MS without pain and to the general population, persons with MS pain report poorer HRQL, poorer overall mental and general health, more social role limitation (Archibald 1994, Murphy 1988, Nortvedt 1999, Svendsen 2005), and more depressive symptoms (Ehde 2005). The results of a systematic review and meta-analysis have indicated that individuals with MS who experience pain are significantly more likely to report a decreased employment rate than individuals with MS who are pain free (Shahrbanian 2013). Moreover, nearly half of persons with MS and pain report that pain interferes with their daily living activities and household work (Ehde 2003), as well as with sleep and enjoyment of life (Hadjimichael 2007). In addition, the cost of six-month burden of MS pain in Canada has been estimated at $80 million (Piwko 2007).

Given the impact of pain on the lives of people with MS, the diagnosis and treatment of pain have received increasing attention over the past decade (Lidgren 2003). However, there are still questions in the literature on pain in MS that remained unanswered. Available data are often limited by methodological and analytical problems; thus, conclusions about MS related pain remain unclear. Nevertheless, pain is very disabling in this population and there are a number of proven modalities for pain reduction which are under utilized by this population.

The majority of MS pain is chronic in nature but it can change from time to time in terms of severity and sensation (Osborne 2007). The accurate assessment of changes in pain over time has become increasingly important in rehabilitation science when interpreting results of clinical studies; however, little is known about pain changes in MS. Pain stability in MS is not a common topic of research and hence it is not adequately understood.

The main purpose of this study, therefore, was among individuals with MS, to estimate the extent to which pain type and severity change over time.

7.2 METHODS

7.2.1 Design

This was a longitudinal study assessing participants' pain type and severity at first assessment and follow-up.

7.2.2 Participants and Procedure

This study was as part of a larger study on Gender Life Impact of MS; previously described (Kuspinar 2010). The target population for this study consisted of all persons with MS, diagnosed since 1995. The available population was all men and women registered at the three major MS clinics in greater Montreal. For the first part of the study, a centre-stratified random sample of 550 persons was drawn, 364 of whom were contacted. From those who were contacted, the first 192 who responded were included. Following exclusion of 3 people with incomplete data, 139 women and 49 men, comprised the study sample. Pain was of interest to this study, but it was not the main focus. Nevertheless, some questions related to pain quality sufficient to identify the presence of symptoms indicative of NP were included. In order to follow-up the pain experience of this sample, after three years of first assessment participants reporting pain at first assessment (n= 78) were re-contacted for our secondary study to answer and complete a questionnaire on pain severity and type; 56 persons agreed to be reinterviewed. Study protocol, measures, and procedures for first assessment and follow up were approved by the ethics committee of each participating hospital; informed consent was obtained.

7.2.3 Measurement

The original study collected relevant sociodemographic and disease-related variables including: MS type, and years since MS diagnosis and symptoms onset. Clinical types of MS recognized at the time of the study included: relapsing remitting (RR), primary progressive (PP), secondary progressive (SP), progressive relapsing (PR), and clinically isolated syndrome (CIS) (Ramagopalan 2010). Persons also were asked to report if they used disease modifying therapy (DMT). The severity of neurological impairment was assessed by the treating neurologists and reported according to the Expanded Disability Status Scale (EDSS), which has become the standard measure for classification of MS related disability, ranging from 0 (no disability) to 10 (maximum disability) (Kurtzke 1983).

Pain type

At first assessment, participants were asked to choose as many as of the words from a list containing 29 of the most common pain sensation descriptors taken from the McGill Pain Questionnaire (MPQ) (Melzack 1983, 1987) as applied to them. Sensations such as tingling,

pricking, itching, numbness, shooting, stabbing, electric shock-like, and burning were considered as NP descriptors (Victor 2008, Wilson 2002). Patients with N-NP were significantly more likely to choose other particular sensory adjectives such as throbbing, gnawing, or grating to describe their pain. The psychometric properties of the MPQ have been well established (Melzack 2001).

For the follow up, we used the ID-Pain Questionnaire (ID-Pain), designed for accurately detecting NP as differentiated from N-NP pain (Portenoy 2006). The development and validation approaches of ID-Pain have been reported (Portenoy 2006). ID-Pain consists of five sensory descriptor items and one item relating to pain in the joints which identifies N-NP; the sum score ranges from -1 to 5, with higher scores suggesting a neuropathic component to the pain (Portenoy 2006).

Pain severity

To measure lowest and worst pain severity over the previous week as well as pain at the time of evaluation we used 0–10 Numeric Rating Scales (NRS), with 0 indicating 'No pain' and 10 indicating 'the most painful sensation imaginable'. NRS is one of most commonly used methods for assessing pain severity (Jensen 1986), and its reliability and validity have been documented (Sharrack 1999). NRS is also strongly associated with other measures of pain severity (Jensen 1986, 1991, 1999) and is responsive to changes in pain treatments (Jensen 1991). NRS was completed at two points in time (first assessment and follow up) to estimate change in pain severity.

7.2.4 Statistical methods

Descriptive statistics were used to characterize the sample. Characteristics of those eligible for the longitudinal component and those participating in this component were compared to those not participating using T-test or Chi square tests depending on the measurement scale of the characteristic being compared.

To determine the stability of the proportion of NP pain type over time among persons with pain at both interviews, we used two approaches.

The first approach was to compare the agreement on the classification of NP based on the results of MPQ and ID-Pain administered at time 1 and time 2. For this analysis, McNemar's test was used to determine if the proportion of participants with NP had significantly changed over time (McNemar 1947). The second approach was a one-by-one comparison of the frequency of the pain quality descriptors from the MPQ that were also included in the ID-Pain using McNemar's test. These included pins and needles (tingling), burning, numbness, and electric shock-like (shooting/ radiating).

To measure the agreement between within-person recorded changes in pain type over time, Cohen's un-weighted Kappa Coefficient was calculated (Carletta 1996). Strength of agreement was interpreted as follows: <0.20 = poor; 0.21 to 0.40 = fair; 0.41 to 0.60 = moderate; 0.61 to 0.80 = good; and 0.81 to 1.00 = very good (Altman 1991). Paired Student t- tests was used to examine if serial ratings of NRS were stable or changed over time.

Longitudinal analysis using generalized estimating equations (GEE) was performed to test change in lowest and worst pain severity between the different pain type groups at first assessment and follow up (Hanley 2003). GEE models are extensions of generalized linear models, where outcomes for each record are not assumed to be independent. Participants were categorized into five groups according to the presence of NP. The reference group was study participants who did not have NP at either time point. We compared the lowest and worst pain intensity of the reference group with participants who had NP at any time point and well as with more detailed groups of participants who lost their NP at follow up, developed NP at follow up, or had NP at both time points. 95% confidence intervals (CI) which took the correlation due to repeated measures into account were obtained through GEE for all potential determinants of pain severity.

Individuals with missing information from the questionnaire were excluded from specific analyses. Statistical significance was considered reached for p-values less than 0.05. Statistical analyses were performed using the Statistical Analysis Systems (SAS) Version 9.2.

7.3 RESULTS

Of the 78 participants who reported pain in the original study, 56 persons (72%) agreed to participate in the second phase of the study. Socio-demographic and clinical characteristics of participants and nonparticipants are presented in Table 7.1. There was no significant difference between responders and non-responders on age, sex, MS severity, date of diagnosis, and duration of symptoms. The sample consisted of substantially more women than men, and they showed mild disability with a median EDSS score of 3. In addition, about half of the sample worked at the time of evaluation.

Table 7.2 summarizes pain characteristics of the study participants. Overall, the result of McNemar's test for comparison between pain type from MPQ and ID-Pain was not significant (p value= 0.44), indicating that there was no difference between type of pain over time (Table 7. 2). Results of Kappa test also indicated that there was an agreement between MPQ and ID-Pain (Kappa = 0.50).

The participants' descriptions of their abnormal sensations using the words from the MPQ and ID-Pain are detailed in Table 7.2. The words most frequently used were numbness, tingling, burning and shooting, indicating that NP was the most commonly reported type of pain. As it is presented in Table 7.2, the McNemar's test statistic revealed no significant difference in the proportions of specific NP quality descriptors from MPQ and ID-Pain at first assessment and follow up.

The mean values of participants' responses to the global pain severity scales are also summarized in Table 7.2. Results of paired t-test on serial measure of NRS showed that on average all ratings have been increased, though only for lowest pain this difference was statistically significant.

Table 7.3 presents the comparison of pain severity measured by NRS across different patterns of pain type over time. Interestingly, a descriptive analysis of the NRS scores revealed discrepancies between change in pain type and the numerical change in pain severity scores. In comparison to reference group (participants who did not have NP at any time point), participants

who had NP at any time point showed the highest increases in the current, lowest, and worst pain severity scores.

Results of a GEE analysis suggest that pain type is a significant predictor of lowest pain severity scores over the follow-up period ($P<0.05$). Participants with NP at either time point had lowest pain intensity score 1.5 points higher than those without NP (CI 95%: 0.68-2.3). In contrast, when modeled, type of pain did not emerge as a significant predictor of worst pain rating. A detailed presentation of these effects is shown in Table 7.4.

7.4 DISCUSSION

This study assessed the change in pain type and severity over time among a sample of individuals with MS. Results of serial measures of NRS showed that, on average, all ratings of pain severity increased, however, only lowest pain showed the significant increase. The group-based analysis showed that pain type was stable in the majority of study participants. This result is expected as there is no evidence in the literature suggesting that type of pain is associated with MS duration or MS progression (Archibald 1994, Indaco 1994, Kerns 2000, Moulin 1998, Stenager 1991). On the other hand, the relationship between pain severity with MS duration has been shown previously (Ehde 2003, 2006, Hadjimichael 2007, Osborne 2007, Solaro 2004). These findings suggest that with time, people with MS can expect an increase in pain severity.

Consistent with previous studies (Beiske 2004, Kalia 2005, Moulin 1998, Vermote 1986), the results of our work confirm that NP is more common than N-NP in MS population. This emphasizes the need for adequate pain investigation, something that is still a challenging task to both researchers and clinicians (Jensen 2006) as there are no universally accepted diagnostic criteria for NP. Although, using the questionnaires have the advantage as they are fast and easy to administer, we acknowledge that a more accurate diagnosis needs to be based on patient history, physical examination, and functional neuro-imaging (Cruccu 2004, Herr 2004).

Although because of small sample size of study there would have been so little power to find strong conclusion, using GEE analysis, we found that everyone who had NP at any time point, had their lowest pain severity significantly higher than those who never had NP, while worst pain

severity was not affected by type of pain. Having high lowest pain intensity is likely to be debilitating as the person is always in a state of pain.

This study had several strengths. It assessed stability over time in pain type and severity which is often not assessed in MS pain literature. The present study was also the first to evaluate the predictive influence of neuropathic type of pain on pain rating over a period of three years in people with MS. In addition, the study sample is representative of the population living with MS in Canada. The ratio of women to men participants in our original study was 3:1, representative of gender differences in MS populations. In addition, the present sample was randomly selected from three MS clinics in different areas of greater Montreal from populations who were culturally diverse and includes the full range of disease severity and type. However, as we only included persons diagnosed with MS since 1995, we acknowledge this recruitment criteria may under represent symptoms and other functioning status in our sample. Since 1995, advances in neuro-imaging techniques such as magnetic resonance imaging (MRI) and DMT have facilitated earlier diagnosis of disease and reduced the speed of disease progression; thus, those people with MS diagnosed since 1995 may differ slightly from populations of people diagnosed with MS prior to 1995 (Mayo 2008).

As with any study, this project has limitations that should be considered when interpreting the results. First, although results of previous studies support the idea that using pain verbal descriptors can be the easiest and most reliable way to discriminate NP from N-NP (Dubuisson 1976, Boureau 1990, Hallström 2011, Melzack 1992), it should be acknowledged that due to overlap in descriptors of NP and N-NP, patients may report spontaneous abnormal sensations of both types of pain (Herr 2004) that make it difficult to accurately discriminate pain types. Second, different measures were used to identify type of pain over time. The MPQ that was used at first assessment, while an established measure for assessing NP, was not primarily developed to distinguish NP from N-NP. Therefore, at follow up, in order to ensure that we accurately characterized pain type of this sample, we administered the ID- Pain questionnaire which is capable of accurately screening for a diagnosis of NP as differentiated from N-NP (Padua 2013, Portenoy 2006). In addition, while the MPQ includes a broad range of pain descriptors that are irrelevant or not required, the ID-Pain's items capture directly the sensations related to NP, thus

making it more contextually relevant. Using different scales to measure same constructs could provide a caution when interpreting the results; the change in pain may be related to use of different measures. Nevertheless, the use of both general and specific screening tools is warranted to ensure that the NP experience is captured accurately. Third, bias may have been introduced by the EDSS scores, as they were not recorded on the day of testing; instead, they were taken from subjects' medical charts as recorded at the last medical visit. Finally, sample size for assessing the stability of pain was small.

By tracking changes in pain over time, the natural history and the dynamic nature of pain can be examined, a feature that has been relatively ignored in the MS pain literature. Additional knowledge about MS pain fluctuations over time would be useful for making treatment decisions and providing prognostic information as well. Given that pain is a frequent symptom in MS, a systematic assessment of pain experience would help healthcare providers and clinicians to identify changes in the progression of disease itself. This would subsequently improve the development of more effective, comprehensive treatment efforts directed toward enabling individuals with MS to maintain their active life.

Findings from the current study provide useful information to help health care professionals, clinicians, and researchers to a have a better understanding about NP in MS. In the clinical setting, distinguishing type of pain is essential for its treatment, since each type of pain needs specific treatment approaches according to its underlying mechanism (Moulin 1988). In addition, as NP is often a symptom over which clinicians cannot have significant control, maintaining an awareness of a patient's pain experience, and an appropriate response, can give both patients and clinicians a greater sense of control, and so significant psychological benefits.

As found in other studies (Spadoni 2004, Victor 2008), results of the present study confirm that a single measure of pain severity such as NRS alone, is an inadequate assessment tool as it may not sufficiently represent the construct of pain. Two individuals, who report same amount of pain severity on a NRS, may indicate different pain sensations. This finding has clinical implications. For treatment to be successful, measuring other aspects of pain using valid and reliable measures is necessary.

Little is known about factors that influence the change in type or severity of pain experienced over time. Given that pain is a complex symptom, the perception of and reaction to pain can be affected by many factors. Therefore, pain assessment necessitates a multidimensional approach within a comprehensive biopsychosocial framework including all contributing factors from biological, behavioural, psychological, and social variables to personal and environmental factors. A biopsychosocial model of pain would advance our understanding of some of the variability in individuals' adjustment to chronic pain (Kerns 2000), and should be considered in any assessment of pain treatment efficacy.

7.5 CONCLUSION

The present study examined stability in pain type and severity among individuals with MS. While pain severity increased with time, pain type was stable. The findings of this study have practical applications for chronic pain management programs. We have argued that because so many factors influence responses on pain measures, a single choice of pain domain measured on a single occasion is likely to be less reliable than serial measures of different domains of pain. Observing changes in serial pain measurements increases our understanding about the nature of pain in MS. In addition, considering that pain is distressing and impacts on functioning, a pain management and action plan needs to be as a part of the MS care plan.

7.6 REFERENCES

Altman DG. Practical statistics for medical research. London: Chapman and Hall, 1991.

Archibald CJ, McGrath PJ, Ritvo PG, Fisk JD, Bahn V, Maxner CE, Maxner E, Murray TJ. Pain prevalence, severity, and impact in a clinical sample of multiple sclerosis patients. Pain 1994; 58:89-93.

Beiske AG, Pedersen ED, Czujko B, Myhr KM. Pain and sensory complaints in multiple sclerosis. Eur J Neurol 2004; 11: 479- 82.

Boureau F, Doubrere JF, Luu M. Study of verbal description in neuropathic pain. Pain 1990; 42,145-152.

Carletta, Jean. Assessing agreement on classification tasks: The kappa statistic. Computational Linguistics 1996; 22(2): 249–254.

Compston A, Confavreux C, Lassmann H. McAlpine's Multiple Sclerosis. Philadelphia: Elsevier, 2005.

Cruccu G, Anand P, Attal N, Garcia-Larrea L, Haanpää M, Jorum E, Serra J, Jensen TS. EFNS guidelines on Neuropathic pain assessment. Eur J Neurol 2004; 11:153–62.

Dubuisson D, Melzack R. Classification of clinical pain descriptions by multiple group discriminant analysis. Exp Neurol 1976; 51: 480–7.

Ehde DM, Gibbons LE, Chwastiak L, Bombardier CH, Sullivan MD, Kraft GH. Chronic pain in a large community sample of persons with multiple sclerosis. Mult Scler 2003; 9:605–11.

Ehde DM, Osborne TL, Jensen MP. Chronic Pain in Persons with Multiple Sclerosis. Physical Medicine and Rehabilitation Clinics of North America 2005; 16: 503-512.

Ehde DM, Osborne TL, Hanley MA, Jensen MP, Kraft GH. The scope and nature of pain in persons with multiple sclerosis. Mult Scler 2006; 12:629–38.

Hadjimichael O, Kerns RD, Rizzo MA, Cutter G, Vollmer T. Persistent pain and uncomfortable sensations in persons with multiple sclerosis. Pain 2007; 127:35–41.

Hallström H, Norrbrink C. Screening tools for neuropathic pain: can they be of use in individuals with spinal cordinjury? Pain 2011; 152 (4):772-9.

Hanley JA, Negassa A, Edwardes MD, Forrester JE. Statistical Analysis of Correlated Data Using Generalized Estimating Equations: An Orientation. Am J Epidemiol 2003; 157:364- 375.

Herr K. Neuropathic pain: a guide to comprehensive assessment. Pain Manag Nurs. 2004; 5 (4 Suppl 1): 9-18.

Indaco A, Iachetta C, Nappi C, Socci L, Carrieri PB. Chronic and acute pain syndromes in patients with multiple sclerosis. Acta Neurol Scand 1994; 16:97-102.

Jamison R.N, Brown G.K. Validation of hourly pain intensity profiles with chronic pain patients. Pain 1991; 45: 123-128.

Jensen MP, Karoly P, Braver S. The measurement of clinical pain intensity: a comparison of six methods. Pain 1986; 27:117-126.

Jensen MP, Karoly P, Harris P. Assessing the affective component of chronic pain: development of the Pain Discomfort Scale. J Psychosom Res 1991; 35:149-154.

Jensen MP, Turner JA, Romano JM, et al. Comparative reliability and validity of chronic pain intensity measures. Pain 1999; 83: 157–162.

Jensen MP. Review of Measures of Neuropathic Pain. Current Pain and Headache Reports 2006, 10:159–166.

Jensen MP, Chodroff MJ, Dworkin RH. The impact of neuropathic pain on health-related quality of life: Review and implications. Neurology 2007; 68; 1178-1182.

Kalia LV, O'Connor PW. Severity of chronic pain and its relationship to quality of life in multiple sclerosis. Mult Scler 2005; 11:322–7.

Kerns R. Psychosocial aspects of pain. Int J Mult Scler Care 2000; 2(4):35-38.

Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983; 33(11): 1444–1452.

Kuspinar A, Andersen R, Mayo NE. Predicting Exercise Capacity through SubMaximal Fitness Testing in Persons with Multiple Sclerosis. Arch Phys Med Rehabil 2010; 91:1410-7.

Lidgren L. The bone and joint decade IASP 2000-2010. Bulletin of the World Health Organization, 81 (9) (2003), p. 629.

Litcher-Kelly L, Stone AA, Broderick Joan E, Schwartz Joseph E. Associations among pain intensity, sensory characteristics, affective qualities, and activity limitations in patients with chronic pain: A momentary, within-person perspective. The Journal of Pain 2004; (5) 8: 433-439.

Mayo N. Setting the agenda for multiple sclerosis rehabilitation research. Mult Scler 2008; 14(9):1154:6.

McNemar Quinn. Note on the sampling error of the difference between correlated proportions or percentages. Psychometrika 1947, 12 (2): 153-157.

Melzack R, eds. Handbook of Pain Assessment. 2nd ed. New York: Guilford Press; 2001:15–34.

Melzack R, Katz J. The McGill Pain Questionnaire: appraisal and current status. In: Turk DC. New York: The Guilford Press; 1992. p. 152–68.

Melzack R. The McGill Pain Questionnaire. In: Melzack R, ed. Pain measurement and assessment. New York: Raven, 1983:41-47.

Melzack R. The short-form McGill Pain Questionnaire. Pain 1987; 30:191-197.

Moulin DE, Foley KM, Ebers GC. Pain syndromes in multiple sclerosis. Neurology 1998; 12: 1830-34.

Murphy DF, McDonald A, Power C, Unwin A, MacSullivan R. Measurement of pain: a comparison of the Visual Analogue Scale with a Nonvisual Analogue Scale. Clin J Pain 1988; 3:197-199.

Nortvedt M, Riise T, Myhr K, et al. Quality of life in multiple sclerosis: measuring the disease effects more. Neurology 1999; 53:1098–103.

Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG. Multiple sclerosis. N Engl J Med. 2000; 343: 938–52.

O'Brien JA, Ward AJ, Patrick AR, Caro J. Cost of managing an episode of relapse in multiple sclerosis in the United States. BMC Health Serv Res. 2003 Sep 2; 3(1):17.

O'Connor Alec B; Schwid Steven R; Herrmann D N. Pain associated with multiple sclerosis: Systematic review and proposed classification. Pain 2008; 137: 96–111.

O'Connor P. Key issues in the diagnosis and treatment of multiple sclerosis: An overview. Neurology 2009; 59: S1-33.

Osborne TL, Jensen MP, Ehde DM, Hanley MA, Kraft G. Psychosocial factors associated with pain intensity, pain-related interference, and psychological functioning in persons with multiple sclerosis and pain. Pain 2007; 127(1-2):52-62.

Osterberg A, Boivie J, Thuomas KA. Central pain in multiple sclerosis- prevalence and clinical characteristics. Eur J Pain 2005; 9(5):531-42.

Padua L, Briani C, Truini A, Aprile I, Bouhassirà D, Cruccu G, Consistence and discrepancy of neuropathic pain screening tools DN4 and ID-Pain. Neurol Sci 2013; 34(3):373-7.

Peters M.L, Sorbi M.J, Kruise D.A, Kerssens J.J, Verhaak P.F.M, Bensing J.M. Electronic diary assessment of pain, disability and psychological adaptation in patients differing in duration of pain. Pain 2000; 84: 181–192.

Piwko C, Desjardins OB, Bereza BG, et al. Pain due to multiple sclerosis: Analysis of the prevalence and economic burden in Canada. Pain Res Manage 2007; 12:259-265.

Portenoy R. Development and testing of a neuropathic pain screening questionnaire: ID Pain. Curr Med Res Opin 2006; 22: 1555–1565.

Ramagopalan SV, Byrnes JK, Orton S-M et al. Sex ratio of multiple sclerosis and clinical phenotype. European Journal of Neurology 2010 (17), 10.1111/j.1468-1331.2009.02850.x

Shahrbanian Sh; Auais M; Duquette P; Andersen K; Mayo N. E. Does Pain in Individuals with Multiple Sclerosis Affect Employment? A Systematic Review and Meta-analysis. Journal of Pain Research and Management 2013; 18 (5): e94-e100.

Sharrack B, Hughes RA, Soudain S, Dunn G. The psychometric properties of clinical rating scales used in multiple sclerosis. Brain 1999; 122 (Pt 1):141-59.

Solaro C, Brichetto G, Amato MP, Cocco E, Colombo B, D'Aleo A. The prevalence of pain in multiple sclerosis: a multicenter cross-sectional study. Neurology 2004; 63:919–21.

Spadoni G F, Stratford P, Solomon P. E, Wishart L. The Evaluation of Change in Pain Intensity: A Comparison of the P4 and Single-Item Numeric Pain Rating Scales. J Orthop Sports Phys Ther 2004; 34 (4):187-192.

Stenager E, Knudsen L, Jensen K. Acute and chronic pain syndromes in multiple sclerosis. Acta Neurol Scand 1991; 84:197-200.

Svendsen KB, Jensen SJ, Overvad K, Hansen HJ, Kock-Henriksen N, Back FW. Pain in patients with multiple sclerosis. Arch Neurol 2003; 60:1089–1094.

Svendsen KB, Jensen TS, Hansen HJ, Bach FW. Sensory function and quality of life in patients with multiple sclerosis and pain. Pain 2005; 114:473–8.

Trapp BD, Nave KA. Multiple Sclerosis: An immune or neurodegenerative Disorder? Annu Rev Neurosci 2008; 31:247-269.

Vendrig A.A, Lousberg R. Within-person relationships among pain intensity, mood and physical activity in chronic pain: A naturalistic approach. Pain 1997; 73: 71–76.

Vermote R, Ketelaer P, Carton H. Pain in multiple sclerosis patients: a prospective study using the McGill pain questionnaire. Clin Neurol Neurosurg 1986; 88:87–93.

Victor TW, Jensen MP, Gammaitoni AR, Gould EM, White RE, Galer BS. The dimensions of pain quality: factor analysis of the Pain Quality Assessment Scale. Clin J Pain 2008; 24(6):550-5.

Von Korff M, Jensen MP, Karoly P. Assessing global pain severity by self-reports in clinical and health services research. Spine 2000; 25:3140–3151.

Wilson M. Overcoming the challenges of neuropathic pain. Nursing Standard 2002; 16, 33, 47-53.

Table 7.1 Characteristics of the sample at first assessment

Variables	Pain full sample at recruitment (n=78)	Participated in the follow up (n=56)	Not participated (n=22)	P value*
Age	44 ± 9.9	45 ± 9.8	43 ± 8.2	0.2
Gender				
Women	63 (81)	46 (82)	17 (77)	0.2
Men	15 (19)	10 (18)	5 (23)	
MS type				
Relapsing-Remitting	41 (84)	26 (81)	13 (86)	0.1
Secondary progressive	4 (8)	3 (9)	1 (7)	0.5
Primary progressive	2 (4)	2 (6)	1 (7)	0.7
Primary relapsing	2 (4)	1 (3)	0	0.2
Years since diagnosis	2.9 ± 4.9	3 ± 4.4	2.4 ± 5.9	0.07
Years since symptom onset	8.8 ± 5.3	8.8 ± 5.1	9.7 ± 5.9	0.09
MS severity (EDSS: median)	3	3	2.5	0.3
Disease modifying therapy				
Yes	68 (82.5)	49 (83)	14 (87)	0.3
Employed				
Yes	38 (48.7)	26 (46.4)	10 (45)	0.5

Mean ± SD or N (%)

*Participants and nonparticipants' characteristics were compared using t-test or Chi square test depending on the measurement scale of the characteristic compared.

Table 7.2 Comparison of pain severity and pain type over time

Variables	Pain full sample, at recruitment (n=78)	Pain at recruitment among those with follow-up (n=56)	Pain at follow-up (n=56)	P value*
Pain Severity, NRS: $\bar{x} \pm SD$				
Lowest Pain	2.2 ± 2	2.2 ± 1.7	3.3 ± 2	0.0006
Worst Pain	6.8 ± 2	7 ± 2	7.5 ± 1.9	0.1
Current Pain	3.3±2.3	3.3±2.2	3.7 ± 2.6	0.3
Type of pain, f (%)				
Neuropathic	25 (37)	20 (36)	16 (30)	0.44
Non- neuropathic	9 (13)	10 (18)	11 (20)	
Pain quality descriptors, f (%)				
Pin and needles: f (%)	29 (37)	30 (44)	26 (46)	0.2
Burning: f (%)	22 (29)	23 (34)	30 (56)	0.06
Numbness: f (%)	36 (46)	38 (56)	38 (68)	0.37
Electric shock: f (%)	21 (27)	25 (37)	18 (32)	0.4

*Paired t- test for pain severity; McNemar test for pain type and pain quality descriptors
NRS= 0-10 Numerical Rating Scale
Pain type and frequency of pain quality descriptors were determined using the McGill Pain Questionnaire at first assessment and ID-Pain Questionnaire at follow up.

Table7.3 Comparison of pain severity measured by NRS across different groups of pain type (N=56)

Type of pain			First assessment			Follow up			First assessment difference*			Follow up difference*		
First assessment	Follow up	Number	Current	Lowest	Worst	Current	Lowest	Worst	Current	Lowest	Worst	Current	Lowest	Worst
Stable														
Mixed	Mixed	14	2.9±2.2	1.7±1.4	7.9±1.8	3.5±2.6	2.8±1.6	8±1.5	0.6	0.9	1.4	0.7	0.8	1.9
NP	NP	13	4.1±2.2	2.6±1.7	7.4±1.8	3.7±3.4	4.4±2.7	7.9±1.6	1.8	1.8	0.9	0.9	2.2	1.8
N-NP	N-NP	6	2.3±2.7	0.8±1	6.5±3	2.8±2.3	2±1.8	6.1±2.7						
Change														
NP	Mixed	12	3.6±2.2	2.7±1.5	6.4±1.4	4.9±1.8	3.8±1.7	7.2±1.9	1.3	1.9	-0.1	2.1	1.8	1.1
Mixed	N-NP	5	3.5±1.6	2.7±2.7	6.5±1.9	2.4±2.3	2.4±1.8	5.6±1.7	1.2	1.9	0	-0.4	0.4	-0.5
N-NP	Mixed+ Y	4	3.4± 0.8	3±0.5	7.3±1.8	3.5±0.8	3.3±0.5	9.5±0.5	1.1	2.2	0.8	0.7	1.3	3.4
Mixed	NP	2	4±2.8	4±1.4	8	7	3±1.4	8.5±0.7	1.7	3.2	1.5	4.2	1	2.4

NP= Participants with neuropathic pain
N-NP= Participants with non-neuropathic
Mixed= Participants with both neuropathic and non-neuropathic pain
NRS= 0-10 Numerical Rating Scale
* In comparison to reference group (participants who did not have NP at any time point)

Table 7.4 The effect of NP at any time on lowest and worst pain intensity over time

Variable	Sample size	Effect*	95% CI
Lower pain intensity			
All pain type groups			
No NP at any time	6	Referent	
Any NP at any time	50	1.5	0.68- 2.3
Post hoc models			
No NP at any time	6	Referent	
Lost NP at follow up	5	1.13	-0.5- 2.8
Developed NP at follow up	4	1.08	-0.43-2.6
NP at both times	41	1.59	0.74-2.4
Worst pain intensity			
All pain type groups			
No NP at any time	6	Referent	
Any NP at any time	50	1.1	-0.78-3
Post hoc models			
No NP at any time	6	Referent	
Lost NP at follow up	5	-0.3	-2.5-1.9
Developed NP at follow up	4	1.66	-0.8-4.2
NP at both times	41	1.2	-0.6-3

NP= Neuropathic pain

Time= two time points: first assessment and follow up

*GEE: Generalized Estimating Equations

CHAPTER 8: Integration of Manuscripts 3 and 4

4.1 Research questions of Manuscript 3 and 4
Manuscript 3:

Long-term stability of pain type and severity among people with multiple sclerosis

Manuscript 4:

Contribution of symptom clusters to MS consequences

4.2 Integration of Manuscripts 3 and 4

Pain is a frequent health problem in persons with MS. A comprehensive and adequate assessment of different aspects of pain is a first step in treatment of pain and an essential component to rehabilitation. The global aim of this thesis is to determine the effect of pain on participation using a conceptual framework and complex analysis method. Naturally then, the first step is to understand the target population, specifically, we first needed to have deep insight into their pain. The second and third manuscript, therefore, provided an overall picture on pain of our sample of community dwelling individuals with MS. In Manuscript 3, we further characterized the pain profile in the MS population; the particular objective was to estimate stability in type and pain severity over time.

Individuals with MS experience a broad array of symptoms that impact significantly on different aspects of their life. Thus the next step is to know more about the nature and amount of the association between pain and other MS symptoms and consequences. This topic will be covered in the fourth manuscript, and the results will provide useful information to help health care professionals, clinicians, and researchers to recognize symptoms clusters in MS. It will be seen that target symptoms often occur together in the same cluster when one or two of them are present. This would be very helpful in providing us with new insights on the identification of priorities in selected appropriate intervention approaches regarded to be as more helpful for the MS population. Therefore, in the next chapter, we want to know to what extent different MS-related symptoms, including pain, cluster. We further want to know the contribution of symptom clusters to MS consequences.

CHAPTER 9 (MANUSCRIPT 4)

Contribution of symptom clusters to MS consequences

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ABSTRACT

Objective: There were two objectives of this study: (i) to identify, among women and men with MS, the extent to which different MS-related symptoms, including fatigue, pain, sleep disturbance, depression, anxiety, irritability, cognitive impairment, spasticity, and poor balance, cluster; and (ii) to compare the contribution of generated symptom clusters to MS consequences including functional walking capacity, perceived health, illness intrusiveness, and quality of life.

Methods: This was a cross sectional study. A centre-stratified random sample comprising 139 women and 49 men were recruited from three major MS clinics in Montreal, Canada. Measures of pain and fatigue were from the RAND-36. Anxiety and depression were measured by the Hospital Anxiety and Depression Scale. To assess cognitive impairments Perceived Deficits Questionnaire, to measure spasticity Modified Ashworth Scale, to examine irritability, irritability questionnaire, to assess balance EQUI scale, and to estimate sleep disturbance, a modified version of the Pittsburgh Sleep Quality Index was used. Functional walking capacity, perceived health status, illness intrusiveness, and quality of life were measured using the six-minute-walk test, EuroQol Visual Analogue Scale, Illness Intrusiveness Ratings Scale, and Patient Generated Index, respectively.

Results: Three symptom clusters were identified. Cluster 1, labeled the "emotional/cognitive symptom cluster", comprised of depression, anxiety, cognitive impairments, and irritability. The second cluster, labeled the "physical symptom cluster", included pain, fatigue, and sleep disorders. Cluster 3, labeled the "motor symptom cluster", included spasticity, and poor balance. Furthermore, the motor symptom cluster had a strong effect on functional walking capacity, while it did not affect illness intrusiveness and quality of life. On the other hand, the physical symptom clusters and emotional/ cognitive symptom clusters showed a significant contribution to prediction of illness intrusiveness and quality of life. All symptom clusters showed a significant effect in predicting the overall variability of perceived health status.

Conclusion: The findings of the current study provided preliminary results for considering contribution of symptom clusters to disease consequences in persons with MS.

9.1 INTRODUCTION

Multiple sclerosis (MS) is a chronic, inflammatory autoimmune demyelinating disease of the central nervous system (CNS) (Noseworthy 2000). The exact cause of MS is not known, but scientists believe that infection, genetics, environment, and viruses play a role (Compston 2005, Ramagopalan 2010a). In most persons, MS begins between the ages of 20 and 40 (Beeson 1994) and the condition is seen more frequently in women than in men (Orton 2006, Ramagopalan 2010b). Canada has one of the highest prevalence rates of MS in the world, affecting as many as 240 people per 100,000 (O'Connor 2009).

MS symptoms can be either a direct result of disease itself, or related to treatments (Lublin 1996). Symptoms of MS affect people differently and, even in the same person, change from time to time. Fatigue is extremely common in people with MS, with a prevalence of 78%-91% (Fisk 1994, Ford 1998). Pain is also a frequent complaint among persons with MS, appearing in almost 50% of persons at some point of their disease course (Archibald 1994, Ehde 2003, Kalia 2005, Svendsen 2003, 2005). Sleep disturbance is another common symptom, occurring in approximately 54% to 60% of the MS population (Bamer 2008, Brass 2010, Stanton 2006, Tachibana 1994). In addition, approximately 48% to 80% of people with MS report problems with balance at some stage during the course of their disease (Grytten 2006). Leg spasms and stiffness have been reported by 40% to 70% of individuals with MS (Leussink 2012). The prevalence of memory and concentration problems, other frequent symptoms in people with MS, ranges from 30% to 70% and can present in persons at any time during their disease process (Rao 1991, Teng 2009). Emotional changes are also common in individuals with MS and are thought to be related to either a normal response to having a serious health condition or the result of damage to the nervous system. The reported prevalence of depression for people with MS has ranged from 40% to 50% (Feinstein 2002). Other symptoms of psychological distress such as anxiety and irritability also affect a large percentage of individuals with MS and often co-occur with depressive symptoms (Bamer 2008, Mohr 2007).

The majority of MS studies are focused on a single symptom and its related prevalence, assessment, and management (Newland 2012). However, symptoms of MS often occur concurrently (D'Alisa 2006, Lovera 2006, Newland 2012). For example, symptoms of fatigue,

depression and pain often appear together (DeLuca 2006, Krupp 2004, Motl 2010). In addition, sleep disturbance, pain and depression can contribute to fatigue (Krupp 2004, Motl 2010), and pain and fatigue are the primary factors that produce sleep disturbance, muscle spasm, and cognitive impairment (DeLuca 2006). However, sleep disturbance often occurs in association with psychological symptoms such as depression or anxiety (Lerdal 2007). Fatigue also occurs in close relationship to depression (Bakhshi 2003). Symptoms such as fatigue, mood disorders, and cognitive impairment may affect pain as well (Kerns 2002, O'Connor 2008).

Two (Kim 2008) or more (Dodd 2001, Mcsweney 2010, Miaskowski 2004, 2006, Motl 2009a) symptoms that are related to each other and occur together are defined as a symptom cluster. The relationships among symptoms are complex, and can be either a real relationship (common etiology mechanism) or a statistical association via a shared common variance (Dodd 2001, Miaskowski 2004, 2006). Symptom clusters of pain, fatigue, and depression (Motl 2009b) as well as poor sleep quality, perceived cognitive dysfunction, fatigue, pain, and depression have been identified in persons with MS (Motl 2009b, 2010a, Newland 2012). Based on the theory of Unpleasant Symptoms (Lenz 1997, 2003), it is believed that multiple concurrent symptoms, in comparison to a single symptom, have a stronger effect on disease consequences (Dodd 2002, Given 2001, 2002, Motl 2009a, b).

Walking difficulty is a frequent disease consequence in more than 75% of persons with MS (Pearson 2004). In persons with MS, reduced walking capacity is related, either alone or in combination, to MS symptoms such as muscle weakness and spasm, poor balance, fatigue, pain, and depression (Motl 2006, 2008a, 2008b, Snook 2008). Diminished perceived health, which is defined as individuals' perception about their general health and well-being, is another frequent disease consequence among individuals with MS and has been found to be associated with the presence and severity of MS symptoms such as muscle weakness, pain, and fatigue (Parkin 2004). Due to the impact of MS on symptoms, activities of daily living, and health perception, MS is one of the more intrusive illnesses, affecting lifestyle, plans for the future, activities, and interests (Devins 1993, 1994, 1996, 2001). Literature on illness intrusiveness in MS is very limited. The few available studies showed that an increased perceived lifestyle disruption is associated with poor sleep quality, psychological distress (Mullins 2001), and mental health

(Turpin 2007). Illness severity, disability, and fatigue have also been found to significantly predict greater illness intrusiveness in MS (Culp 2010). As a result of the psychological and physical challenges confronted by people with MS they rate their quality of life (QOL) lower than healthy peers. Physical disability, fatigue, depression, cognitive impairment, muscle weakness, poor coordination, gait disturbance, and disease severity and duration have been found to be associated with poor QOL among MS persons (Amato 2001, Benedict 2005, Benito-Leon 2002, Egner 2003, Janssens 2003, Miller 2003, O' Connor 2001).

Symptom clusters have been investigated broadly in other clinical conditions such as cancer (Esper 2005, Wilmoth 2004), brain tumors (Armstrong 2004), and heart disease (Dodd 2001; Gift 2003, 2004). A search of the MS literature using the term "symptom cluster" provided only a few citations of cluster analyses (Drew 2008, Motl 2009a, b, 2010a, b, Newland 2012, Nocentini 2006). The majority of studies on MS and symptom clusters has examined the clusters of pain- depression- fatigue, and sometimes sleep disturbance, and cognitive impairment. However, the existence and composition of many of MS-related symptoms such as balance, spasticity, anxiety, and irritability across the symptom clusters still remains unanswered. In addition, some of the previous studies on symptom clusters in MS used small samples of convenience (Newland 2012), and a single statistical approach.

There were two objectives of this study: (i) to identify, among women and men with MS, the extent to which different MS-related symptoms, including fatigue, pain, sleep disturbance, depression, anxiety, irritability, cognitive impairment, spasticity, and poor balance, cluster; and (ii) compare the contribution of generated symptom clusters to MS consequences including functional walking capacity, perceived health, illness intrusiveness, and QOL.

9.2 METHODS

9.2.1 Participants

The target population was all persons with MS, diagnosed since 1995. Available population was all men and women registered at the three major MS clinics in greater Montreal including: Montreal Neurological Hospital (MNH), Centre Hospitalier de l'Université de Montréal (CHUM), and Clinique Neuro Rive-Sud (CNRS). To ensure that people from each area were

included, the time frame was stratified into 3 eras: 1995 to 1999, 2000 to 2004 and 2005 to 2006. The number of persons with MS diagnosed since 1995 were 1000, 200, and 750 for the clinics at MNH, CHUM, and CNRS, respectively (N= 1950). A centre-stratified random sample of 550 persons was drawn, of which 364 were contacted. From those who were contacted, the first 188 who responded (139 women and 49 men) shaped the study sample population. Eligibility was based on diagnosis of MS or Clinically Isolated Syndrome (CIS) since 1995. In addition, participants had to be older than 18 years old. Participants with severe cognitive impairments and pre-existing health conditions affecting functionality, such as cancer, heart disease, arthritis and malignancy, were excluded from participating in the study. Subjects who had a relapse in the preceding month were excluded from participating in the study as well. Further, persons were not eligible if they were unable to understand either English or French.

9.2.2 Measures

Study protocol, measures, and procedures were approved by the ethics committee of each participating hospital; informed consent was obtained and signed by all subjects on the day of testing**.** A research coordinator later contacted the candidates to verify if they met the eligibility criteria, and invited them to participate if they did. If persons consented to participate, an appointment was arranged for assessment of study measures. If they refused to participate, socio-demographic and clinical information were collected. All of the measures chosen for the purpose of this study have been used in the MS population, adequately representing the components of the underlying construct. Table 1 outlines the measurement strategy, study variables and their related constructs, units, and scales.

9.2.2.1 Socio-demographics characteristics

Socio- demographic factors of gender, age, weight, and employment status were recorded on the day of testing using the socio-demographic questionnaire.

9.2.2.2 Disease-related characteristics

The clinical records of each person were reviewed to obtain data on MS type, years since MS diagnosis, and symptoms onset. Clinical types of MS recognized at the time of the study included: relapsing remitting (RR), primary progressive (PP), secondary progressive (SP),

progressive relapsing (PR), and CIS (Ramagopalan 2010b). Persons also were asked to report if they used disease modifying therapy (DMT). The severity of neurological impairment was assessed by a neurologist based on the Expanded Disability Status Scale (EDSS) which is a widely-used scale to measure the level of disability in persons with MS, and evaluates functioning across eight functional systems; it scores from 0 (no disability), to 10 (maximum disability) (Kurtzke 1983).

9.2.2.3 Symptoms

Pain

The two-item bodily pain subscale (BPS) from RAND -36, a person-reported health related QOL measure (HRQL), was used as a measure of pain severity (Hays 2001). Two items are included in BPS. The first item asks about pain severity during the past 4 weeks, and the second item grades the impact of pain on work and daily activities. These two items are combined into a single composite score and transformed to a 0-100 scale, with lower scores indicating higher levels of pain severity (Hays 2001). Internal consistency of this scale in the MS population has been reported to range from 0.77 to 0.94 (Brunet 1996, Freeman 2000).

Fatigue

The Vitality subscale of RAND -36 was used, which comprised of 4 items asking about the level of energy and feeling of tiredness. Subjects were asked to rate their answers on a 6-point Likert scale ranging from 1 ‘all of the time’ to 6 ‘None of the time’ (Hays 2001). At the end the four items were combined to produce a sum value for a continuous total raw score from 0 (worst) to 100 (best). Higher score indicates greater energy/ lower fatigue. RAND-36 has been used widely in MS population and its psychometric properties have been provided (McHorney 1993, 1994).

Sleep disorder

To assess sleep disturbance we used a specific sleep questionnaire created from a Rasch analysis of items from the Pittsburgh Sleep Quality Index **(**PSQI) (Buysse 1989). R- PSQI contains 4 items that assess factors affecting sleep quality during the previous month. Total score ranges from 0 to 8, with a higher score indicating worse sleep quality. Reliability and validity of the original questionnaire have been determined (Buysse 1989).

Depression/ Anxiety

The levels of anxiety and depression of persons were measured using the Hospital Anxiety and Depression Scale (HADS) (Zigmond 1983, Herrmann 1997). The HADS has 14 items, 7 of them relate to anxiety and 7 relate to depression. Each item on the questionnaire is scored from 0 'most of the time' to 3 'not at all', and the total score ranges between 0 and 21 for either anxiety or depression (Bjelland 2002). Higher scores indicate worse depression/ anxiety symptoms. The HADS is a reliable and valid tool and has been used in a number of MS studies (Bjelland 2002, Da Silva 2011, Honarmand 2009, Zigmond 1983).

Irritability

Irritability was measured using a specific irritability index created from Rasch analysis of Psychiatric Symptom Index (PSI) (Illfeld 1976) which measures the presence of depressive or anger-related symptoms indicating the need for referral to a mental-health professional. It comprised 4 items each with a 4-point Likert response options ranging from 1 'never' to 4 'very often'. Persons were asked to tell how often, during the past week, they lost their temperature, felt critical of others, felt easily annoyed or irritated, and got angry over things that were not too important. A maximum total score of 16 representing the most irritability.

Cognitive impairment

Cognitive impairment was assessed using the Perceived Deficits Questionnaire (PDQ). The 20-item PDQ is person-reported measure of perceived cognitive deficits developed by Sullivan (1992) specifically for persons with MS. The PDQ items assess frequency of difficulties with attention/concentration, retrospective memory, prospective memory, and planning/organization during the past month on a 5-point Likert scale ranging from 'never' to 'almost always'. PDQ contains 20 items, each score ranging from zero to 4 with a maximum total score of 80, where higher scores indicate greater cognitive impairment (Shevil 2006). The validity and reliability of PDQ in MS persons has been widely accepted (Marrie 2003, Sullivan 1992).

Spasticity

In the current study, spasticity of the lower and upper limbs was assessed using the Modified Ashworth Scale (MAS) (Bohannon 1987), which is a widely used clinical measure of spasticity

in persons with neurological conditions including MS. This scale can be used quickly and easily in the clinical setting for the evaluation of muscle stiffness and spasticity (Pandyan 1999, 2001). The Modified Ashworth Scale assigns grades to a manually determined resistance of muscle (elbow flexors, wrist flexors/ extensors, knee extensors /flexors, ankle dorsi flexors) to passive stretching (Bohannon 1987). For each segment scores range from 0 (no increase in muscle tone) to 5 (affected part rigid in flexion or extension) with a maximum total score of 60 for both sides. Validity and reliability of MAS in a number of MS studies have been examined (Ashworth 1964, Bohannon 1987, Leslie 1992, Nuyens 1994, Pandyan 1999).

Balance

To assess balance we used the EQUI-Scale, which is a MS-specific balance scale and has been created using Rasch modeling from the items of Tinetti Performance Oriented Balance Scale and the Berg Balance Scale (Tesio 1997). The EQUI-Scale has 10 items that are listed in order of difficulty. Each item scores from 0 to 2 with a maximum total score of 20; higher scores indicate better balance skills. The test starts with question number 7. If the participants pass the test, then they go to the next item with a harder level. If they fail, they go back to an easier level. The 10-item version of scale includes questions on sitting/standing, standing with eyes open and closed, standing with eyes closed and head extended, leaning forward while standing, picking up an object from floor, resisting nudges on the sternum, turning around, and tandem stance (Tesio 1997).

9.2.2.4 Disease consequences

Walking capacity

Walking capacity was measured using the Six-Minute Walk Test (6MWT) in which the maximum distance a person can walk over six minute at their own pace is recorded (Butland 1982). In the present study, standardized instructions and encouragement were used (ATS statement 2002). The 6MWT has been used widely in MS population (Savci 2005), and is correlated strongly with EDSS ($r = 0.73$, $P < .0001$), the 12-Item Multiple Sclerosis Walking Scale (MSWS-12; $r = 0.81$, $P < .001$) (Goldman 2007) and the shuttle Walk Test ($r = .68$) (Morales 1999). An excellent test-retest reliability (ICC = 0.96), and inter-rater reliability (ICC= .93) has been reported for the 6MWT (Paltamaa 2005).

Perceived health status

Perceived health status was measured using the EuroQOL Visual Analogue Scale (EQ-VAS) (EuroQol Group 1990). Participants were asked to rate their overall health on 0 to 100 VAS scale, with 0 showing the worst perceived health and 100 showing the best perceived health. VAS has been widely used in research and clinical settings and has several good qualities in terms of practicality, sensitivity, reliability and adaptability (Nortvedt 1999). Good concurrent and discriminative validity has also been demonstrated for the EQ-5D (Dorman 1997, 1999).

Illness intrusiveness

Illness Intrusiveness was measured using the Illness Intrusiveness Ratings Scale, a self-report measure, which determines the ratings of the degree to which one's illness interferes with life domains including health, diet, work, active and passive recreation, financial situation, relationship with spouse, family and others, sex life, self expression/improvement, religious and spiritual expression, and community and civic involvement (Devins 1983). It consists of 13 questions each with a 7-point response option, ranging from 1 'Not very much' to 7 'very much' with a maximum total score that can range from 13 to 91. Higher scores indicate increased illness intrusiveness. The psychometric properties of the scale have been administered across numerous chronic-disease populations including MS (Devins 2001, 2010).

Quality of Life

Person Generated Index (PGI) was used to capture domains affecting QOL. The PGI is an open-ended person-reported disease specific questionnaire that first asks persons to identify areas of their lives affected by MS and its related treatment (Ruta 1994, Lintern 2001). They then rate how much they are affected in each of their chosen areas on a scale of 0-10 where 0 means that they are not affected at all and 10 means they are affected very badly. In the final step they were asked to divide up twelve imaginary tokens among the chosen areas. The points distributed to each area represented the relative importance of that area to the individual. A total score, ranging from 0 to100, was derived by multiplying the figure elicited in stage one with that of stage two for each life domain, and summing the totals. The reliability, validity and responsiveness of the PGI have been assessed (Ahmed 2005, Ruta 1994, 1999, Garratt 1999).

9.2.3 Statistical Analyses

Descriptive statistics (e.g., mean, standard deviations, and frequency) were used to describe the sample and summarize data. The potential for selection bias, differences between responders and non-responders on targeted variables (e.g., socio-demographic and clinical characteristics of persons), was tested using Chi square test for categorical variables, t-test for continuous variables with homogenous variances, and U Mann-Whitney test for continuous variables with non-homogenous variances. Associations between all variables were assessed using Spearman and Pearson correlation coefficients for categorical and continuous variables, respectively.

As higher scores from fatigue, pain, and balance scales indicated better health status, while higher scores obtained from other scales represented a worse health status, scores from fatigue, pain, and balance scales were reversed. As the measurement scale also differed, each variable was transformed into a 0-100 scale. Hierarchical (Centroid, Average, and Ward methods) and non-hierarchical clustering (K-Means) with a Squared Euclidean Distance was used. Additionally, a hierarchical tree diagram, called a dendrogram, and a scree plot were produced to help identify the correct number of clusters. As different statistical methods may produce different symptom clusters, exploratory factor analysis was also carried out for comparison purposes.

As each generated cluster was to be used as a predictor of downstream outcomes, a unique value per person on each symptom cluster was generated as a linear combination of all symptoms inside that particular cluster. This was done using principal component analysis and the weighted score or factor loading for each symptom in a particular cluster was combined to create the symptom cluster latent variable. This cluster was then entered in multiple regression analysis to identify the relative contribution of each cluster latent on the downstream disease consequences including walking capacity, perceived health status, illness intrusiveness, and QOL.

Other predictor variables were all other symptoms, disease severity, weight, sex, and age. Using stepwise multiple regression each predictor variable was entered into the model, and retained or discarded based on their contribution to the overall model (statistical significance at the 0.05, beta estimate, and R square). The standardized coefficient of each predictor was also calculated

by multiplying the standard deviation for the variable by its unstandardized parameter estimate permitting a quantifiable way of identifying which predictor had the largest effect on disease consequences.

There are no rules-of-thumb about the appropriate number of participants in cluster analysis. The only recommendation that has been given concerning sample sizes and variable numbers is to critically question if the dimensionality is not too high for the number of participants to be grouped (Anderberg 1973, Everitt 2001). It is clear that the large numbers of variables require large data sets. Among MS literature, the sample size ranged from 40 participants to 292; the range of variable numbers varied between 3 and 7. Considering that there were 9 symptoms in our analysis, and in most rules-of-thumb criteria 10-20 cases per variable are recommended, a sample size of 188 participants would be suitable for the purpose of this study.

9.3 RESULTS

9.3.1 Descriptive statistics

Response rate was 52% and no significant difference was found between responders (n=188) and non-responders (n = 176) on age, sex, MS severity, date of diagnosis, and duration of symptom. Socio-demographic and clinical characteristics of the sample are presented in Table 2. The ratio of of women to men participants in our study was 3: 1.

Descriptive characteristics of the study variables are presented in Table 3. The mean values of pain severity and fatigue measured by RAND- 36 for the whole sample were lower than age-expected norms of Canadian general population (76/100 and 66/100, respectively) (Hopman 2000). In addition, 14% of the sample reported cognitive impairment as they had scores above 40 on PDQ (0-80), and in the literature a cut-off point score above 40 indicates cognitive impairment (Marrie 2005). Forty percent of the sample reported sleep deficits as they had scores above 4 on R-PSQI (0-8). Additionally, as a cut-off point above 8/21 for anxiety or depression indicates psychological distress (Bjelland 2002), the mean scores of depression (4/21) and anxiety (5/21) scores of our sample indicated no serious depression and anxiety symptoms. Distance walked was 66% of predicted for healthy individuals with the same age, height, and weight (range 400m to 700m) (Enright 2003). Mean rating on perceived health was 73 out of

100, lower that what has been reported for a general Quebec population (mean 80) (Mayo 1997). QOL was rated at 50 out of 100 using the PGI.

Results of correlation analysis among symptoms and outcomes of the study are presented in Table 4. Most of the variables were correlated. However, spasticity, poor balance, and walking capacity were not correlated to anxiety, cognitive deficits, and irritability. Furthermore, it was indicated that among all symptoms, poor balance and spasticity were strongly associated with walking capacity. Fatigue and depression were strongly associated with illness intrusiveness, and moderately with QOL and perceived health.

9.3.2 Cluster analysis on symptoms

As shown in Table 5, 9 symptoms formed 3 symptom clusters which were the same irrespective of the method used to generate clusters (hierarchical and non- hierarchical clustering, and factor analysis. Cluster 1, labeled the emotional/cognitive symptom cluster, comprised depression, anxiety, cognitive impairments, and irritability and. The second cluster, labeled the physical symptom cluster, included pain, fatigue, and sleep disorders. Cluster 3, labeled the motor symptom cluster, included spasticity, and poor balance. Figures 2 and 3 show the resulting dendrogram and scree plot which further confirmed the 3-cluster solution for the study. There were some differences in cluster composition by gender.

9.3.3 Impact of symptom clusters on disease consequences

Results of principal component analyses on each symptom cluster are presented in Table 6. The factor loading coefficient of each symptom shows the importance of that particular symptom for its related cluster. As it is indicated, the factor loadings for the indicators of the symptom cluster latent variable were all sufficiently large. Additionally, all symptoms indicated almost equal weight on their particular cluster, except fatigue that has the greatest factor loading on its related latent cluster.

Table 7 displays the results of multiple linear regression analyses. Considering 6MWT, symptom clusters of spasticity and poor balance were the only clusters that showed a significant strong effect. Gender, MS severity, age, and weight also made a significant contribution to prediction of

the 6MWT ($p<0.05$). The final multiple regression model explained 75% of the variance. The regression coefficients for gender indicated that women, on average, walked 73 meters less than men. In addition, for every unit increase in spasticity and balance problems the distance walked at the 6MWT decreased by 78 meter ($p<.0001$), holding all other variables constant. A difference of 54 meters is considered clinically important (Redelmeier 1997).

All symptom clusters showed significant effect in predicting the overall variability of EQ-VAS; however, the effect of physical symptom clusters was greater than others. MS severity also made a significant contribution to prediction of the perceived health ($p<0.05$). The final multiple regression model explained 50% of the variance in EQ-VAS. The regression results further showed that for every unit increase in MS severity (EDSS), the individual's perception about their health status decreased by 2, holding all other variables constant.

Illness intrusiveness was predicted by physical and emotional/cognitive symptom clusters (Table 7). The final multiple regression model explained 60% of the variance in illness intrusiveness measure. MS severity and age also made a significant contribution to prediction of illness intrusiveness. For every unit increase in MS severity (EDSS) the person's disruption of lifestyle increased by 3, while for every unit increase in age (year), it decreased by 0.4.

Finally, as displayed in Table 7, the results of multiple linear regression analysis on QOL indicated that again physical and emotional/cognitive symptom clusters contributed in predicting the overall QOL. However, physical symptom clusters showed the greater effect. MS severity also made a significant contribution to prediction of the QOL. The final multiple regression model explained only 43% of the variance in PGI. The results of regression results further showed that for every unit increase in MS severity (EDSS), scores of QOL decreased by a multiple of 5.

9.4 DISCUSSION

We conducted this study to determine which MS symptoms are clustered together and to examine the effect of the common concurrent, interrelated symptoms of MS on disease consequences in a sample of persons with MS. Results of both cluster and factor analyses on

symptoms identified 3 symptom clusters. The first cluster (emotional/ cognitive symptom clusters) was made up of depression, anxiety, irritability, and cognitive impairments. Cluster 2 (physical symptom clusters) included pain, fatigue, and sleep disorders; while spasticity, and poor balance made up the third cluster (motor symptom clusters). In addition, this study showed how patterns of women's symptoms clusters were different from men's. Furthermore, the current study indicated that motor symptom cluster had a strong effect on functional walking capacity, while it did not affect illness intrusiveness and QOL. On the other hand, physical symptom clusters and emotional/cognitive symptom clusters showed a significant contribution to prediction of illness intrusiveness and QOL. Results further suggested that all symptom clusters showed significant effect in predicting the overall variability of perceived health status.

An important finding of this study was the confirmation of the existence of symptom clusters of fatigue and pain, and sleep disorders in individuals with MS. This symptom cluster has been identified previously in the MS population (Motl 2009a, b, Newland 2012) and other chronic conditions such as cancer (Fox 2006). These symptoms often co-occur among persons with MS. It is expected that pain and fatigue together may produce sleep disturbance, and poor sleep can also contribute to fatigue. Moreover, they are possibly correlated through common etiology due to the simultaneous damage to axon of nerve fibers across different parts of the CNS (Lublin 2005).

The symptom cluster of fatigue, pain, and depression has also been identified in persons with MS (Motl, 2009b) as they may share a common biologic mechanism related to nerve damage (Lublin 2005, Cleeland 2007). However, in the current study, depression was not placed in the same cluster along with pain and fatigue. This may be partly explained by the greater number of symptoms included in the analysis, especially other psychological symptoms that have a greater association to depression.

Another important finding of this study was the confirmation of the existence of a symptom cluster of emotional and cognitive deficit symptoms in persons with MS. The association between depression and perceived cognitive dysfunction among persons with MS has been reported in the literature (Lovera et al., 2006). These symptoms may also be linked through a

common etiological mechanism based on the sickness behavior or simultaneous occurrence of pathological changes in similar regions of the CNS (Kelley 2003, Motl 2010).

The current study, furthermore, for the first time provided preliminary evidence for the existence of symptom clusters of poor balance and spasticity in individuals with MS, and this is consistent with the finding in persons with cancer (Fox 2006). Symptoms of poor balance and spasticity probably linked through a common etiology related to the inflammatory processes across CNS, or can be secondary to other MS symptoms. For example, muscle weakness, spasm, and stiffness in the legs may produce unsteady gait and walking problems and difficulty with keeping balance.

We further compared the predictability of three symptom clusters as correlates of disease consequences in individuals with MS. Interestingly, findings of the current study suggested that motor symptom cluster with only 2 symptoms, i.e. spasticity and poor balance, showed stronger effect on a particular outcome (such as walking capacity) than a broader cluster with 3 or 4 symptoms. This is linked with the results reported by Motl (2010a) and inconsistent with the Theory of Unpleasant Symptoms that says a greater number of symptom clusters have a stronger impact on an outcome of interest in comparison to a smaller number of symptom clusters (Lenz & Pugh 2003, Lenz 1997). The strong significant effect of motor symptom clusters may be partly explained by nature of the symptoms included in the cluster. Walking capacity, in comparison to other outcomes of the current study, is the only physical consequence of MS, so it should be more affected by synergistic effects of motor symptoms such as balance, leg spasm, and muscle weakness. Another explanation can be related to the greater amount of association between walking capacity with spasticity, and poor balance in comparison to other symptoms. Such findings support consideration of nature and the magnitude of association of symptoms rather than a broadly defined cluster of a higher number of symptoms. Further investigations are needed to examine this finding.

Further findings of the current study suggested that QOL and illness intrusiveness are only affected by emotional/cognitive and physical symptom clusters. These results are acceptable as illness intrusiveness has been found to be associated more with sleep quality, fatigue, psychological distress, and mental health (Culp 2010 Mullins 2001 Turpin 2007). QOL has also

been reported to be correlated with fatigue, pain, depression and cognitive impairments (Amato 2001, Benedict 2005, Benito-Leon 2002, Egner 2003, Janssens 2003, Miller 2003, O' Connor 2001). Previous works on symptom cluster in MS have also shown that symptom clusters of pain, fatigue, and depression as well as symptom clusters of pain, fatigue, depression, poor sleep, and cognitive deficits were associated with diminished QOL (Motl 2009a, b, Newland 2012). Perceived health, however, was affected by all three clusters. This shows that symptoms, despite their nature and severity, all impact persons' well-being and general health perception. Association between diminished perceived health and MS symptoms such as pain and fatigue has been found (Parkin 2004). As both cluster and factor analyses work based on the association between and among symptoms, these results are understandable and are accepted. Interestingly, physical symptom clusters indicated to be the most disabling symptom clusters in our study as it significantly affected all disease consequences except walking capacity. Considering that fatigue is the most distressing symptom of MS, and based on the results of principal component analysis which showed the greatest symptom loading within the physical cluster, this result is not far from our expectations.

To be able to compare the results of our study with other works, we used hierarchical and non-hierarchical clustering as well as explanatory factor analysis. Interestingly, the results of the factor analysis were fully compatible with those of different clustering methods. Using both analytic (Kim & Abraham, 2008) and conceptual (Miaskowski 2006) approaches has been recommended in the literature for identifying a symptom cluster (Motl 2010a). The conceptual approaches suggest using both bivariate correlations and factor analysis for identifying symptom clusters (Miaskowski 2006). It is believed that cluster analysis in comparison to factor analysis may produce clusters with less overlapping (Parkar 2005). Furthermore, cluster analysis is often used when there is no prior hypothesis about which symptoms should be grouped together.

In order to verify if symptom clusters are reproducible across genders, we compared the existence of such symptom clusters among men and women. Although the existence of emotional/cognitive and motor symptom clusters were confirmed across groups, fatigue and sleep disorders were clustered differently. In women, fatigue made a cluster with other psychological symptoms and cognitive deficits rather than pain and sleep disorders. This

association between cognitive impairments, fatigue, and emotional status has already been reported (Marrie 2005). In addition, fatigue and depression have been identified as determinants of perceived cognitive dysfunction (DeLuca 2006). On the other hand, results of cluster analyses on men placed sleep disorders in the same cluster with spasticity and poor balance rather than with pain and fatigue. This difference in the sex symptom cluster compositions might be linked with different synergetic effects of symptoms or underlying mechanisms of symptoms in men and women (Dodd 2001, 2002, Kim 2008, Miaskowski 2004, Mcsweney 2010).

This study provided important information for addressing symptom clusters in MS. While the majority of previous studies on symptom clusters in MS had a small sample size and included mostly women, we believe this is the first application of cluster analysis to gender differences using a well-designed epidemiological study of MS. The sample consisted of substantially more women than men; the ratio of of women to men participants in our study was 3:1, indicating that our sample is representative of gender difference in MS population. The sample of study was randomly selected from three different MS clinics in the greater Montreal area from populations who were culturally diverse and who were living in different areas of the city, including the whole range of disease severity, type, and gender. So we believe it is representative of the general MS population. However, as we included only persons diagnosed for MS after 1995, this sample may not be fully generalizable to MS persons diagnosed before 1995 (Mayo 2008). In addition, while the focus of most previous studies was on limited number of symptoms, we on the other hand considered a broader range of symptoms in our analysis. Additionally, the current study applied suggested both conceptual (Miaskovski 2004, 2006) and statistical (Kim 2008) approaches for creating the symptom cluster (Motl 2010b). Using different analytical methods enhanced the validity of our results and conclusions. Finally we, for the first time, compared the predictability of different clusters on the downstream disease consequences such as walking capacity, illness intrusiveness, perceived health status and QOL.

On the other hand, this study suffered several limitations. First, we examined symptom clusters and their association with several MS consequences using a cross-sectional rather than longitudinal design when subjects were assessed at one point in time. So it was not possible to examine changes in the number and pattern of symptom clusters and their effects on outcomes

over the time. This issue is particularly important in MS because as disease progresses throughout its course, variables contributing to each cluster could be different. Another limitation of this study returns to the EDSS scores that were not recorded on the day of testing; instead, they were taken from subjects' medical charts during the last medical visit. Although in the current study we standardized the data from all included scales using the transformation of each variable into a 0-100 scale, an additional limitation of this study goes to the different symptom dimensions and timeframes of some scales. For instance, as Motl reported in his studies, the pain scale measured pain severity, while the HADS measured the frequency of depression and anxiety symptoms, PSQI assessed factors affecting sleep quality, and PDQ measured the frequency of perceived cognitive impairments (Motl 2009a, b, 2010a, b). Researchers will need to determine which dimensions of a symptom (i.e. presence, severity, distress and duration) are critical for the assessment of a symptom within a symptom cluster.

Results from the current study provided useful information to help health care professionals, clinicians, and researchers to recognize symptom clusters in MS, and target symptoms that are often in the same cluster when one or two of them are present. Another foreseeable contribution of this research could be related to the comparison of the effects of different symptom clusters on various disease consequences. Identification of the strength of the contributions of each symptom cluster to the targeted MS consequences is essential for their improvement as this would further help researchers, clinicians, and professionals to prioritize treatment approaches for the MS population.

There are many questions in the area of symptom clusters that need more research and consideration, for instance: methodological and statistical challenges related to symptom cluster definition, number of symptoms included in the cluster, common etiologies of symptom clusters, degree of correlation among symptoms, the length of time the symptoms occur concurrently, and dimension and severity of symptoms included in a cluster (Kirkova 2011, Dodd 2001, Miaskowski 2004, 2006). An additional area that warrants more investigation is developing valid and reliable multidimensional scales to assess multiple symptoms that frequently occur simultaneously in individuals with MS. Longitudinal studies and randomized controlled trials are also needed to evaluate the change in pattern of clusters over time. Including more symptoms

such as gait speed, vision, and coordination disturbance to the analysis is also suggested. Finally, future efforts also need to examine the validity of these symptom clusters across different MS types, severity, and age.

9.5 CONCLUSION

Overall, our results demonstrate that the symptom cluster of pain, fatigue, and sleep disorders occurs in persons with MS. In addition, depression, anxiety, cognitive impairment, and irritability emerged as a cluster, as did poor balance with spasticity. Furthermore, the findings of the current study provided preliminary results for considering the role of the motor symptom clusters as an independent correlate of functional walking capacity in persons with MS. Moreover, physical symptom clusters indicated to be the most disabling symptom clusters as it affected all other health outcomes except walking capacity. Illness intrusiveness has been affected mostly by the emotional/cognitive symptom cluster, while perceived health status and QOL are mostly affected by physical symptoms. The role of symptoms in MS consequences is an important area of research as it may lead to identification of appropriate and comprehensive intervention approaches that manage adequately symptoms in persons with MS and enhance QOL.

9.6 REFERENCES

Ahmed S, Mayo NE, Wood-Dauphinee S, Hanley JA, Cohen SR. Using the Person Generated Index to evaluate response shift post-stroke. Qual Life Res 2005; 14:2247-2257.

Amato M.P, Ponziani G, Rossi F, Liedl C.L, Stefanile C, Rossi L. Quality of life in multiple sclerosis: the impact of depression, fatigue and disability. Mult Scler 2001; 7: 340–344.

Anderberg, M. R. Cluster Analysis for Applications, 1973, New York: Academic Press, Inc.

Archibald CJ, McGrath PJ, Ritvo PG. Pain prevalence, severity and impact in a clinic sample of multiple sclerosis persons, Pain. 1994; 58: 89–93.

Armstrong TS, Cohen MZ, Eriksen LR, Hickey JV. Symptom clusters in oncology persons and implications for symptom research in people with primary brain tumors. J Nurs Scholarsh 2004; 36: 197-206.

Ashworth B. Preliminary trial of carisoprodal in multiple sclerosis. Practitioner 1964; 192: 540–42.

ATS statement: guidelines for the six-minutewalk test. Am J Respir Crit Care Med2002 July 1;166(1):111-7.

Bakhsi R. Fatigue associated with MS: diagnosis, impact and amangement. Mult Scler 2003; 9 (3):219-27.

Bamer AM, Johnson KL, Amtmann D, Kraft GH. Prevalence of sleep problems in individuals with multiple sclerosis. Mult Scler. 2008; 14(8): 1127–1130.

Beeson PB. Age and sex associations of 40 autoimmune diseases. Am J Med 1994; 96(5):457-9.

Bender CM, Ergyn FS, Rosenzweig MQ, Cohen SM, Sereika SM: Symptom clusters in breas t cancer across 3 phases of the disease. Cancer Nurs 2005; 28:219–225.

Benedict R, Wahlig E, Bakshi R, Fishman I, Munschauer F, Weinstock-Guttman B. Predicting quality of life in multiple sclerosis: accounting for physical disability, fatigue, cognition, mood disorder, personality, and behavior change. Journal of the Neurological Sciences 2005; 231 (1, 2): 29–34.

Benito-Leon J., J.M. Morales, J. Rivera-Navarro. Health-related quality of life and its relationship to cognitive and emotional functioning in multiple sclerosis persons. Eur. J. Neurol 2002; 9: 497–502.

Bjelland I, Dahl AA, Haug TT, Neckelmann D,: The validity of the Hospital Anxiety and Depression Scale; an updated review. J Psychiat Res 2002, 52:69-77.

Bohannon, R. and Smith, M. (1987). "Interrater reliability of a modified Ashworth scale of muscle spasticity." Physical Therapy 67(2): 206-7.

Brass SD, Duquette P, Proulx-Therrien J, Auerbach S. Sleep disorders in persons with multiple sclerosis. Sleep Medicine Reviews 2010, 14: 121–129.

Brunet DG, Hopman WM, Singer MA, Edgar CM, MacKenzie TA Measurement of health-related quality of life in multiple sclerosis persons. The Canadian Journal of Neurological Sciences 1996, 23(2):99-103.

Butland RJA, Pang J, Gross ER, Woodcock AA, Geddes DM. Two-, six- and 12-minute walking tests in respiratory disease. BMJ 1982; 284:1607–1608.

Buysse, D.J., Reynolds, C.F., Monk, T.H., Beman, S.R., & Kupfer, D.J. The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. Psychiatry Research 1989, 28, 193 – 213.

Chen ML, Lin CC: Cancer symptom clusters: a validation study. J Pain Symptom Manage 2007; 34:590–599.

Cleeland CS. Symptom Burden: Multiple Symptoms and Their Impact as Person-Reported Outcomes Cancer and its treatm. J Natl Cancer Inst Monogr 2007; 37: 16 – 21.

Compston A, Confavreux C, Lassmann H. McAlpine's Multiple Sclerosis. Philadelphia: Elsevier, 2005.

Culp D. Illness intrusiveness and sexual satisfaction among women with multiple sclerosis. Master of Arts Thesis in Psychology, Ryerson University, 2010.

D'Alisa, S., Miscio, G., Baudo, S., Simone, A., Tesio, L., & Mauro, A. (2006). Depression is the main determinant of quality of life in multiple sclerosis: A classification-regression (CART) study. Disability, 28(5), 307 Y314.

da Silva A M, Vilhena E, Lopes A, Santos E . Depression and anxiety in a Portuguese MS population: Associations with physical disability and severity of disease. Journal of the Neurological Sciences 2011; 306, Issues (1–2, 15): 66–70.

DeLuca, J. (2006). What we know about cognitive changes in multiple sclerosis. In: N.L. LaRocca & R. Kalb (Eds.), Multiple sclerosis: Understanding the cognitive changes (pp. 17 – 39). New York: Demos Medical Publishing.

Devins GM, Binik YM, Hutchinson TA, Hollomby DJ, Barré PE, Guttmann RD. The Emotional Impact of End-Stage Renal Disease: Importance of Persons' Perceptions of Intrusiveness and Control. The International Journal of Psychiatry in Medicine 1983; 13 (4): 1983-84.

Devins GM, Seland TP, Klein GM, et al. Stability and determinants of psychosocial well-being in multiple sclerosis. Rehabil Psychol 1993; 38: 11-26.

Devins GM. Illness intrusiveness and the psychosocial impact of lifestyle disruptions in chronic life-threatening disease. Adv Ren Repl Ther 1994; 1: 251-263.

Devins GM, Styra R, O'Connor P. Psychosocial impact of illness intrusiveness moderated by age in multiple sclerosis. Psychol Hlth Med 1996; 1: 179-191.

Devins GM, Rene D, Luc P, Colin S. Structure of Lifestyle Disruptions in Chronic Disease: A Confirmatory Factor Analysis of the Illness Intrusiveness Ratings Scale. Medical Care 2001; 39 (10): 1097-1104.

Devins, Gerald M. Using the Illness Intrusiveness Ratings Scale to understand health-related quality of life in chronic disease. Journal of Psychosomatic Research 2010; 68 (6): 591-602.

Dodd, M.J., Miaskowski, C., & Paul, S.M. Symptom clusters and their effect on the functional status of persons with cancer. Oncology Nursing Forum 2001; 28: 465 – 470.

Dodd M, Miaskowski C, West C, et al. The prevalence of symptoms clusters and comorbidities in oncology out-persons. Paper presented at the 27th Oncology Nursing Society's Annual Congress, Washington, DC, 2002.

Dorman PJ, Slattery J, Farrell B, Dennis MS, Sandercock PA. A randomised comparison of the EuroQol and Short Form-36 after stroke. United Kingdom collaborators in the International Stroke Trial. BMJ1997 August 23; 315 (7106):461.

Dorman PJ, Dennis M, Sandercock P. How do scores on the EuroQol relate to scores on the SF-36 after stroke? Stroke1999; 30 (10):2146-51.

Drew M, Tippett L.J, Starkey N.J, Isler R.B. Executive dysfunction and cognitive impairment in a large community-based sample with Multiple Sclerosis from New Zealand: A descriptive study. Archives of Clinical Neuropsychology 2008; 23: 1–19.

Egner A., Phillips V.L., Vora R., Wiggers E. Depression, fatigue, and health-related quality of life among people with advanced multiple sclerosis: results from an exploratory telerehabilitation study. Neurorehabilitation 2003; 18: 125–133.

Ehde DM, Gibbons LE, Chwastiak L, Bombardier CH, Sullivan MD, Kraft GH. Chronic pain in a large community sample of persons with multiple sclerosis. Mult Scler. 2003; 9:605–11.

Enright P. The six-minute walk test. Respiratory care 2003; 48(8):783-5.

Esper P, Heidrich D. Symptom clusters in advanced illness. Semin Oncol Nurs 2005; 21:20-8.

EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. The EuroQol Group. Health Policy 1990 Dec; 16(3):199-208.

Everitt BS, Landau S, Leese M. Cluster analysis. New York: Oxford University Press; 2001.

Feinstein A. An examination of suicidal intent in persons with multiple sclerosis. Neurology 2002; 59:674-8.

Fisk JD, Pontefract A, Ritvo PG, Archibald CJ, Murray TJ. The impact of fatigue on persons with multiple sclerosis. Can J Neurol Sci 1994; 21:9-14.

Ford H, Trigwell P, Johnson M. The nature of fatigue in multiple sclerosis. J Psychosom Res 1998; 45:33–8.

Fox SW, Lyon DE. Symptom clusters and quality of life in survivors of lung cancer. Oncol Nurs Forum 2006; 33:931–936.

Freeman, J.A., Hobart, J.C., Langdon, D.W., & Thompson, A.J. Clinical appropriateness: A key factor in outcome measure selection: the 36 item short form health survey in multiple sclerosis. Journal of Neurology and Neurosurgery 2000, 68: 150-156.

Garratt AM, Ruta DA. The person generated index. In: Joyce CRB, O'Boyle CA, McGee H, eds. Individual quality of life: Approaches to conceptualization and assessment. Amsterdam: Harwood Academic Publishers; 1999; 105-118.

Garrett, M., & Coote, S. Multiple sclerosis and exercise in people with minimal gait impairment—A review. Physical Therapy Reviews 2009, 14, 169 – 180.

Gerald M. DevinsUsing the Illness Intrusiveness Ratings Scale to understand health-related quality of life in chronic disease. Journal of Psychosomatic Research 2010, 68 (6):591–602.

Gift AG, Jablonski A, Stommel M, Given CW. Symptom clusters in elderly persons with lung cancer. Oncol Nurs Forum 2004; 31:202-12.

Gift AG, Stommel M, Jablonski A, Given W. A cluster of symptoms over time in persons with lung cancer. Nurs Res 2003; 52:393-400.

Given C, Given B, Azzouz F, et al. Predictors of pain and fatigue in the year following diagnosis among elderly cancer persons. J Pain Symptom Manage 2001; 6:456-466.

Given B, Given C, McCorkle R, et al. Pain and fatigue management: results of a nursing randomized clinical trial. Oncol Nurs Forum 2002; 29:949-956.

Goldman m, Marrie RA, Cohen JA. Evaluation of Six minutes walk test in MS and healthy population. Mult Scler 2007; 14: 383- 390.

Grytten N, Maseide P. 'When I am together with them I feel more ill.' The stigma of multiple sclerosis experienced in social relationships. Chronic Illn 2006; 2:195-208.

Hays Ron D, Morales Leo S. The RAND-36 measure of health- related quality of life. Ann Med 2001; 33:350-7.

Herrmann C. International experiences with the Hospital Anxiety and Depression Scale-A review of validation data and clinical results. Journal of Psychosomatic Research 1997, 42 (1): 17-41.

Honarmand K, and Feinstein A. Validation of the Hospital Anxiety and Depression Scale for use with multiple sclerosis persons. Multiple Sclerosis; 2009 15(12): 1518–1524.

Hopman W.M, Towheed T, Anastassiades T, Tenenhouse A, Poliquin S. Canadian normative data for the SF-36 health survey. Canadian Medicine Association Journal 2000; 163 (3) 265- 71.

Ilfeld FW Jr. Further validation of a psychiatric symptom index in a normal population. Psychol Rep 1976; 39:1215-1228.

Janssens A.C, van Doorn P.A, de Boer J.B, Kalkers N.F, van der Meche F.G, Passchier J. Anxiety and depression influence the relation between disability status and quality of life in multiple sclerosis. Mult Scler 2003; 9:397–403.

Kalia LV, O'Connor PW. Severity of chronic pain and its relationship to quality of life in multiple sclerosis. Mult Scler2005; 11:322–7.

Kelley KW, Bluthé RM, Dantzer R, Zhou JH, Shen WH, Johnson RW, Broussard SR. Cytokine-induced sickness behavior. Brain Behav Immun. 2003 Feb; 17 Suppl 1:S112-8.

Kerns R, Kassirer M, Otis J. Pain in multiple sclerosis: a biopsychosocial perspective. J Rehabil Res Dev 2002; 39: 225–32.

Kim, H.J., & Abraham, I.L. Statistical approaches to modeling symptom clusters in cancer persons. Cancer Nursing 2008; 31, 162 – 220.

Kirkova Jk, Aktas A, Walsh D, Davis MP. Cancer Symptom Clusters: Clinical and Research Methodology. Journal of Palliative Medicine 2011, 14 (10), 1149- 1166.

Krupp, L.B. (2004). Fatigue in multiple sclerosis: A guide to diagnosis and management. New York, NY: Demos Medical Publishing.

Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983; 33(11): 1444–1452.

Lerdal A, Gulowsen E, Krupp L, Dahl AA. A prospective study of patterns of fatigue in MS. European Journal of Neurology 2007; 14: 1338- 43.

Lenz, E.R., & Pugh, L.C. The theory of unpleasant symptoms. In: M.J. Smith & P.R. Liehr (Eds.), Middle range theory for nursing 2003, pp: 69 – 90. New York: Springer.

Lenz, E.R., Pugh, L.C., Milligan, R.A., Gift, A., & Suppe, F. The middle-range theory of unpleasant symptoms: An update. Advances in Nursing Science 1997, 19(3), 14 – 27.

Leslie GC, Muir C, Part NJ, and Roberts RC. A comparison of the assessment of spasticity by the Wartenberg pendulum test and the Ashworth grading scale in persons with multiple sclerosis. Clin Rehabil 1992; 6: 41–48.

Leussink VI, Husseini L, Warnke C, Broussalis E, Hartung HP, Kieseier BC. Symptomatic therapy in multiple sclerosis: the role of cannabinoids in treatingspasticity. Ther Adv Neurol Disord. 2012; 5(5):255-66.

Lintern T. C., Beaumont J. G., Kenealy P. M., Murrell R. C. Quality of life (HRQL) in severely disabled multiple sclerosis persons: Comparison of three HRQL measures using multidimensional scaling. Quality of Life Research 2001, 10: 371-378.

Lovera, J., Bagert, B., Smoot, K. H., Wild, K., Frank, R., Bogardus, K., I Bourdette, D. Correlations of perceived deficits questionnaire of multiple sclerosis Quality of Life Inventory with Beck Depression Inventory and neuropsychological tests. Journal of Rehabilitation Research and Development 2006, 43(1): 73-82.

Lublin F, Reingold SC. Defining the clinical course of multiple sclerosis: results of an international survey. National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis". Neurology 1996; 46 (4): 907–11.

Lublin F. History of modern multiple sclerosis therapy. J Neurol. 2005 Sep; 252 Suppl 3:iii3-iii9.

Marrie RA, Miller DM, Chelune GJ, Cohen JA. Validity and reliability of the MSQLI in cognitively impaired persons with multiple sclerosis. Mult Scler 2003; 9(6):621-6.

Marrie RA, Chelune GJ, Miller DM, Cohen JA. Subjective cognitive complaints relate to mild impairment of cognition in multiple sclerosis. Mult Scler 2005 February; 11(1):69-75.

Mayo N.; Goldberg,M.S.; Kind,P. Calibrating the EQ-5D for a Canadian Population. Proceedings from 1997 EuroQol Plenary Meeting, Center for Health Policy and Law, Erasmus University, Rotterdam, The Netherlands. pp: 25-40.

Mayo N. Setting the agenda for multiple sclerosis rehabilitation research. Mult Scler 2008 November; 14(9):1154-6.

McHorney CA, Ware JE, Jr., Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. A psychometric and clinical test of validity in measuring physical and mental health constructs. Medical Care 1993; 31:247-263.

McHorney CA, Ware JE, Lu JFR, Sherbourne CD. The MOS 36-item short-form health survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse person groups. Med Care 1994; 32: 40–66.

McSweeney JC, Cleves MA, Lefler L, Yang S. Cluster Analysis of Women's Prodromal and Acute Myocardial Infarction Symptoms by Race and Other Characteristics. Journal of Cardiovascular Nursing 2010, 25(4): 311-322.

Miaskowski C. Gender Differences in Pain, Fatigue, and Depression in Patients with Cancer. Journal of the National Cancer Institute Monographs 2004; 32: 139 – 43.

Miaskowski C. Symptom clusters: establishing the link between clinical practice and symptom management research. Support Care Cancer 2006; 14:792-4.

Miller D.M., Rudick R.A., Baier M., Cutter G., Doughtery D.S., Weinstock-Guttman B. Factors that predict health-related quality of life in persons with relapsing–remitting multiple sclerosis. Mult Scler 2003; 9: 1–5.

Mohr DC. Stress and multiple sclerosis. J Neurol 2007; 254 Suppl 2: II 65-II68.

Morales FJ, Martinez A, Mendez M, Agarrado A, Ortega F, Fernandez:Guerra J, Montemayor T, Burgos J. A shuttle walk test for assessment of functional capacity in chronic heart failure. Am Heart J 1999 August; 138(2 Pt 1): 291:8.

Motl RW, Snook EM, McAuley E, Gliottoni R. Symptoms, self-efficacy, and physical activity among individuals with multiple sclerosis. Res Nurs Health. 2006; 29:597–606

Motl RW, Arnett PA, Smith MM. Worsening of symptoms is associated with lower physical activity levels in individuals with multiple sclerosis. Mult Scler. 2008a; 14:140–142

Motl RW, Snook EM, Schapiro RT. Symptoms and physical activity behavior in individuals with multiple sclerosis. Res Nurs Health 2008b; 31:466–475.

Motl R.W & McAuley, E. Symptom cluster as a predictor of physical activity in multiple sclerosis: Preliminary evidence. Journal of Pain and Symptom Management 2009a, 38, 270 – 280.

Motl, R.W & McAuley, E. Pathways between physical activity and quality of life in adults with multiple sclerosis. Health Psychology 2009b, 28, 682 – 689.

Motl RW, Weikert M, Suh Yoojin, Dlugonski D. Symptom Cluster and Physical Activity in Relapsing-Remitting Multiple Sclerosis. Research in Nursing & Health, 2010a, 33, 398 – 412.

Motl RW, Suh Y, Weikert M. Symptom Cluster and Quality of Life in Multiple Sclerosis. Journal of Pain and Symptom Management 2010b; 39 (6): 1025- 32.

Mullins LL, Cote MP, Fuemmeler BF, Jean VM, Beatty WW, Paul RH. Illness intrusiveness, uncertainty, and distress in individuals with multiple sclerosis. Rehabilitation Psychology 2001, 46 (2): 139-153.

Newland PK, Fearing A, Riley M, Neath A. Symptom clusters in women with relapsing-remitting multiple sclerosis. J Neurosci Nurs. 2012 Apr; 44(2):66-71. doi: 0.1097/JNN.0b013e3182478cba.

Nocentini U, Pasqualetti P, Bonavita S, Buccafusca M, De Caro M F, Farina D, Girlanda P.Cognitive dysfunction in patients with relapsing-remitting multiple sclerosis. Mult Scler 2006; 12: 77.

Nortvedt M, Riise T, Myhr K, et al. Quality of life in multiple sclerosis: measuring the disease effects more. Neurology 1999; 53: 1098–103.

Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG. Multiple sclerosis. N Engl J Med. 2000; 343: 938–52.

Nuyens G, Weerdt W De, Ketelaer P, Feys H. Inter-rater reliability of the Ashworth scale in multiple Sclerosis. Clinical Rehabilittaion1994 (8):286- 292

O'Brien, 2003, online article, http : // www. Pubmedcenteral. Nih. Gov/ articlerender. Fcgi?art ID=201004.

O'Connor Alec B; Schwid Steven R; Herrmann D N. Pain associated with multiple sclerosis: Systematic review and proposed classification. Pain 137 (2008) 96–111.

O'Connor P. Key issues in the diagnosis and treatment of multiple sclerosis: An overview. Neurology 2009; 59: S1-33.

O'Connor P, Lee L, Ng P.T, Narayana P, Wolinsky J.S. Determinants of overall quality of life in secondary progressive MS: a longitudinal study. Neurology 2001; 57: 889–891.

Orton SM, Herrera BM, Yee IM et al. Sex ratio of multiple sclerosis in Canada: a longitudinal study. Lancet Neurol 2006; 5(11):932-936.

Paltamaa J, West H, Sarasoja T, Wikstrom J, Malkia E. Reliability of physical functioning measures in ambulatory subjects with MS. Physiother Res Int 2005;10(2):93:109.

Pandyan AD, Price CIM, Curless RH, et al. A review of the properties and limitations of the Ashworth & modified Ashworth Scales. Clin Rehabil 1999; 13(5):373-83.

Pandyan AD, Price CIM, Rodgers H, et al. Biomechanical examination of a commonly used measure of spasticity. Clin Biomechan 2001; 16:859-65.

Parker KP, Kimble LP, Dunbar SB, Clark PC. Symptom Interactions as Mechanisms Underlying Symptom Pairs and Clusters. Journal of Nursing Scholarship 2005; 37:3, 209-215.

Parkin D, Rice N, Jacoby A, Doughty J. Use of a visual analogue scale in a daily person diary: modelling cross-sectional time-series data on health-related quality of life. Soc Sci Med 2004 July; 59(2):351-60.

Pearson O.R., Busse M.E. Deursen R.W.M. and Wiles C.M. Quantification of walking mobility in neurological disorders. Q J Med 2004; 97:463–475.

Ramagopalan S. Genes and Environmental Factors in Multiple Sclerosis 2010a, 16: 259-259.

Ramagopalan SV, Byrnes JK, Orton S-M et al. (2010b). Sex ratio of multiple sclerosis and clinical phenotype. European Journal of Neurology, vol. 17, 10.1111/j.1468-1331.2009.02850.x

Rao SM, Leo GJ, Bernardin L, Unverzagt F. Cognitive dysfunction in multiple sclerosis. Frequency, patterns, and prediction. Neurology 1991 May; 41(5):685-91.

Redelmeier D, Bayoumi A, Goldstein R, Guyatt G. Interpreting small differences in functional status: the Six Minute Walk test in chronic lung disease persons. American Journal of Respiratory and Critical Care Medicine. 1997; 155:1278 - 82.

Ruta DA, Garratt AM, Leng M, Russell IT, MacDonald LM. A new approach to the measurement of quality of life. The Person-Generated Index. Med Care 1994; 32:1109-1126.

Ruta DA, Garratt AM, Russell IT. Person centred assessment of quality of life for persons with four common conditions. Qual Health Care 1999; 8:22-29.

Savci S, InalInce D, Arikan H, Guclu-Gunduz, Cetisli-Korkmaz, Armutlu, Karabudak. Six-minute walk distance as a measure of functional exercise capacity in multiple sclerosis. 2005, 27 (22): 1365-1371.

Shevil E, Finlayson M. Perceptions of persons with multiple sclerosis on cognitive changes and their impact on daily life. Disabil Rehabil 2006 June 30; 28(12):779-88.

Snook, E.M., & Motl, R.W. Physical activity behaviors in individuals with multiple sclerosis: Roles of overall and specific symptoms, and self-efficacy. Journal of Pain and Symptom Management 2008; 36, 46 – 53.

Stanton BR, Barnes F, Silber E. Sleep and fatigue in multiple sclerosis. Mult Scler 20 06; 12 (4):4 81–6.

Sullivan MJL, Edgley K, Mikail S, et al. Psychological correlates of health care utilization in chronic illness. Can J Rehabil 1992; 6:13–21.

Svendsen KB, Jensen TS, Hansen HJ, Bach FW. Sensory function and quality of life in persons with multiple sclerosis and pain. Pain 2005; 114:473–8.

Svendsen KB, Jensen TS, Overvad K, Hansen HJ, KochHenriksen N, Bach FW (2003). Pain in persons with multiple sclerosis. Arch Neurol 60:1089–1094.

Tachibana N, Howard RS, Hirsch NP, Miller DH, Moseley IF, Fish D. Sleep problems in multiple sclerosis. Eur Neurol 1994; 34 (6):320–3.

Teng SY, Bartlett S, Koski L, Chamelian L, Duquette P, Grand'Maison F, Lapierre Y, Mayo NE. Self-perceived and tested cognition in multiple sclerosis: Differences across gender. Journal of Multiple Sclerosis Clinical and Laboratory research, 2009. 15 (2).

Tesio L, Perucca L, Franchignoni FP, Battaglia MA. A short measure of balance in multiple sclerosis: validation through Rasch analysis. Funct Neurol. 1997 Sep-Oct; 12(5):255-65.

Turpin KV, Carroll LJ, Cassidy JD, Hader WJ. Deterioration in the health-related quality of life of persons with multiple sclerosis: the possible warning signs. Mult Scler 2007 Sep; 13(8):1038-45.

Walsh D, Rybicki L. Symptom clustering in advanced cancer. Support Care Cancer2006; 14:831-6.

Wilmoth MC, Coleman EA, Smith SC, Davis C. Fatigue, weight gain, and altered sexuality in persons with breast cancer: exploration of a symptom cluster. Oncol Nurs Forum 2004; 31: 1069-75.

Zigmond, A.S., & Snaith, R.P. (1983). The Hospital Anxiety and Depression Scale. Acta Psychiatrica Scandinavica, 67, 361 – 370.

Table 9.1 Classification and Measurement of Variables Included in the Study

Variable	Measure	Scale	Unit /Coding
Socio-demographic Variables			
Sex	SDQ	Binary	0 = men; 1 = women
Age	SDQ	Continuous	Years
weight	SDQ	Continuous	Kilogram
Employment status	SDQ	Binary	0 = No; 1= Yes
Disease-related factors			
MS severity	EDSS	Quasi-continuous	Scores 0- 10
Disease course	MC	Categorical	1=RR, 2=SP, 3=PP, 4=PR
Years since diagnosis	MC	Continuous	Years
Years since symptoms onset	MC	Continuous	Years
Disease modifying therapy	MC	Binary	0 = No ; 1 = yes
Symptoms			
Pain	RAND -36	Continuous	Scores 0- 100
Fatigue	RAND -36	Continuous	Scores 0- 100
Sleep problems	R- PSQI	Quasi-continuous	Rasch model: 0- 8
Spasticity	MAS	Quasi-continuous	Scores 0- 60
Poor balance	R-EQUI	Quasi-continuous	Rasch model: 0- 20
Depression/ Anxiety	HADS	Quasi-continuous	Scores 0- 21
Cognitive impairments	PDQ	Continuous	Scores 0- 80
Irritability	IQ	Quasi-continuous	Scores 4- 16
Outcome variables			
Walking capacity	6MWT	Continuous	Meters
Perceived health status	EQ-VAS	Continuous	Scores 0- 100
Illness intrusiveness	IIRS	Continuous	Scores 13- 91
Quality of life	PGI	Continuous	Scores 0- 100

SDQ=Socio-demographic Questionnaire; EDSS=Expanded Disability Status Scale; MC= Medical chart; RAND -36= The Medical Health Outcomes Study; HADS=Hospital Anxiety and Depression Scale; PDQ= Perceived Deficits Questionnaire; R-PSQI= Rasch- Pittsburgh Sleep Quality Index**;** MAS= Modified Ashworth Scale; R-EQUI= EQUI Balance Scale; IQ= Irritability questionnaire; 6MWT= Six-Minute Walk Test; EQ- VAS= Euro Quality of Life Visual Analogue Scale; IIRS= Illness intrusiveness Rating Scale; PGI= Person Generated Index.

Table 9.2 Demographic and clinical characteristics of study participants (N=188)

Variables	**($\bar{x}$± SD) or N (%)**
Current age ($\bar{x}$± SD)	43 ±10
Gender N (%)	
Women	139 (74)
Men	49 (26)
Weight	74±17
MS type N (%)	
Relapsing-Remitting	97 (78)
Secondary progressive	7 (5)
Primary progressive	8 (7)
Primary relapsing	3 (3)
Clinically isolated syndrome	9 (7)
Years since diagnosis	3 ± 4
Years since symptom onset	9 ± 5
MS severity (EDSS)	2.4 ± 2
Disease modifying therapy	
Yes	110 (85)
No	20 (15)
Employed	
Yes	119 (64)
No	64 (35)

Table 9. 3 Characteristics of the sample at target variables (n=188)

Symptoms	**Mean**	**SD**
Pain (BP-RAND-36: 0- 100)	67	26.6
Fatigue (VIT-RAND-36: 0- 100)	49.5	20.5
Sleep problems (R- PSQI: 0 to 8*)*	2.6	3.35
Spasticity (MAS: 0- 60)	2.3	5.8
Poor balance (EQUI: 0- 20)	17	5
Cognitive impairments (PDQ: 0-80)	24.5	14.8
Depression (HADS: 0- 21)	4.2	3.4
Anxiety (HADS: 0- 21)	5.3	3.4
Irritability (IQ: 4- 16)	7.6	2.8
Disease consequences		
Walking Capacity (6MWT: meter)	418	171
Perceived health (EQ-VAS: 0-100)	73	17
Illness intrusiveness (IIQ: 0-78)	29	23
Quality of life (PGI: 0-100)	50	25

SD: Standard Deviation; BP-RAND-36=Bodily Pain subscale of Short Form-36 Health Survey; VIT-RAND-36=Vitality subscale of Short Form-36 Health Survey; R- PSQI= Rasch Pittsburgh Sleep Quality Index; MAS= Modified Ashworth Scale; EQUI= EQUI Balance Scale; PDQ= Perceived Deficits Questionnaire; HADS=Hospital Anxiety and Depression Scale; IQ= Irritability Questionnaire; 6MWT= Six-Minute Walk Test; EQ-VAS= EuroQol Visual Analogue Scale; IIQ= Illness intrusiveness Questionnaire; PGI= Person Generated Index

Table 9.4 Correlation matrix among target variables (n=188)

Variables	Pain	Fatigue	Sleep disorders	Spasticity	Poor balance	Cognitive deficits	Depression	Anxiety	Irritability	Walking capacity	Perceived health	Illness intrusiveness	Quality of life
Pain	1.00000	0.5	0.3	0.2	0.3	0.4	0.3	0.2	0.2	-0.3	-0.4	0. 4	-0.3
		<.0001	<.0001	0.03	<.0001	<.0001	<.0001	0.001	0.02	<.0001	<.0001	<.0001	<.0001
Fatigue	0.5	1.00000	0.5	0.2	0.3	0. 6	0.6	0.4	0. 4	-0.3	-0.6	0.6	-0.5
	<.0001		<.0001	0.05	0.0008	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001
Sleep disorders	0.3	0.5	1.00000	0.2	0.2	0.3	0. 4	0.2	0.2	-0.3	-0.3	0.4	-0. 4
	<.0001	<.0001		0.01	0.007	<.0001	<.0001	0.005	0.002	0.0004	<.0001	<.0001	<.0001
Spasticity	0. 2	0.1	0.2	1.00000	0.7	-0.1	0.3	-0.04	-0.04	-0.6	-0.4	0.3	-0.4
	0.03	0.05	0.01		<.0001	0.2	0.0005	0.6	0.6	<.0001	<.0001	<.0001	<.0001
Poor balance	0.3	0.2	0.2	0.7	1.00000	0.1	0. 4	0.003	0.05	-0.8	-0.5	0.5	-0.4
	<.0001	0.0008	0.007	<.0001		0.2	<.0001	0.9	0.5	<.0001	<.0001	<.0001	<.0001
Cognitive deficits	0.4	0.6	0.3	-0.1	0.1	1.00000	0.6	0.5	0.5	-0.1	-0. 4	0.5	-0. 4
	<.0001	<.0001	<.0001	0.2	0.2		<.0001	<.0001	<.0001	0.1	<.0001	<.0001	<.0001

Variables	Pain	Fatigue	Sleep disorders	Spasticity	Poor balance	Cognitive deficits	Depression	Anxiety	Irritability	Walking capacity	Perceived health	Illness intrusiveness	Quality of life
Depression	0.3	0.6	0.4	0.3	0.4	0.6	1.00000	0.5	0.5	-0.4	-0.5	0.72	-0.5
	<.0001	<.0001	<.0001	0.0005	<.0001	<.0001		<.0001	<.0001	<.0001	<.0001	<.0001	<.0001
Anxiety	0.2	0.4	0.2	-0.04	0.002	0.6	0.5	1.00000	0.6	0.02	-0.2	0.3	-0.2
	0.0015	<.0001	0.005	0.6	0.1	<.0001	<.0001		<.0001	0.8	0.0014	<.0001	0.007
Irritability	0.2	0.4	0.2	-0.04	0.05	0.5	0.5	0.6	1.00000	-0.07	-0.2	0.4	-0.2
	0.02	<.0001	0.002	0.6	0.5	<.0001	<.0001	<.0001		0.4	0.003	<.0001	0.007
Walking capacity	-0.3	-0.3	-0.3	-0.6	-0.8	-0.1	-0.4	0.02	-0.07	1.00000	0. 6	-0.5	0.5
	<.0001	<.0001	0.0004	<.0001	<.0001	0.09	<.0001	0.8	0. 4		<.0001	<.0001	<.0001
Perceived health	-0.4	-0. 6	-0.3	-0.4	-0.5	-0. 4	-0.5	-0.2	-0.2	0. 6	1.00000	-0.5	0. 6
	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	0.001	0.003	<.0001		<.0001	<.0001
Illness intrusiveness	0. 4	0. 6	0.4	0. 3	0. 5	0.5	0.7	0.3	0. 4	-0.5	-0.5	1.00000	-0.5
	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001		<.0001
Quality of life	-0.3	-0.5	-0. 4	-0. 4	-0.4	-0. 4	-0.5	-0.2	-0.2	0.5	0. 6	-0.5	1.00000
	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	0.008	0.007	<.0001	<.0001	<.0001	

Table 9.5 Cluster pattern among study sample, and genders

Focus group	Symptoms
All participants	
Cluster 1	Depression, anxiety, cognitive impairments, irritability
Cluster 2	Spasticity, poor balance
Cluster 3	Fatigue, pain, sleep disorders
Men	
Cluster 1	Depression, anxiety, cognitive impairments, irritability
Cluster 2	Spasticity, poor balance, sleep disorders
Cluster 3	Fatigue, pain
Women	
Cluster 1	Depression, anxiety, cognitive impairments, irritability, fatigue
Cluster 2	Spasticity, poor balance
Cluster 3	Pain, sleep disorders

Table 9.6 Symptoms' weight on their related clusters*

Symptoms	**Cluster 1**	**Cluster 2**	**Cluster 3**
Depression	0.80		
Anxiety	0.82		
Irritability	0.81		
Cognitive impairments	0.82		
Pain		0.75	
Fatigue		0.85	
Sleep disorders		0.73	
Spasticity			0.91
Poor balance			0.91

* Loading coefficients obtained from principal component analysis

Cluster 1: Emotional/cognitive symptom cluster: cognitive impairments, depression, anxiety, and irritability

Cluster 2: Physical symptom cluster: pain, fatigue, and sleep problems

Cluster 3: Motor symptom cluster: Spasticity and poor balance

Table 9.7 Multiple Linear Regression Models for outcomes of the study

Outcomes	Walking capacity 6MWT: R^2=0.75 P <.0001				Perceived health perception EQ-VAS: R^2=0.50 P <.0001				Illness intrusiveness IIQ: R^2=0.60 P <.0001				Quality of life PGI : R^2=0.43 P <.0001			
Predictors	**β**	**SE**	**SC**	**P value**	**β**	**SE**	**SC**	**P value**	**β**	**SE**	**SC**	**P value**	**β**	**SE**	**SC**	**P value**
MS severity	-30	5	-60	<.0001	-2	0.7	-4	0.03	3	0.4	6	<.0001	-5	0.7	-10	<.0001
Age	-2.5	0.7	-25	0.0003					-0.4	0.1	4	0.03				
Gender	-73	15	-	<.0001												
Weight	-2	0.4	-34	<.0001												
Emotional/cognitive cluster					-3	1.2	-3	0.02	6	1	6	<.0001	-4	1.7	-4	0.03
Physical cluster					-6	1.2	-6	<.0001	4.5	1	4.5	<.0001	-8	1.8	-8	<.0001
Motor cluster	-78	10	-78	<.0001	-4	1.5	-4	0.01								

6MWT= Six-Minute Walk Test; EQ-VAS= EuroQOl Visual Analogue Scale; IIQ= Illness intrusiveness Questionnaire; PGI= Person Generated Index; β = Parameter estimate; SC= Standardized coefficient

Emotional/cognitive symptom cluster: cognitive impairments, depression, anxiety, and irritability

Physical symptom cluster: pain, fatigue, and sleep problems

Motor symptom cluster: Spasticity and poor balance

Standardized coefficient = β x 1 Standard Deviation of each predictor

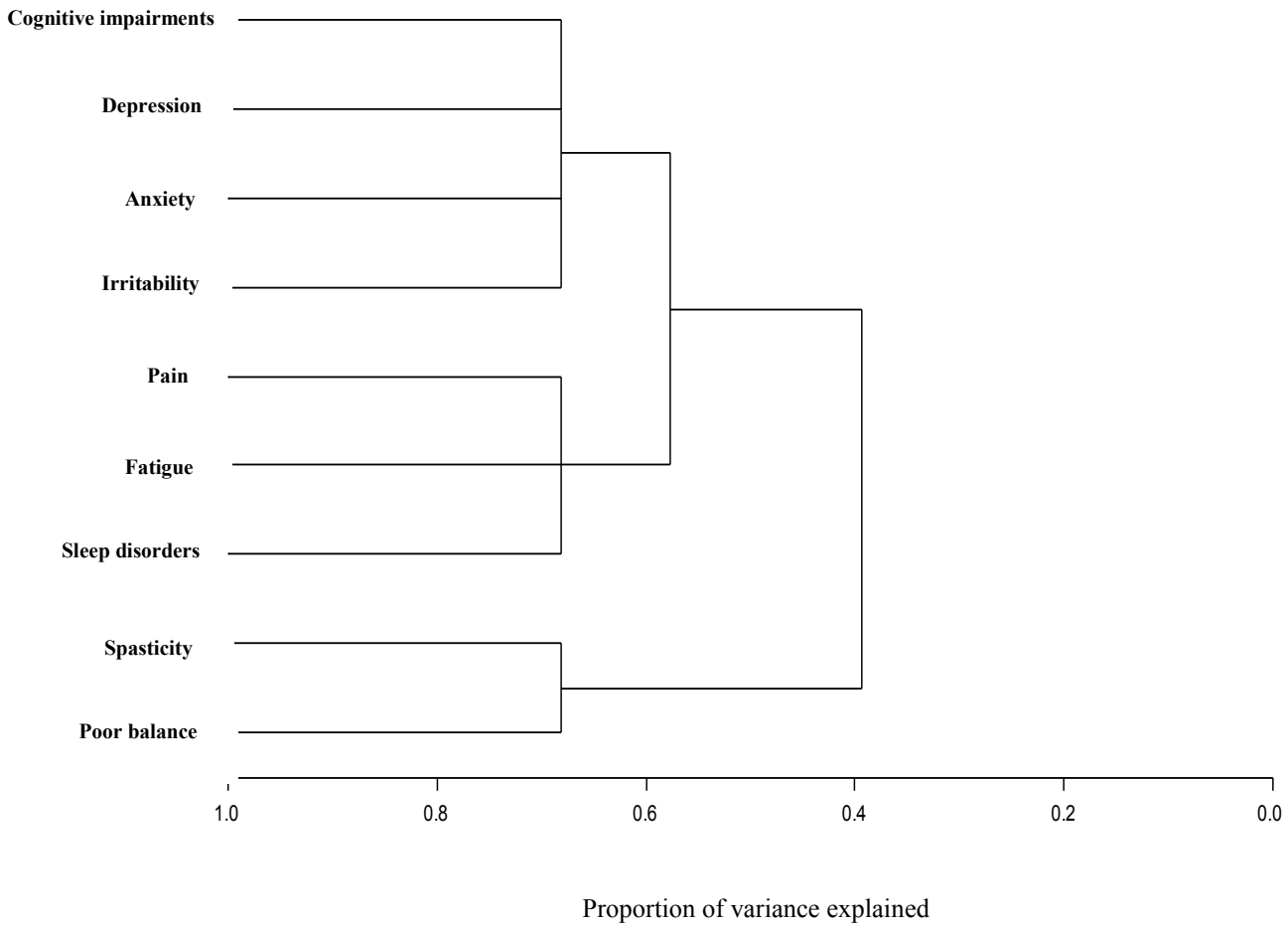

Figure 9.1 Dendrogram for variable clusters using agglomerative hierarchical cluster analysis including all participants

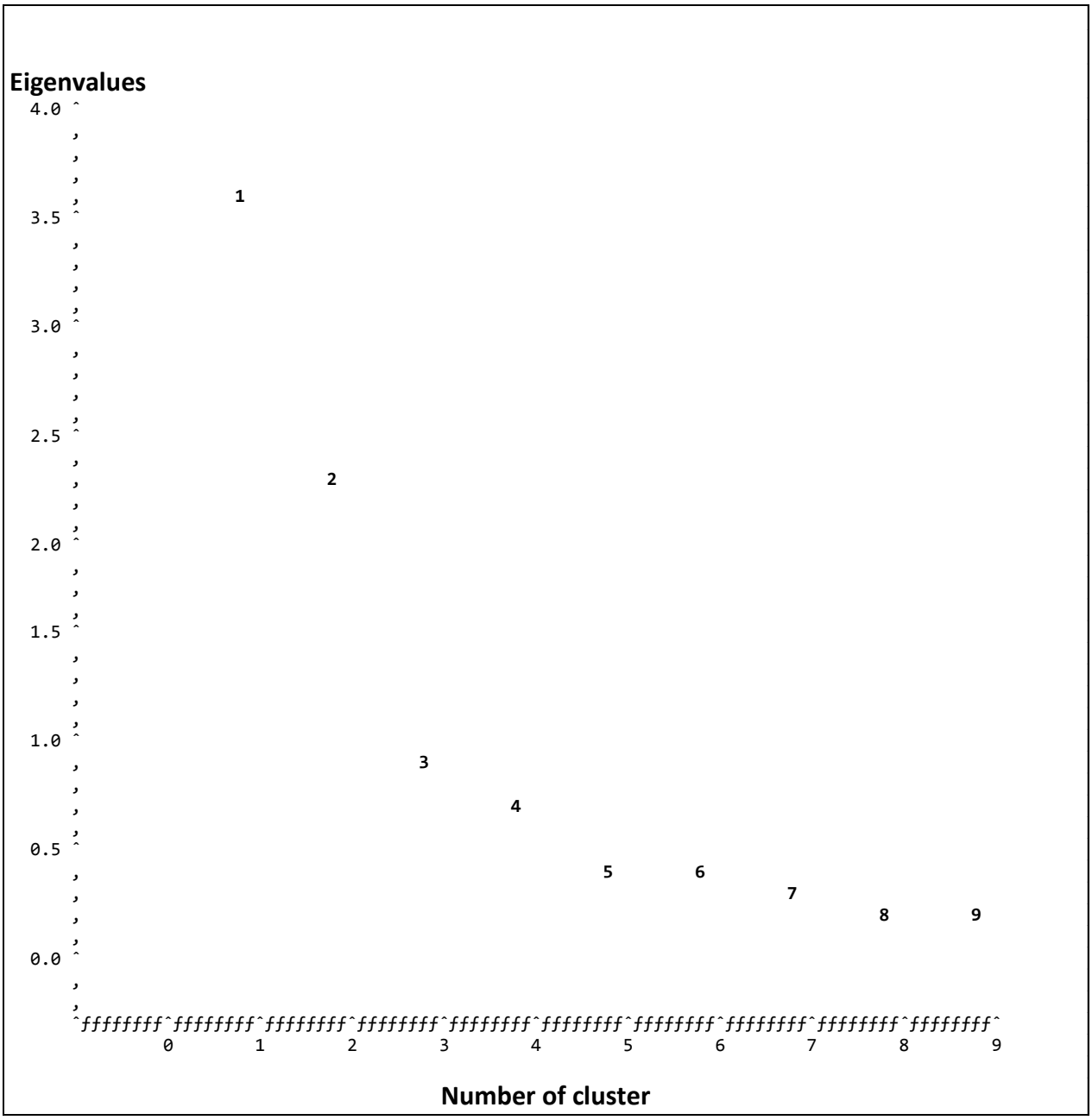

Figure 9.2 Scree Plot resulting from cluster analysis- Elbow rule

CHAPTER 10: Integration of Manuscripts 4 and 5

10.1 Research questions of Manuscript 4 and 5

Manuscript 4:

Contribution of symptom clusters to MS consequences

Manuscript 5:

Pain acts through fatigue to affect participation in individuals with MS

10.2 Integration of Manuscripts 4 and 5

The primary aim of this thesis is to contribute evidence towards a model for understanding the direct and indirect effects of pain and other MS symptoms and functions upon participation. In order to understand how participation has been affected by MS, the first step would be to understand how specific MS-related impairments influence participation. Next, it is important to identify how those specific impairments are connected to each other. Like pain, participation is a global construct, and this complexity emphasizes the need for a multidimensional assessment. The complexity of pain, its collateral and downstream effects, highlights that the need to study these relationships within an interactive statistical framework that considers all contributing factors.

In the fourth manuscript, using an variety of approaches to cluster analysis of the most common symptoms of MS, we estimated the extent to which different MS related symptoms, including pain, cluster. The preliminary results of Manuscript 4 provided us with new insights on the relationship between and among MS symptoms and several important disease consequences. However, analytical methods that we used in Manuscript 4, such as multiple regression analysis, exploratory factor analysis, cluster analysis and principal component analysis, could only determine the direct relationship among symptoms.

Structure Equation Modeling (SEM) approach aimed at identification of the predictors of the latent construct of participation within the hypothesized theoretical model. SEM has ability to simultaneously examine both direct and indirect relationships between and among contributor

factors and their impacts on an individual's life. SEM begins with a hypothesized model or diagram that consists of a number of variables connected together based on theoretical background knowledge or some pre-analyses. The current challenge in SEM is to demonstrate convincingly the presence and direction of the paths between and among the variables in the model as to establish the model researcher should consider all possible relationships among variables. Evaluation of the relationship among symptoms and MS consequences that was covered in the fourth manuscript would be very helpful for identifying the appropriate hypothetical path models.

CHAPTER 11 (MANUSCRIPT 5)

Pain acts through fatigue to affect participation in individuals with MS

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ABSTRACT

Background: Multiple sclerosis (MS) is the most common disabling neurological disease among young adults in North America. Participation and social activities are key domains affecting quality of life (QOL). Symptoms such as fatigue, pain, and impairments of physical and mental capacity, can make participation in life's roles a challenge for people with MS. However, how factors that predict variations in participation of people with MS interact with one another to influence participation is still unknown. The **objective** of this study was to estimate the extent to which pain and other MS- related symptoms, physical function, psychological variables, and individual characteristics predict participation in people with MS.

Methods: This study was a secondary analysis of data from a longitudinal study on Gender Life Impact of MS. A centre-stratified random sample of persons registered at the 3 MS clinics in Montreal was drawn, comprising 139 women and 49 men. Subjects completed a battery of self-report and performance-based measures that assessed participation and domains affecting participation. In order to understand the relationships between pain, other symptoms, physical and mental function, participation, and contextual factors we tested a conceptual framework based on the Wilson & Cleary Model that posits specific relations between different levels of these health outcomes. Specific analyses of pain and its consequences led to the development of a Structural Equation Model (SEM) aimed at identification of the predictors of the latent construct of participation within the hypothesized theoretical model.

Results: The results of the analysis suggests fatigue (β= 0.63, p= 0.00), physical function (β = 0.37, p= 0.00), and psychological variables (β = 0.15, p= 0.04) as significant predictors of participation. Pain (β = 0.4, p= 0.00) and age (β = 0.12, p= 0.00) were significant indirect predictors through fatigue and physical function, respectively. Together these effects explained 88% of the variance of participation. Overall, the results of fit indicators (Chi Square= 113.8, df= 94, p value= 0.08; RMSEA = .90, p value= 0.03; CFI = .98; TLI = .98; SRMR= 0.05) showed that the model fit the data adequately.

Conclusion: A theoretical approach to role participation would expand its clinical use as a valid and reliable outcome measure and increase its relevance. Current symptoms, functional status,

and contextual factors can be used to identify individuals likely to have restriction in their social participation in the future. Identification of the strength of the contributors to participation is important for MS rehabilitation as a clear understanding of participation repercussions and so application of appropriate intervention for their removing or reducing would maximize health related quality of life of people with MS.

11.1 INTRODUCTION

Multiple sclerosis (MS) is the most common disabling neurological disease among young adults in North America (Noseworthy 2003). Canada has one of the highest rates of MS in the world affecting as many as 240 per 100,000 people (MS Society of Canada 2009, O'Connor 2009). MS is more likely to occur in women than in men (Orton 2006, Ramagopalan 2010), and typically affects adults between the ages of 20 and 40 (Beeson 1994).

MS is a chronic disease with a wide range of sequelae that affect different aspects of life's quality (Brunet 1996, Devins 1993, Hopman 2009, Nortvedt 1999). Symptoms of fatigue, pain, and depression, interfere with capacity for physical effort, psychological functioning, work, leisure activities, lifestyle, plans for the future, and health perception, making it one of the more intrusive illnesses (Devins 1993a, 1993b,1994, 2001). Treatment for MS focuses on modifying the disease processes through pharmacological agents (Castro-Borrero 2012) or by reducing the impact of the disease through rehabilitation (Asano2009) and self-management interventions (Ploughman 2010, Plow 2011). Increasingly, the ultimate target of rehabilitation interventions is on enhancing participation in life's roles (Brasure 2013, Neubeck 2012) an outcome known to be affected by impairments and activity limitations but also a factor contributing strongly to quality of life (QOL) (Barclay-Goddard 2012, Mayo 2002, WHO 2001). For people with MS, participation has been defined as taking part in valued activities despite the barriers they may experience (Yorkston 2005).

The World Health Organization's (WHO) International Classification of Functioning, Disability and Health (ICF) (WHO 2001) defines participation as "involvement in life situations" (WHO 2001). Participation is considered as a global construct that covers recreational activities, relationships with other, and work (Johnson 2004, Salter 2005) but from the perspective of society, that is society expects people to have this roles but the specifics are determined by the individual. The concept of participation has been studied extensively in traumatic brain injury (Johnston 2005), spinal cord injury (Whiteneck 2004), and stroke (Barclay-Goddard 2012, Chau 2009, Desrosiers 2002, Mayo 2002), but less so for people with MS. Existing literature suggests that individuals with MS have a lower employment rate, less involvement in social activities, lower perceptions of social support, less marital satisfaction, and a shrinking social network

(Stuifbergen 1997, Yorkston 2005). Knowledge of the contributors to participation and how they interact can help focus rehabilitation interventions so that, ultimately, QOL can be optimized.

According to the ICF biopsychosocial model, participation is influenced by impairments and activity limitations. While fatigue is the most common impairment or symptom reported by people with MS, pain is also a common but it has had less attention in the context of MS. Pain is reported by almost 50% of people with MS at some point of their disease course (Archibald 1994, Ehde 2003, Kalia 2005, Svendsen 2003, 2005). In comparison to those MS people without pain, people with pain report more depressive symptoms, increased psychological distress (Ehde 2005), poorer physical function (Ehde 2003), and poorer mental health (Archibald 1994). The results of a systematic review and meta analysis have indicated that individuals with MS who experience pain are significantly more likely to report a decreased employment rate than individuals with MS who are pain free (Shahrbanian 2013). Pain can also catalyze the social isolation of persons with MS (Archibald 1994, Hadjimichael 2007, Warnell 1991). However, in MS research the contribution of pain, directly and indirectly, to participation is not well understood.

Pain in MS is conceptualized as a multidimensional phenomenon (Kerns 2002). This suggests that the relationship between pain and other complex health-related outcomes such as participation can be mediated by many other factors across a range of different physical, psychological, behavioral, personal and environmental factors. The complexity of pain and participation necessitates developing an interactive multidimensional framework that simultaneously target and evaluate the complex interrelationships among all contributing factors.

There are several theoretical frameworks that have been developed to explain the relationship among health outcomes. One of the commonly applied conceptual models is the Wilson Cleary Model (WCM) (Wilson & Cleary 1995). As illustrated in Figure 11.1, WCM is an interactive multidimensional theoretical model of health-related quality of life (HRQL) that explains the interrelationship between and among biological & physiological, symptoms status, functional status, general health perception, and overall QOL (Wilson & Cleary 1995). The model also

acknowledges that each of these components can be affected by individual and environment characteristics (Wilson & Cleary 1995).

Previous work, mostly cross-sectional studies have generally focused on a single dimension of pain or participation and have considered only a relatively limited range of potential variables that might account for the variability in participation. A model for understanding and measuring participation in MS population has been proposed by Yorkston in 2005 (Figure 11.2); however, the model has not been tested as a whole. This schematic model represents the different domains of participation component as well as the factors affecting participation (Yorkston 2005). This model illustrates that the relationships are complex and, as a result, standard descriptive or correlational type analyses would not be useful in identify the contributors to participation.

The main objective of this study, therefore, was to contribute evidence to support a framework to conceptualize the construct of participation in the context of MS by clarifying the direct and indirect effects of pain and other MS-related symptoms, physical function factor, psychological variables, and individual characteristics on participation in people with MS. It is hypothesized that the effect of pain can be either a direct effect or it is mediated by other factors such as psychological distress and fatigue.

11.2 METHODS

11.2.1 Design of study

This study was cross sectional in design.

11.2.2 Participants

The target population was people with MS, diagnosed since 1995. Available population was all men and women registered at the three major MS clinics in greater Montreal including Montreal Neurological Hospital (MNH), Centre Hospitalier de l'Université de Montréal (CHUM), and Clinique Neuro Rive-Sud (CNRS). Eligibility was based on diagnosis of MS or Clinically Isolated Syndrome (CIS) since 1995. In addition, participants were 18 years of age or older. Participants with severe cognitive impairments and pre-existing health conditions affecting functioning, such as cancer, heart disease, arthritis and malignancy, were excluded from

participating in the study. Subjects who had a relapse in the preceding month were excluded from participating in the study as well. Further, persons were not eligible if they were unable to understand either English or French. The numbers of persons meeting these criteria were 1000, 200, and 750 for the clinics at MNH, CHUM, and CNRS, respectively (N= 1950). A centre-stratified random sample of 550 persons was drawn, of which 364 were contacted. From those who were contacted, the first 192 who responded were included. Following exclusion of 3 people with incomplete data, 139 women and 49 men, comprised the study sample.

11.2.3 Procedure

Study protocol, measures, and procedures were approved by the ethics committee of each participating hospital; informed consent was obtained and signed by all subjects on the day of testing. Methods for recruiting subjects have been reported previously (Kuspinar 2010). Eligible people were sent a letters of invitation from the director of each related MS clinic. A research coordinator contacted the participants to verify if persons met the eligibility criteria, and invited them to participate. If persons consented to participate, an appointment was arranged for assessment of study measures. On the day of testing, participants were asked to complete several patient reported outcome measures and performance based measures representing the domains identified in the WCM.

11.2.4 Measurement

All of the measures chosen for the purpose of this study have been used in MS population; adequately represent the components of the underlying construct; and their validity and reliability have been determined. Appendix A outlines the study variables and their related constructs, measures, units, and psychometric properties.

11.2.4.1 Personal Characteristics of the Individual

Personal Characteristics of gender, age, education, and employment status were recorded on the day of testing using the socio-demographic questionnaire.

11.2.4.2 Biological and Physiological variables

The clinical records of each person were reviewed to obtain data on MS type, years since MS diagnosis and symptoms onset. Clinical types of MS recognized at the time of the study included: relapsing remitting (RR), primary progressive (PP), secondary progressive (SP), progressive relapsing (PR), and clinically isolated syndrome (CIS) (Ramagopalan 2010). Persons also were asked to report if they used disease modifying therapy (DMT). The severity of neurological impairment was assessed by neurologist based on the Expanded Disability Status Scale (EDSS) which is a widely used scale to measure level of disability in persons with MS, evaluates functioning across eight functional systems; scores from 0 (no disability), to 10 (maximum disability) (Kurtzke 1983).

A measure to indicate neurological impairments was created by using Rasch analysis to align hierarchically items on the questionnaire relating to neurological signs and symptoms reflecting lesion location, and clinical information such as EDSS, MS type, the use of DMTs, and disease duration (Ng 2012, 2013). A total of 9 items were included in the final Rasch model with a threshold range of -1.5 to +1.5 logits scored on a linear scale from 0 to 10.

11.2.4.3 Symptoms

Pain

For pain, several measures were used to create a pain latent variable. Worst pain in the past week was measured using a 0 to 10 Numeric Rating Scales (NRS) (Jensen 1999, 2001). Pain location and distribution was quantified using the Margolis Drawing Rating System (Margolis 1986, 1988). Muscle pain was assessed using the 0–10 Visual Analogue Scale (VAS), and bodily pain was measured using the Bodily Pain (BP) subscale of RAND-36 (Hays 1993, 2001).

Psychological variables

Anxiety, depressive symptoms, irritability, mood, memory, concentration, processing speed, sustained attention, and mental health made up a latent variable for psychological variables. The Hospital Depression and Anxiety Scale (HADS) were used for depression and anxiety (Bjelland 2002). Irritability was measured using a specific irritability index created from Rasch analysis of Psychiatric Symptom Index (PSI) (Illfeld 1976). Mood was measured by VAS. For cognitive

symptoms, the Perceived Deficits Questionnaire (PDQ) was used (Sullivan 1992). Innate processing speed and sustained attention was assessed through the Paced Auditory Serial Addition Task (PASAT) (Gronwall 1977, Rao 1991a, 1991b). Mental health was measured using the Mental Health Index (MHI) subscale of RAND-36 (Hays 1993, 2001).

Fatigue

Fatigue is a complex construct defined by severity, frequency, duration, and impact and is also characterized by general fatigue, physical fatigue, and mental fatigue (Elbers 2012). As such, no single measure with one total score can adequately represent fatigue. We had previously combined items relating to the fatigue construct from several questionnaires using Rasch Analysis. The items for the Rasch analysed Fatigue Measure came from the RAND-36 sub-scale for Vitality (Hays 1993, 2001), as well as non-redundant items from the thinking/fatigue subscale of the Functional Assessment of Multiple Sclerosis (FAMS) (Cella 1996), the Modified Fatigue Impact Scale (MFIS) from the Multiple Sclerosis Quality of Life Inventory (MSQLI) (Ritvo 1997), and the Multidimensional Fatigue Inventory (MFI) (Weinshenker 1989). A total of 14 items fit the Rasch model with a threshold range of -9.7 to +7.0 logits corresponding to a total score ranging from 0 to 43.

11.2.4.4 Functioning

Participation

The main outcome of interest in this manuscript was role participation. Participation is a multidimensional construct, and this poses a measurement challenge emphasizing that it should be studied within a multidimensional approach targeting all contributing factors. A number of measures have been developed to assess participation (Cardol 1999, Ostir 2006, Perenboom 2003); however, there is no single universally accepted scale for measuring it (Heinemann 2005). Yet, there is no specific measure related to the MS population. Role-Physical, Role-Emotional, and Social Functioning of RAND-36 (Hays 1993, 2001), Reintegration to Normal Living Index (RNLI) (Wood-Dauphinée 1988, Stark 2005), and Community Integration Questionnaire (Willer 1993) are examples of tools that have been reported in literature to assess participation. Using multiple measures of participation makes it difficult to interpret and compare the results across studies.

Therefore, to have a valid and reliable measure of participation, we created a latent component using several corresponding representative measures of participation in MS population. In the current study, participation was conceptualized by work, exercise, and leisure, and was assessed using several measures. Role physical (RP), role emotional (RE), and social functioning (SF) subscales of RAND-36 were used to identify the extent to which subjects reported problems with work or other regular daily activities as a result of their physical or emotional problems (Hays 1993, 2001). Information was also available on work time (hours of paid worked) and work activity (hours taking care of people and worked). A single-item on perceived capacity for work was also available (Poissant 2003) and Exercise Barriers Scale (EBS) was used to assess participants' exercise barriers and facilitators (Becker 1991). Preference Based Multiple Sclerosis Index (PBMSI) was used to indicate participants ability to accomplish work or other activities such as recreational activities and driving considering their own health on the day of evaluation (Poissant 2003). Finally, Illness Intrusiveness Rating Scale (IIRS) measured the illness intrusiveness (Devins 1994, 2010), which has been defined as "illness and treatment-induced lifestyle disruptions that interfere with continued involvements in valued activities and interests" (Devins 1994, 2010).

Physical function

A latent for Physical Function was created from walking capacity, walking speed (comfortable and fast), balance, spasticity, exercise capacity, lower extremity power, grip strength, physical function, upper limb and abdominal muscle endurance, and upper extremity dysfunction. Theses outcomes were measured using the 6 minute walk test (6MWT) (Goldman 2008), gait speed test (Tyson 2009), Equi-Scale (Tesio 1997), the modified Ashworth scale (MAS) (Bohannon 1987), the Modified Canadian Aerobic Fitness Test (mCAFT) (CSEP Health & Fitness Program's Health-Related Appraisal & Counselling Strategy 2004, Iris 1994, Jette 1976, Weller 1998), the vertical jump test (Markovic 2004), the Jamar TM dynamometer (Mathiowetz 1984, Desrosiers 1995), and Physical Functioning Index (PFI) of RAND -36 (Hays 1993, 2001), respectively. Push-ups and partial curl-ups tests (CSEP Health & Fitness Program's Health-Related Appraisal & Counselling Strategy 2004) were used to assess upper limb and abdominal muscle endurance, and the Disabilities of the Arm, Shoulder and Hand (DASH) scale applied to measure upper extremity dysfunction (Cano 2011, Padua 2003).

11.2.5 Statistical methods

Descriptive statistics (e.g., mean, standard deviations, and frequency) were used to describe the sample and summarize data. The potential for selection bias, differences between responders and non responders on targeted variables (e.g., socio-demographic and clinical characteristics of persons), was tested using Chi square test for categorical variables, t- test for continuous variables with homogenous variances, and U Mann-Whitney test for continuous variables with non-homogenous variances. Associations between all variables were assessed using Spearman and Pearson correlation coefficients for categorical and continuous variables, respectively.

The main objective of this study was to estimate, among persons with MS, the most important contributors to participation, as among variables representing biological and physiological factors, symptoms, functional status, and individual characteristics, as illustrated in the WCM. Testing the hypothesized conceptual model with complex direct and indirect relationship among factors influencing participation was not possible by usual statistical analyses of association such as regression models. Regression only predicts variance in a single outcome variable due to the direct effects of variability of several observed predictors, and not an indirect effect where the relationship between a predictor and outcome is mediated by an intervening variable.

To model the complexity of participation, structure equation modeling (SEM) was considered the most appropriate option of analysis. SEM, a combination of factor analysis and path analysis, is a powerful and advanced statistical approach that has the ability to simultaneously evaluate both direct and indirect relationships between observed and latent variables within multiple alternative theoretical models (Duncan 1999, Hays 2005, Kline 2011, MacCallum 1995, 2000, Suhr 2000).

SEM has two components: measurement model and structural model. The measurement model sets out the relationship between a latent variable and a set of its related indicators or observed variables using exploratory factor analysis (EFA) (Kline 2011). The structural model using confirmatory factor analyses (CFA) permits the estimation of direct and indirect relationships among latent variables and if any measured construct that are not factor indicators.

To develop the theoretical model, determine the presence and direction of the paths, and identify the exogenous and endogenous variables, the literature and multiple linear regressions were used. The assumptions of SEM such as multivariate normality, collinearity, and homoscedasticity were tested prior to the analysis. All models were estimated using maximum likelihood estimator with robust standard errors (MLR). MLR produces more accurate standard error estimates with non-normally distributed variables and a more accurate Chi-square statistic. MLR is also estimable with missing data as long as participants responded to at least one variable placed in the model, they were retained in the analysis.

The goodness of fit of the model was examined using several fit indices including the Chi-square statistic, Comparative Fit Index (CFI), Tucker- Lewis Index (TLI), Root Mean Square Error of Approximation (RMSEA), and the Standardized Root Mean Squared Residual (SRMR) (Hu & Bentler 1999). A p value greater than 0.05 for Chi square test, a cutoff value 0.95 or larger for CFI and TLI; a p value smaller than 0.06 with a cutoff value0.90 for RMSEA; and a p value below 0.08 for SRMR suggest an adequate fitting model (Hu & Bentler 1999).

If the model did not fit the data well, the model was modified to determine whether a better model could be developed with an acceptable fit index (Kline 2011, 2011, Martens 2005). Evaluation of the alternative models was based on the theoretical knowledge, along with the statistical criteria for adding or removing paths. We used the Modification Index (MI) for adding or removing paths in the model. We used Lagrange Multiplier test for adding the paths. A critical ratio (t value) that exceeds +1.96 or fall below -1.96 along with a non significant p value as well as the Wald test (Harrell 2001) was used for eliminating the paths.

SEM often requires a large sample size. In general, 10 to 20 subjects per parameter estimated or an optimal sample size of greater than 200 subjects is recommended (Kline 2011, Hoyle 1995). The parameters of the model are the number of path coefficients, variances, covariances, and errors (Hatcher 1994). If the sample size is small, the model will be low power. However, as the sample of the current study included 188 participants who were sampled to be representative of the MS population who were diagnosed post-1995, in the era when MRI became the standard for diagnosis and disease modifying drugs standard of care, we are confident that the strength of the

relationships in this model would be maintained with a larger sample size drawn from a similar population.

The power of the model was computed using the MacCallum method (MacCallum 1996, 2006) which is an extension of Satorra and Saris' power analysis procedure (Satorra & Saris 1993). MacCallum method estimates the level of power for any specified pair of RMSEA values, where RMSEA values in the range of .05 or lower indicates close fit and less than 0.08 indicates a fair fit (MacCallum 2006).

Statistical analyses, sample size estimation, and power analysis were conducted using the Mplus statistical software version 7.1 (Muthen & Muthen 2012), and Statistical Analysis Systems (SAS) version 9.2 (Hatcher 1994). Mplus has the advantage of handling missing data as well as data that are neither continues nor normally distributed (Muthen & Muthen 2012).

1.3 RESULTS

11.3.1 Description of the sample

Recruitment ended when a sample size of 192 had been recruited and this represented 52% of those initially invited to attend. No significant difference was found between responders (n=188) and those not further approached for study enrollment (n=176) on age, sex, MS severity, date of diagnosis, and duration of symptoms. Socio- demographic, clinical characteristics, and means and standard deviations for the observed variables of the sample are presented in Table 11.1 and 11.2, respectively.

The sample consisted of substantially more women than men (the ratio 3:1). Both men and women had mild disability with a median EDSS score of 2.4. The results of the correlation analyses showed that most variables were correlated with participation indicators. Fatigue showed high correlation with physical function, and participation indicators. Spasticity, balance, and walking capacity were not correlated to anxiety, and irritability. Age was associated to RP, RE, PBMSI, pain distribution, and all physical function indicators (Table 11.3).

11.3.2 Structural equation modelling

11.3.2.1 Construction of the initial hypothesized path model

A total of 32 variables representing the different domains of the WCM were initially included in the analysis. The hypothesized measurement model consisted of four latent variables: physical function, psychological variables, pain, and participation. Physical function consisted of 12 indicators targeting activity and motor function of subjects potentially required to perform social activities. Psychological variables consisted of 7 indicators that assess cognitive impairments and capture changes in emotional health after MS. While it is not clear where psychological constructs fit within the Wilson and Cleary model, we included mental or emotional health as a symptom, allowed it to be in relation with other symptoms, and modeled paths to function and participation. The latent of pain was reflected by 5 indicators covering different dimensions of pain outcome. Finally, eight indicators measured different aspects of participation component. A number of variables, such as fatigue and neurological impairments, were further included as single-indicator latent variable to the structural part of the model. Fatigue was assigned a reliability of 90%. 74% reliability was applied to neurological impairment for estimation of the amount of variance attributable to measurement error (Ng 2012).

The SEM model was built in phases beginning with the paths from the observed exogenous variable, neurological impairment, to the fatigue, to the physical function latent factor, and finally to the outcome, participation. In the next phase, paths were added between pain, fatigue, psychological variables, physical function, and participation. Age, a factor affecting both the drivers of participation and participation itself was then incorporated into the model. Paths were then drawn from age, as an observed exogenous variable, to psychological variables, physical function, and finally to participation. Covariance between pain, age, and neurological impairment were added next. Additional paths and correlations between variables were added as it was hypothesized that many of these factors would influence one another.

Gender was not included in the analysis as there was no significant difference between genders on participation indicators in this study. Further analysis also revealed no association between participation and other personal factors such as education or living situation. These variables were not incorporated into the path model.

The presence and direction of the paths and identification of the exogenous and endogenous variables to develop the theoretical model was based on the results of several multiple linear regressions, along with literature review. The original hypothesized structural model is illustrated in Figure 11.3.

11.3.2.2 Simplified path model

As expected, considering that we had a complex model with many indicators and the number of parameters included in the model was large with respect to the available sample size, the fit of the original hypothesized path model was not adequate [χ^2 = 1532 (p= 0.00), CFI = 0.77, TLI = 0.75, SRMR=0.11, RMSEA = 0.1 (90% CI: 0.09- 0.102, p = 0.00)]. Thus, several steps were taken for reducing the complexity of the model.

The PFI from the RAND-36 was selected to be removed from the physical function latent, as it was highly correlated to the several other indicators of function such as walking capacity, gait speed, and balance. Moreover, in comparison to other function indicators that all were performance based measures RAND-PFI was the only general self reported measure and so may not be sensitive enough to pick up functional differences between those who participate and those who do not. More than half (56%) of the sample scored in the very low disability range on the DASH and it was also strongly correlated with walking capacity (0.81), so owing to this co-linearity, it was removed from the model (Hatcher 1994). The two gait speed variables were strongly correlated. Gait speed- comfortable was chosen over the gait speed- fast as it is reasonable to accept that gait comfortable would be more important for participation in social activities than gait fast.

Results of factor analysis demonstrated that not all of the indicators fit with their hypothesized latent factors. Thus, variables that did not fit in one factor solution were dropped from the further analysis (weak factor loading and a non significant p value). Pain location was removed as a result of factor analyses as it did not load onto pain component. PASAT was also removed from the model because it did not load strongly onto the psychological variables latent. Similarly, physical capacity tests (jump test, MCAFT, curl ups, and push ups) were removed from physical function component as they did not load onto the related component. Curl ups and push ups,

count variables, showed a non-normal distribution. Among the participation indicators, the PBMSI did not load onto participation latent, while it was loaded on physical function and psychological variables components; thus, it was removed from the model. RE subscale of RAND-36 was non-normal and did not also load onto the participation latent and was removed. The variables of work time and work activity showed weak factor loadings in the factor analysis thus were removed. However, despite the exclusion of work variables from the model, they were still captured using the Illness Intrusiveness questionnaire as it has items on work. A schematic representation of the modified model is displayed in Figure 11.4.

11.3.2.3 Re- specified path model

The model was then re-specified; however the fit indices were not still adequate [χ^2 = 419 (p= 0.000), CFI = .89, TLI = .87, SRMR (.08), RMSEA = .08 (90% CI .07–.09), p = 0.000] owing to its complexity and low power.

The factor loadings were re-examined and it was noted that SF subscale of RAND-36, that was one of the participation indicators, loaded onto the psychological variables and physical function latent components as well. These indicate potential multi-dimensional measurement. In this case, there are several solutions: allow the indicators to load onto multiple factors, correlate their error residuals, or remove them from the model (Kline 2011). Given that the SF subscale of RAND-36 is meant to capture different constructs, it does not make sense to allow it to load onto two factors; therefore, it was removed from the model. However, despite the exclusion of SF from the model, it was still captured using the Illness Intrusiveness questionnaire as it includes items on social functiong.

Using a critical ratio (t value) that exceeds +1.96 or fall below -1.96 and a non significant p value of standardized model results, we further revised the hypothesized model by eliminating several paths: (a) direct effect of age on participation, (b) direct effects of pain on physical function and psychological variables components, and (c) direct effect of pain on participation.

Depression was excluded from the model as our sample did not include many people with a high depressive symptoms; also, an initial path analysis found no significant moderate or strong effect

of depression on physical function or participation. However, despite the exclusion of depression, measured byHADS, it could still be captured by the mood and irritability scales. Additionally, cognitive impairment was removed from the model as it showed associations with several indicators from other latent factors as well as loading on all other latent components. Moreover, only 14% of sample reported cognitive impairment. MHI of RAND-36 was also removed from the psychological latent as its exclusion increased the model fit. After this step, muscle pain was excluded from the analysis because almost 70% of the sample scored zero on 0-10 pain VAS scale and the modification indices confirmed that its exclusion would increase the model fit (Figure 11.5).

The model was then re-calculated; however the fit indices were not still adequate [χ^2 = 147 (p= 0.005), CFI = .97, TLI = .96, SRMR (.05), RMSEA = 0.7 (90% CI .07–.09), p = 0.04]. Thus, the model modified further to reach an adequate model fit and less complex model. The association between pain and neurological impairment was not significant anymore and was dropped from the model. Indirect effects of neurological impairments on participation through physical function latent variable were also eliminated from the model. Neurological impairments included in the model covered clinical information such as EDSS, and symptoms that some of them were already asked through other included variables of the study, such as spasm, pain, and balance (Ng 2012). In addition, the current sample had mild disability levels (EDSS< 3) showing the less severely impaired individuals. Thus, considering the non significant effects of neurological impairments on several parts of the model, it was removed from the analysis.

The post hoc model modifications further suggested that adding covariance arrows between RP subscale of RAND-36 and Barrier scale would increase the model fit. In addition, based on the theoreticl knowledge and confirmation of the post hoc modifications indices we further added covariance arrows between pain extension and pain worse intensity. Table11.4 presents a comparison of fit indices among the models of study.

11.3.2.4 The final path model

The final model is shown in Figure 11.6. Overall, the results of fit indices (χ^2 =113.8, df= 94, p value= 0.08; RMSEA = .90, p value= 0.03; CFI = .98; TLI = .98; SRMR= 0.05) indicated good

fit of the model suggesting that the model provides an adequate description of the pattern of relationship in the data. According to the model, participation was directly predicted by fatigue (β= 0.63, p= 0.00), physical function (β = 0.37, p= 0.00), and psychological variables (β = 0.15, p= 0.04) (Table11.5). Pain was significant indirect predictor of participation through fatigue (β = 0.4, p= 0.00). The effect of age on participation mediated through physical function (β = 0.12, p= 0.00) as well. Fatigue also showed an indirect effect on participation through physical function (β = 0.14, p= 0.00). Together these effects explained 88% of the variance of participation, 35% of the variance in psychological variables, and 29% of the variance in physical function. Table11.6 presents the maximum likelihood estimates of re-specified model on participation. Theses standardized path coefficients represent the strength of the relationship among variables. All parameter estimates were statistically significant and appear substantively meaningful. An examination of the modification indices of the re-specified model revealed no significant reduction of the chi-square statistic that could be obtained by adding or removing paths. The power of the final model was estimated to be high as much as 93% (N=188, df= 94, α= 0.05, RMSEA range= 0.05 - 0.08).

11.4 DISCUSSION

This study modeled participation using the framework of the WC model and SEM, in a sample of people with MS. Overall our results provided support for fatigue, physical function, and psychological variables as most important direct contributors for participation in persons with MS. Pain and age showed indirect effects.

Fatigue was found to not only contribute to participation in this study, but was also a contributor to all other variables in the model, thus confirming its role as the most disabling symptom of MS. Similar to the study by Kempen (Kempen 2012), our results also indicated that fatigue acts as independent determinants of physical functioning. A cognitive-behavioral approach suggests that fatigue is worsened by the individual's interpretation of symptoms or associated symptoms and not only by disease severity (Skerrett & Moss-Morris 2006; Van Kessel & Moss-Morris 2006). The present study also shows that cognitive-behavioral factors are more involved in the persistence of MS fatigue than biological factors, such as neurological impairments or disease severity, as in our final model no causal relationship was found between those factors and fatigue. However, we acknowledge that our sample had low level of disability (with a median

EDSS score of < 3), but our sample is also typical of the "New MS" (people diagnosed in the era of diagnostic imaging and disease modifying drugs) (Mayo 2008), and it is this population that is currently being targeted for interventions.

In link with other studies (Phillips & Stuifbergen 2009, 2010), the current study provided results for considering the role of physical function as an important correlate of social activities and participation in persons with MS. In persons with MS, difficulty with walking is related, either alone or in combination, to MS symptoms such as muscle weakness, spasticity, fatigue, pain, and depression (Motl 2006, 2008a, 2008b, Snook 2008), which in turn can produce unsteady gait and difficulty with keeping balance and thus avoiding participation in social activities.

In contrast with other studies (Andresen 1994, Phillips & Stuifbergen 2009, 2010), our result revealed that depression measured by HADS was not a predictor in the perpetuation of participation in people with MS. This can be partly related to the fact that our sample reported no serious depressiove symptom (the mean scores of depression scores of our sample was 4 out of 21 on HADS). However, despite the exclusion of depression, measured byHADS, it could still be captured by the mood and irritability scales. In addition, those studies used different measure to assess depression, such as the short form of the Center for Epidemiological Studies Depression Scale (CES-D) (Andresen 1994, Phillips & Stuifbergen 2009, 2010). This arise the concern of how different measures for assessing the same construct may find different results across different studies.

Results of this study further indicated the indirect effects of pain on participation. Pain is often considered as one of the MS symptoms that may contribute to problems with role participation (Archibald 1994, Hadjimichael 2007, O'Connor 2008, Shahrbanian 2013, Warnell 1991). Thus, it is reasonable to think that in the presence of pain, people may be reluctant to engage in physical and social activities. The results of the current study, however, showed no direct effect of pain on participation. The only effect of pain on participation was through fatigue, indicating that study participants with higher levels of pain, who experienced higher levels of fatigue, reported lower levels of participation.

The existence of illness intrusiveness in the final model of study as one of the representative of participation confirm the finding of another study in MS population, where the results of the ICF mapping indicated that illness intrusiveness likely reflects a construct in the participation domain (Bouchard 2012).

Comparing our model to the WC model confirms that symptoms like pain and fatigue were placed on the left side of the model, followed by the consequences of these symptoms on function, which then all together affect participation. What we found is also in agreement with Sullivan (2011) and Mayo (2013) who concluded from their SEM model in stroke that symptoms are important contributors to participation.

The current study has several strengths. The sample of study is a representative of the population living with MS in Canada as it was randomly selected from three MS clinics in different areas of the greater Montreal from populations who were culturally diverse including the whole range of disease severity, type, and gender. However, as we only included persons diagnosed for MS since 1995, we acknowledge this recruitment criteria may under represent symptoms and other functioning status in our sample. Since 1995 advances in neuroimaging techniques such as magnetic resonance imaging (MRI), and disease modifying therapies (DMTs) facilitate earlier diagnosis of disease, and reduce the speed of disease progression (Mayo 2008). In addition, while there are conflicting ideas in the literature as to what aspect of participation should be measured, we conceptualized participation with the appropriate selection of parameters and measurement scales, adequate research method, and complex statistical methods.

On the other hand, this study has limitations, which should be taken into account when interpreting the results. First, this was a cross-sectional study when subjects were assessed at one point in time. This issue is particularly important in MS due to its progress course as factors contributing to outcomes of interest could change over time. Longitudinal studies are needed to evaluate changes in the participation over time and if any changes in the contributing factors. Randomized controlled trials investigating the effects of different intervention approaches on participation and its contributors, is also suggested. Second, EDSS scores were not recorded on

the day of testing; instead, they were taken from subjects' medical charts during the last medical visit.

The results of this study help our understanding of the multidimensional concept of participation into domains of assessment and intervention. In the area of assessment, it verified how well the different measures captured different aspects of the construct. The created latent variable could expand its clinical relevance as a valid and reliable outcome measure of participation. In the area of intervention, the result of this study suggests the need to having the multidisciplinary treatment approach for participation. In addition, identification of the strength of the contributors to participation would help prioritize intervention approaches for its improvement. For example, our results suggest that in persons with MS a careful assessment of fatigue, physical function, and psychological variables would provide a much better guide to an individual's participation than any combination of biologic and physiologic variables or contextual factors. Unlike the pathological variables associated with MS, those symptoms may be modified to improve participation.

Future efforts need to assess the impact of more environmental factors, such as weather temperature, neighborhood, facilities, transportation, insurance and health policy on participation. Expanding the assessment to include more MS related symptoms, and other personal factors such as societal attitudes, beliefs, and engagement as well as satisfaction, self efficacy, and coping strategy to the analysis is suggested as well. It would also be of great interest to see if topography of brain damage and structure from MRI has any effect on participation in individuals with MS. Another area that warrants more investigation is developing a more specific valid and reliable multidimensional scale to assess different aspect of participation in individuals with MS. Obviously, each measure used in this study conceptualized participation differently; each captured only a portion of the complexity of the construct, and none of them assessed all aspects of participation concept. Further research needs to be done to go beyond role function and participation to health perception and QOL. This study would serve as a model for future research for these important constructs.

11.5 CONCLUSIONS

The purpose of this study was to propose a theoretical framework based on WCM that presents information as to what impacts the person with MS in their role participation. Although it is a first model, overall our results provided support for fatigue, physical function, and psychological variables as most important contributors for participation in persons with MS. Pain and age showed indirect effects. In addition, results of the current study brought new evidence of the validity of the conceptualization of participation in MS population due to the full appropriate selection of participation measures, adequate research method, and complex statistical methods used. The inclusion of fatigue, pain, physical function, and psychological variables is recommended in improving participation for MS population.

11.6 REFERENCES

Andresen, E. M., Malmgren, J. A., Carter, W. B., & Patrick, D. L. Screening for depression in well older adults: Evaluation of a short form of the CES-D. American Journal of Preventive Medicine 1994; 10 (2), 77–84.

Andrich D, Sheridan B, Luo G. Rumm2020: A windows interactive program for analysing data with rasch unidimensional models for measurement. 2004

Archibald CJ, McGrath PJ, Ritvo PG. Pain prevalence, severity and impact in a clinic sample of multiple sclerosis patients, Pain 1994; 58: 89–93.

Asano M, Dawes DJ, Arafah A, Moriello C, Mayo NE. What does a structured review of the effectiveness of exercise interventions for persons with multiple sclerosis tell us about the challenges of designing trials? Mult Scler 2009; 15(4):412-21.

Barclay-Goddard R, Ripat J, Mayo N. Developing a model of participation post-stroke: a mixed-methods approach. Qual Life Res 2012; 21:417–426.

Bartholomew David, Steel Fiona, Moustaki Irini, Galbraith Jane. The Analysis and Interpretation of Multivariate Data for Social Scientists, Chapman & Hall/CRC, 2002, p: 145.

Baylor C, Yorkston K, Bamer A, Britton D, Amtmann D. Variables Associated with Communicative Participation in People With Multiple Sclerosis: A Regression Analysis. American Journal of Speech-Language Pathology 2010, (19): 143–153.

Beeson PB. Age and sex associations of 40 autoimmune diseases. Am J Med 1994; 96(5):457-9.

Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the hospital anxiety and depression scale: An updated literature review. Journal of Psychosomatic Research 2002; 52: 69-77.

Bohannon RW, Schaubert KL. Test-retest reliability of grip-strength measures obtained over a 12-week interval from community-dwelling elders. J Hand Ther 2005; 18(4):426-7, quiz.

Bol Y, Duits AA, Lousberg R. Fatigue and physical disability in patients with multiple sclerosis: a structural equation modeling approach. J Behav Med 2010; 33:355-363.

Bouchard V. Illness intrusiveness in multiple sclerosis: An exploration from the perspective of modern outcome measurement theory. McGill University. Master thesis, Rehabilitation Science, 2012.

Brasure M, Lamberty GJ, Sayer NA, Nelson NW, Macdonald R, Ouellette J, Wilt TJ. Participation after multidisciplinary rehabilitation for moderate to severe traumatic brain injury in adults: a systematic review. Arch Phys Med Rehabil 2013; 94(7):1398-420.

Brown TR,Kraft GH. Exercise and rehabilitation for individuals with multiple sclerosis. Phys Med Rehabil Clin N Am 2005; 16: 513-55.

Browne MW, Cudeck R. Alternative ways of assessing model fit. Social Methods Res 1992; 21: 230–58.

Brunet DG, Hopman WM, Singer MA, Edgar CM, MacKenzie TA Measurement of health-related quality of life in multiple sclerosis persons. The Canadian Journal of Neurological Sciences 1996, 23(2):99-103.

Busche KD, Fisk JD, Murray TJ, Metz LM. Short term predictors of unemployment in multiple sclerosis patients. Can J Neurol Sci. 2003; 30:137- 42.

Cano S, Barrett L, Zajicek J, Hobart J. Beyond the reach of traditional analyses: Using rasch to evaluate the dash in people with multiple sclerosis. Multiple Sclerosis Journal 2011; 17:214-222.

Cardol M, de Haan RJ, van den Bos GAM, de Jong BA, de Groot IJM. The development of a handicap assessment questionnaire: The Impact on Participation and Autonomy (IPA). Clinical Rehabil 1999; 13: 411- 419.

Castro-Borrero W, Graves D, Frohman TC, Flores AB, Hardeman P, Logan D, Orchard M, Greenberg B, Frohman EM. Current and emerging therapies in multiple sclerosis: a systematic review. Ther Adv Neurol Disord 2012; 5(4):205-20

Cella DF, Dineen K, Arnason B, Reder A, Webster KA, Karabatsos G, et al. Validation of the functional assessment of multiple sclerosis quality of life instrument. Neurology 1996; 47:129-139

Chau JP, Thompson DR, Twinn S, Chang AM, Woo J. Determinants of participation restriction among community dwelling stroke survivors: a path analysis. BMC Neurol 2009; 9:49.

CSEP Health & Fitness Program's Health-Related Appraisal & Counselling Strategy. The Canadian Physical Activity, Fitness and Lifestyle Approach. 3rd ed. Ontario: Canadian Society for Exercise Physiology; 2004.

Desrosiers J, Hebert R, Bravo G, Dutil E. Comparison of the Jamar dynamometer and the Martin vigorimeter for grip strength measurements in a healthy elderly population. Scand J Rehabil Med1995 September;27(3):137-43.

Desrosiers J, Noreau L, Rochette A, et al. Predictors of handicap situations following poststroke rehabilitation. Disabil Rehabil 2002;24(15):774–85.

Devins GM, Dion R, Pelletier LG, Shapiro CM, Abbey S, Raiz LR, Binik YM, McGowan P, Kutner NG, Beanlands H, Edworthy SM. Structure of lifestyle disruptions in chronic disease: a confirmatory factor analysis of the Illness Intrusiveness Ratings Scale. Med Care 2001 October; 39(10):1097-104.

Devins GM, Edworthy SM, Paul LC, Mandin H, Seland TP, Klein G, Costello CG, Shapiro CM. Restless sleep, illness intrusiveness, and depressive symptoms in three chronic illness conditions: rheumatoid arthritis, end-stage renal disease, and multiple sclerosis. J Psychosom Res 1993a; 37(2):163-70.

Devins GM, Edworthy SM, Seland TP, Klein GM, Paul LC, Mandin H. Differences in illness intrusiveness across rheumatoid arthritis, end-stage renal disease, and multiple sclerosis. J Nerv Ment Dis 1993b June; 181(6):377-81.

Devins GM. Illness intrusiveness and the psychosocial impact of lifestyle disruptions in chronic life-threatening disease. Advances in renal replacement therapy. 1994; 1:251-263

Devins GM. Using the illness intrusiveness ratings scale to understand health-related quality of life in chronic disease. J Psychosom Res 2010 June; 68(6):591-602.

Duncan, T. E., Duncan, S. C., Strycker, L. A., Li, F., & Alpert, A. (1999). An introduction to latent variable modeling: Concepts, issues, and applications. Mahwah, NJ: Lawrence Erlbaum Associates, Publishers.

Ehde DM, Gibbons LE, Chwastiak L, Bombardier CH, Sullivan MD, Kraft GH. Chronic pain in a large community sample of persons with multiple sclerosis. Mult Scler. 2003; 9:605–11.

Enright P. The six-minute walk test. Respiratory care 2003; 48(8):783-5.

Goldman MD, Marrie RA, Cohen JA. Evaluation of the six-minute walk in multiple sclerosis subjects and healthy controls. Mult Scler 2008 April; 14 (3):383-90.

Gronwall DM. Paced auditory serial-addition task: a measure of recovery from concussion. Percept Mot Skills 1977 April;44(2):367-73.

Hadjimichael O, Kerns RD, Rizzo MA, Cutter G, Vollmer T. Persistent pain and uncomfortable sensations in persons with multiple sclerosis. Pain 2007; 127:35–41.

Hammel J, Jones R, Gossett A & Morgan E. Examining barriers and supports to community living and participation after a stroke from a participatory action research approach.Topics in Stroke Rehabilitation 2006, 13, 43–58.

Harrell, Frank E., Jr. Regression modeling strategies. “Sections 9.2, 10.5”. New Yor: Springer-Verlag. ISBN 0387952322.

Hatcher L. A step-by-step approach to using the SAS system for factor analysis and structural equation modeling. Cary NC: SAS Institutes Inc; 1994.

Hays R, Revicki D, Coyne K. Application of Structure Equation Modeling to Health Outcome Research. Evaluation & The Health Profession 2005; 28 (3): 295-309.

Hays RD, Sherbourne CD, Mazel RM. The RAND 36-Item Health Survey 1.0. Health Econ 1993 October; 2(3):217-27.

Hays Ron D, Morales Leo S. The RAND-36 measure of health- related quality of life. Ann Med 2001; 33:350-7.

Heinemann, A. (2005). Putting outcome measurement in con-text: A rehabilitation psychology perspective. Rehabilitation Psychology, 50(1), 6–14. doi:10.1037/0090-5550.50.1.6

Hopman W.M, Towheed T, Anastassiades T, Tenenhouse A, Poliquin S. Canadian normative data for the SF-36 health survey. Canadian Medicine Association Journal 2000; 163 (3) 265- 71.

Hoyle RH. Structural equation modeling. Thousand Oaks (CA): SAGE Publications; 1995.

Hu L, Bentler PM. Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. Structural Equation Modeling: A Multidisciplinary Journal. 1999; 6:1 – 55.

Ilfeld FW Jr. Further validation of a psychiatric symptom index in a normal population. Psychol Rep 1976; 39:1215-1228.

Iris M.R.Weller, Scott G.Thomas, Norm Gledhill, Don Paterson, Art Quinney. A study to validate the modified canadian aerobic fitness test. Canadian Journal of Applied Physiology1994 14; 20(2):211-21.

Jamison R.N, Brown G.K. Validation of hourly pain intensity profiles with chronic pain patients. Pain 1991; 45: 123-128.

Jamison R.N, Gracely R.H, Raymond S.A, Levine J.G, Marino B, Herrmann T.J, Daly M. Comparative study of electronic vs paper VAS ratings: A randomized, crossover trial using healthy volunteers. Pain 2002; 99: 341–347.

Jensen MP, Karoly P. (2001). Self-report scales and procedures for assessing pain in adults. In: Handbook of Pain Assessment, 2nd. Turk DC, Melzack R. eds. Guilford Press, New York.

Jensen MP, Turner JA, Romano JM, et al. Comparative reliability and validity of chronic pain intensity measures. Pain. 1999;83: 157–162.

Jette AM, Keysor J, Coster W, Ni P, Haley S. Beyond function: predicting participation in a rehabilitation cohort. Arch Phys Med Rehabil 2005; 86:2087-94.

Jette M, Campbell J, Mongeon J, Routhier R. The Canadian Home Fitness Test as a predictor for aerobic capacity. Can Med Assoc J1976 April 17; 114(8):680-2.

Johnson KL, Klasner ER, Amtmann D, Kuehn CM, Yorkston KM. Medical, pyschological, social, and programmatic barriers to employment for people with multiple sclerosis. Journal of Rehabilitation 2004; 70:38-49.

Johnston MV, Miklos CS. Activity-related quality of life in rehabilitation and traumatic brain injury. Arch Phys Med Rehabil 2002;83(Suppl 2):S26–38.

Kalia LV, O'Connor PW. Severity of chronic pain and its relationship to quality of life in multiple sclerosis. Mult Scler2005; 11:322–7.

Kempen JCE, de Groot V, Knol DL, Lankhorst GJ, Beckerman H. Self-reported fatigue and energy cost during walking are not related in patients with multiple sclerosis. Archives of Physical Medicine and Rehabilitation 2012; 93 (5): 889–895.

Kerns R, Kassirer M, Otis J. Pain in multiple sclerosis: a biopsychosocial perspective. J Rehabil Res Dev 2002; 39:225–32.

Kline RB. Principles and practice of structural equation modeling. 2011

Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983; 33(11): 1444–1452.

Kuspinar A, Andersen R, Mayo NE. Predicting Exercise Capacity through SubMaximal Fitness Testing in Persons with Multiple Sclerosis. Arch Phys Med Rehabil 2010; 91:1410-7.

Lapierre Y, Hum S. Treating fatigue. The International MS Journal 2007; 14:64-71

Litcher-Kelly L, Stone AA, Broderick Joan E, Schwartz Joseph E. Associations among pain intensity, sensory characteristics, affective qualities, and activity limitations in patients with chronic pain: A momentary, within-person perspective. The Journal of Pain 2004; (5) 8: 433-439.

MacCallum, R. C. & Austin, J. T. Applications of structural equation modeling in psychological research. Annual Review of Psychology 2000; 51, 201-226.

MacCallum, R. C. Model specification: Procedures, strategies, and related issues. In Structural equation modeling: Concepts, issues, and applications, R. H. Hoyle (editor). Thousand Oaks, CA: Sage Publications, Inc 1995; pp. 16-29.

MacCallum, R. C., Browne, M. W., & Cai, L. (2006). Testing differences between nested covariance structure models: Power analysis and null hypotheses. Psychological Methods, 11, 19-35.

MacCallum, R. C., Browne, M. W., & Sugawara, H. M (1996). Power analysis and determination of sample size for covariance structure modeling. Psychological Methods, 1, 130-149.

Margolis RB, Chibnall JT, Tait RC. Test-retest reliability of the pain drawing instrument. Pain 1988; 33: 49- 51.

Margolis RB, Tait RC, Krause SJ. A rating system for use with patient pain drawings. Pain 1986; 24: 57-65.

Markovic G, Dizdar D, Jukic I, Cardinale M. Reliability and factorial validity of squat and countermovement jump tests. J Strength Cond Res 2004 August; 18(3):551-5.

Marrie RA, Chelune GJ, Miller DM, Cohen JA. Subjective cognitive complaints relate to mild impairment of cognition in multiple sclerosis. Mult Scler 2005 February; 11(1):69-75.

Marrie RA, Miller DM, Chelune GJ, Cohen JA. Validity and reliability of the MSQLI in cognitively impaired persons with multiple sclerosis. Mult Scler 2003; 9(6):621-6.

Martens Matthew P. The Use of Structural Equation Modeling in Counseling Psychology Research. The Counseling Psychologist 2005; 33: 269-298.

Mathiowetz V, Weber K, Volland G, Kashman N.Reliability and validity of grip and pinch strength evaluations. J Hand Surg [Am] 1984;9(2):222-6.

Mayo N. Setting the agenda for multiple sclerosis rehabilitation research. Mult Scler 2008 November; 14(9):1154-6.

Mayo N.E, Scott S.C, Bayley M, Cheung A, Garland J, Jutai J, Wood-Dauphinee S. Modeling Health-Related Quality of Life in People Recovering From Stroke. Quality of Life Research, 2013, in press.

Mayo NE, Wood-Dauphinee S, Cote R, Durcan L, Carlton J. Activity, participation, and quality of life six months post-stroke. Arch Phys Med Rehab 2002; 83:1035-1042.

Motl RW, Arnett PA, Smith MM. Worsening of symptoms is associated with lower physical activity levels in individuals with multiple sclerosis. Mult Scler. 2008a; 14:140–142.

Motl RW, Snook EM, McAuley E, Gliottoni R. Symptoms, self-efficacy, and physical activity among individuals with multiple sclerosis. Res Nurs Health 2006; 29:597–606.

Motl RW, Snook EM, Schapiro RT. Symptoms and physical activity behavior in individuals with multiple sclerosis. Res Nurs Health 2008b; 31:466–475.

Multiple Sclerosis Society of Canada. www.mssociety.ca. 2009. Canada, MS Society of Canada. Ref Type: Generic.

Muthén L.K & Muthén B.O. Mplus User's Guide. Seventh Edition. Los Angeles, CA: Muthén & Muthén, 1998-2012.

Neubeck L, Freedman SB, Clark AM, Briffa T, Bauman A, Redfern J. Participating in cardiac rehabilitation: a systematic review and meta-synthesis of qualitative data. Eur J Prev Cardiol 2012; 19(3):494-503.

Ng Pamela. The Path to Work in People with Multiple Sclerosis. Master Thesis. School of Physical and Occupational Therapy, Faculty of Medicine, McGill University, August 2012.

Ng P, Finch L, Hum S, Lapierre Y, Duquette P, Bartlett S, Mayo N. The Path to Work Capacity in People with Multiple Sclerosis. Submitted to Archives Phys Med Rehabil, Oct 2013.

Nortvedt M, Riise T, Myhr K, et al. Quality of life in multiple sclerosis: measuring the disease effects more. Neurology 1999; 53: 1098–103.

Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG. Multiple sclerosis. N Engl J Med. 2000; 343: 938–52.

O'Connor A, Schwid S, Herrmann D, Markman D, Dworkin R. Pain associated with multiple sclerosis: Systematic review and proposed classification. Pain 137 (2008) 96–111.

O'Connor P. Key issues in the diagnosis and treatment of multiple sclerosis: An overview. Neurology 2009; 59: S1-33.

Orton SM, Herrera BM, Yee IM et al. Sex ratio of multiple sclerosis in Canada: a longitudinal study. Lancet Neurol 2006; 5(11):932-936.

Ostir GV, Granger CV, Black DA. Preliminary results for the PAR-PRO: A measure of home and community participation. Arch Phys Medicine Rehabil 2006; 87: 1043-1053.

Padua R, Padua L, Ceccarelli E, Romanini E, Zanoli G, Amadio PC, et al. Italian version of the disability of the arm, shoulder and hand (dash) questionnaire. Cross-cultural adaptation and validation. The Journal of Hand Surgery: Journal of the British Society for Surgery of the Hand 2003; 28:179-186.

Perenboom RJM, Chorus AMJ, Measuring participation according to the International Classification of Functioning, Disability and Health (ICF). Disabil Rehabil 2003; 25 (11- 12): 577- 585.

Peters M.L, Sorbi M.J, Kruise D.A, Kerssens J.J, Verhaak P.F.M, Bensing J.M. Electronic diary assessment of pain, disability and psychological adaptation in patients differing in duration of pain. Pain 2000; 84: 181–192.

Phillips L. & Stuifbergen, A. Structural equation modeling of disability in women with fibromyalgia or multiple sclerosis. Western Journal of Nursing Research 2009; 31, 89-109.

Phillips L., & Stuifbergen, A. The relevance of depressive symptoms and social support to disability in women with multiple sclerosis or fibromyalgia. International Journal of Rehabilitation Research 2010; 33(2), 142-150.

Ploughman M, Austin MW, Murdoch M, Kearney RN, Godwin M. The Path to Self-Management: A Qualitative Study Involving Older People with Multiple Sclerosis. Physiother Can 2012; 64(1): 6–17.

Plow MA, Finlayson M, Rezac M. A scoping review of self-management interventions for adults with multiple sclerosis. PM R 2011; 3(3):251-62.

Poissant L, Mayo NE, Wood-Dauphinee S, Clarke AE. The development and preliminary validation of a preference-based stroke index (pbsi). Health & Quality of Life Outcomes. 2003; 1:43-15.

Ramagopalan SV, Byrnes JK, Orton S-M et al. (2010). Sex ratio of multiple sclerosis and clinical phenotype. EUROPEAN JOURNAL OF NEUROLOGY vol. 17, 10.1111/j.1468-1331.2009.02850.x

Rao S.M. The neuropsychological Screening Battery for Multiple Sclerosis. Milwaukee, WI: Medical College of Wisconsin; 1992.

Rao SM, Leo GJ, Bernardin L, Unverzagt F. Cognitive dysfunction in multiple sclerosis. Frequency, patterns, and prediction. Neurology 1991a; 41(5):685-91.

Rao SM, Leo GJ, Ellington L, Nauertz T, Bernardin L, Unverzagt F. Cognitive dysfunction in multiple sclerosis. II. Impact on employment and social functioning. Neurology 1991b; 41(5):692-6.

Ritvo P, Fischer JS, Miller D, Andrews H, Paty D, LaRocca NG. Multiple sclerosis quality of life: A user's manual. National Multiple Sclerosis Society; 1997.

Salter K, Jutai JW, Teasell R, Foley NC, Bitensky J, Bayley M. Issues for selection of outcome measures in stroke rehabi-litation: ICF Participation. Disabil Rehabil 2005; 27(9): 507- 528.

SAS 9.2 [computer program]. Version 9.2. Cary, NC: SAS Institute Inc.; 2008. This is related to the statistical analysis.

Satorra, A. and Saris, W. E. (1993). Power Evaluations in Structural Equation Models, pp 181–204. Newberry Park, CA: Sage.

Shahrbanian Sh; Auais M; Duquette P; Anderson K; Mayo N. E. Does Pain in Individuals with Multiple Sclerosis Affect Employment? A Systematic Review and Meta-analysis. Journal of Pain Research and Management 2013; 18 (5): 94-100.

Snook, E.M., & Motl, R.W. (). Physical activity behaviors in individuals with multiple sclerosis: Roles of overall and specific symptoms, and self-efficacy. Journal of Pain and Symptom Management 2008; 36, 46 – 53.

Stark SL, Edwards DF, Hollingsworth H, Gray DB. Validation of the reintegration to normal living index in a population of community-dwelling people with mobility limitations. Arch Phys Med Rehabil 2005; 86:344-5.

Stuifbergen A, Rogers S. Health promotion: an essential component of rehabilitation for persons with chronic disabling conditions. Adv Nurs Sci 1997; 19(4):1–20.

Suhr Diana D. SEM for Health, Business and Education. Statistics and Data Analysis. 1: 243-27.

Sullivan KJ, Cen SY. Model of disablement and recovery: knowledge translation in rehabilitation research and practice. Phys Ther 2011; 91(12):1892-1904.

Sullivan MJL, Edgley K, Mikail S, et al. Psychological correlates of health care utilization in chronic illness. Can J Rehabil 1992; 6:13–21.

Svendsen KB, Jensen TS, Hansen HJ, Bach FW. Sensory function and quality of life in patients with multiple sclerosis and pain. Pain 2005; 114:473–8.

Svendsen KB, Jensen TS, Overvad K, Hansen HJ, KochHenriksen N, Bach FW (2003). Pain in patients with multiple sclerosis. Arch Neurol 60:1089–1094.

Tesio L, Perucca L, Franchignoni FP, Battaglia MA. A short measure of balance in multiple sclerosis: validation through Rasch analysis. Funct Neurol 1997 September;12(5):255-65.

Tyson S, Connell L. The psychometric properties and clinical utility of measures of walking and mobility in neurological conditions: a systematic review. Clin Rehabil 2009 November;23(11):1018-33.

Vendrig A.A, Lousberg R. Within-person relationships among pain intensity, mood and physical activity in chronic pain: A naturalistic approach. Pain 1997; 73: 71–76.

Von Korff M, Jensen MP, Karoly P. Assessing global pain severity by self-reports in clinical and health services research. Spine 2000; 25:3140–3151.

Warnell P. The pain experience of a multiple sclerosis population: a descriptive study. Axon 1991; 13: 26–8.

Weinshenker BG, Bass B, Rice GPA, Noseworthy J, Carriere W, Baskerville J, et al. The natural history of multiple sclerosis: A geographically based study. Brain 1989; 112:133-146

Weller IM, Corey PN. A study of the reliability of the Canada Fitness Survey questionnaire. Med Sci Sports Exerc 1998 October;30(10):1530-6.

Whiteneck GG, Charliefue SW, Gerhart KA, et al. Quantifying handicap: a new measure of long-term rehabilitation outcomes. Arch Phys Med Rehabil 1992;73:519–26.

Willer B, Rosenthal M, Kreutzer JS, Gordon WA, Rempel P. Assessment of community integration following rehabilitation for traumatic brain injury. J Head Trauma Rehabil 1993; 8(2): 75- 87.

Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. JAMA 1995; 273(1):59-65.

Wood-Dauphinée SL, Opzoomer MA, Williams JI, Marchand B, Spitzer WO. Assessment of global function: The reintegration to normal living index. Arch Phys Med Rehabil 1988; 69:583-90.

World Health Organization. International classification of functioning, disability and health.Available at: http://www3.who.int/icf/icftemplate.cfm. Second revision ed. Geneva: 2001.

Yorkston K, Johnson K, Klasner E. Taking Part in Life: Enhancing Participation in Multiple Sclerosis. Phys Med Rehabil Clin N Am 2005 (16): 583–594.

Yorkston K, Kuehn C. M, Johnson K, EHDE D. M, Jensen M. Measuring participation in people living with multiple sclerosis: A comparison of self-reported frequency, importance and self-efficacy. Disability and Rehabilitation, 2008; 30(2): 88 – 97.

Table 11.1 Description of the sample on the Wilson Cleary Rubrics of Personal, Environmental and Biological and Physiological Factors (N=188)

Variables	Mean or Frequency	Percent or SD
Personal Characteristics of the Individual		
Current age	42.9	10.2
Gender		
Women	139	74
Men	49	26
Level of education		
University	83	47.4
High School	54	30.9
Less than High School	38	21.7
Living Situation		
Alone	34	19.3
Spouse/ partner	108	61.4
Family member (s)	32	18.2
Friend (s)	1	0.6
Other	1	0.6
Environmental Characteristics		
Employed		
Yes	122	70
Biological and Physiological variables		
MS type		
Relapsing-Remitting	97	78
Secondary progressive	7	5
Primary progressive	8	7
Primary relapsing	3	3
Clinically isolated syndrome	9	7
Years since diagnosis	3	4
Years since symptom onset	9	5
MS severity (EDSS: median)	2.4	2
Disease modifying therapy		
Yes	110	85

Table11. 2 Description of the sample on the Wilson Cleary Rubrics of Symptoms and Functional Factors (N=188)

Symptoms (Impairments)	Mean or N	SD or %	Legend for models
Pain			pain
Pain (BP-RAND-36:0-100)	67	27	randpain
Muscle Pain (VAS:0-10)	1.3	2.3	painvas
Pain Distribution (MRS:0-100)	7.2	12.6	painext
Pain Location (MRS:0-45)	2.9	5	painsite
Pain Worst (NRS:0-10)	2.3	8.2	painwors
Psychological variables			psycho
Depression (HADS: 0- 21)	4	4.2	depress
Anxiety (HADS: 0-21)	5.3	4	anxiety
Irritability (IQ: 4-16)	7.6	2.7	irritab
Mood (VAS:0-10)	8.3	2	moodvas
Mental Health (MHI-RAND-36: 0-100)	68.7	19.3	mhealth
Cognitive deficits (PDQ: 0-80)	24.5	14.7	cog
Decreased memory and attention (PASAT: 0-60)	39.2	11.8	pasat
Single Indicator Components			
Fatigue	15.9	9.7	fatigue
Neurological Impairments	6.3	2.3	neuro
Functioning			
Participation			part
Role Physical (RP-RAND-36: 0- 100)	55.7	43.2	randphys
Role Emotional (RE-RAND-36: 0- 100)	67.7	40.2	randemo
Social Functioning (SF-RAND-36: 0- 100)	70.8	26	randsoc
Social activities (PBMSI: 11 to 33)	27.4	5.4	pbmsi
Exercise Barriers (EBS:0-42)	20.3	15	barrier
Illness Intrusiveness (IIRS: 0-78)	20.5	16.4	illint
Work Time	25.3	18.3	paidwork
Work Activity	51	28.8	carework
Physical Function			function
Physical Functioning (PF-RAND-36: 0- 100)	67.8	31.3	randpfi
Walking Capacity (6MWT: meter)	418	171	walktest
Spasticity (MAS: 0- 60)	2.3	5.8	spastic
Balance (EQUI: 0- 20)	17	4.9	balance
Lower Extremity Power (Jump height: cm)	62.7	39	jump
Curl-ups (≠)	84.3	87	curlup
Push-ups (≠)	26.8	41.5	pushup
Grip Strength (JTM D: kg)	97.9	28	grip
Gait Speed (comfortable) (m/s)	115.6	37.5	gaitcomf
Gait Speed (fast) (m/s)	165.4	61.3	gaitfast
Aerobic Capacity (MCAFT: ≠)	49.6	19.8	aerocap
Upper Extremity Dysfunction (DASH: 0-84)	16.3	19.3	dash

EBS= Exercise Barriers Scale; IIRS = Illness intrusiveness Scale; PBMSI= Preference Based Multiple Sclerosis Index; PF= Physical Function Scale of RAND-36; 6MWT= Six-Minute Walk Test; MAS= Modified Ashworth Scale; EQUI= EQUI Balance Scale; JTMD= Jamar TM Dynamometer; MCAFT= modified Canadian Aerobic Fitness Test; DASH= Disabilities of the Arm, Shoulder and Hand; PDQ= Perceived Deficits Questionnaire; PASAT= Paced Auditory Serial Addition Test; HADS=Hospital Anxiety and Depression Scale; IQ= Irritability Questionnaire; VAS= Visual Analogue Scale; MHI= Mental Health Scale of RAND-36; BP-RAND-36=Bodily Pain subscale of RAND-36; MRS= Margolis Rating System; NRS= Numeric Rating Scale.

Table11. 3 Correlation matrix of variables included in the re-specified path model

	Exercise Barrier	Illness Intrusiveness	Role Physical	Walk test	Gait Comfort	Balance	Spasticity	Grip	Irritability	Anxiety	Mood	Pain Extent	Bodily Pain	Worst Pain	Fatigue	Age
Exercise Barrier	-															
Illness Intrusiveness	0.52	-														
Role Physical	-0.36	-0.62	-													
Walk test	-0.46	-0.5	0.47	-												
Gait Comfort	-0.41	-0.45	0.41	0.8	-											
Balance	-0.35	-0.48	0.46	0.8	0.8	-										
Spasticity	0.24	0.28	-0.28	-0.67	-0.66	-0.66	-									
Grip	-0.35	-0.29	0.29	0.43	0.44	0.42	-0.3	-								
Irritability	0.35	0.37	-0.21	-0.05	-0.08	-0.06	-0.05	-0.006	-							
Anxiety	0.33	0.36	-0.22	0.03	-0.03	-0.005	-0.06	-0.05	0.59	-						
Mood	-0.2	-0.22	0.15	0.01	0.08	0.05	0.002	0.11	-0.32	-0.39	-					
Pain Extent	0.16	0.3	-0.48	-0.28	-0.22	-0.31	0.13	-0.27	0.08	0.05	-0.1	-				
Bodily Pain	-0.26	-0.39	0.53	0.25	0.27	0.35	-0.16	0.2	-0.2	-0.23	0.2	-0.53	-			
Worst Pain	0.17	0.14	-0.26	-0.17	-0.18	-0.17	0.1	-0.21	0.04	0.09	-0.02	0.34	-0.32	-		
Fatigue	0.6	0.67	-0.65	-0.42	-0.38	-0.34	0.22	-0.25	0.4	0.44	-0.27	0.41	-0.53	0.26	-	
Age	0.03	0.09	-0.22	-0.34	-0.34	-0.33	0.29	-0.24	-0.08	-0.08	-0.08	0.17	-0.17	0.05	0.14	-

Table 11.4 Model Progression

Model	χ^2	χ^2 P value	SRMR	CFI	TLI	RMSEA	RMSEA 90% CI RMSEA P value
Initial path model 32 variables representing the four latent variables (physical function, psychological variables, pain, and participation), and fatigue, NI, and age were included in the initial model (Figure 11.3).	1532	0.00	0.1	0.77	0.75	0.1	0.09 - 0.10 p = 0.00
Simplified path model The RAND-PFI, DASH, gait speed-fast, jump test, MCAFT, curl ups, and push ups were removed from the physical function latent. Pain location and PASAT were removed from the pain and the psychological variables components. RAND-RE, PBMSI, work time and work activity were removed from the participation latent (Figure 11.4).	419	0.000	.08	.89	.87	.08	0.07 - 0.09 p = 0.000
Re-specified path model Direct effect of age on participation and fatigue as well as direct effects of pain on physical function, psychological variables and participation were eliminated. Depression, RAND-MHI, cognitive impairment, RAND-SF, and muscle pain were removed from their related latent components (Figure 11.5).	147	0.005	.05	.97	.96	0.7	0.07 - 0.09 p = 0.04
Final model NI was dropped from the model. Correlations were added between pain extension and pain worse intensity and between RAND-RP and Barrier scale (Figure 11.6).	113.8	0.08	.05	.98	.98	.90	0.000 - 0.054 p = 0.03

χ^2 = Chi-square Test
CI= Confidence Interval
NI= Neurological Impairments

Table 11.5 Direct, indirect and total effects of study variables on participation

	Direct	Indirect	Total
Physical function	0.37	-	0.37
Psychological variables	0.15	-	0.15
Fatigue	0.63	.14	0.77
Pain	-	0.4	0.4
Age	-	0.12	0.12

Significant at < 0.05

Table 11.6 Maximum Likelihood Estimates of Respecified Model

	Estimate (β)	Standard Error	Critical ratio
Participation BY			
Exercise Barrier	.70	.05	14.22
Illness Intrusiveness	.79	.04	21.75
Role Physical	-.75	.05	-16.46
Physical Function BY			
Walk test	.92	.02	54.1
Gait Comfortable	.88	.03	34.5
Balance	.90	.02	37.95
Spasticity	-.73	.05	-14.52
Grip	.49	.07	6.58
Psychological variables BY			
Irritability	.72	.07	9.67
Anxiety	.82	.05	17.82
Mood	-.46	.07	-6.35
Pain BY			
Pain Distribution	.62	.06	9.89
Pain scale of Rand-36	-.86	.05	-17.1
Worst Pain Severity	.74	.05	13.99
Participation ON			
Physical Function	-.37	.06	-6.17
Psychological variables	.15	.08	1.9
Fatigue	.63	.07	8.5
Physical Function ON			
Fatigue	-.38	.06	-6.39
Age	-.33	.07	-4.63
Psychological variables ON			
Fatigue	.59	.06	9.31
Age	-.18	.07	-2.43
Fatigue ON			
Pain	.63	.05	11.9
Physical Function WITH Psychological variables	.22	.08	2.79
Pain WITH Age	.21	.07	2.9
Pain distribution WITH Worst Pain Severity	.44	.09	4.60
Exercise Barrier WITH Role Physical	.34	.09	3.47

Note. All critical ratios had significant results/paths.
Parameter estimates (β) are interpreted in the same way as regression coefficients.
BY: Factor loading of indicator variables; ON: Path coefficients; WITH: Associations

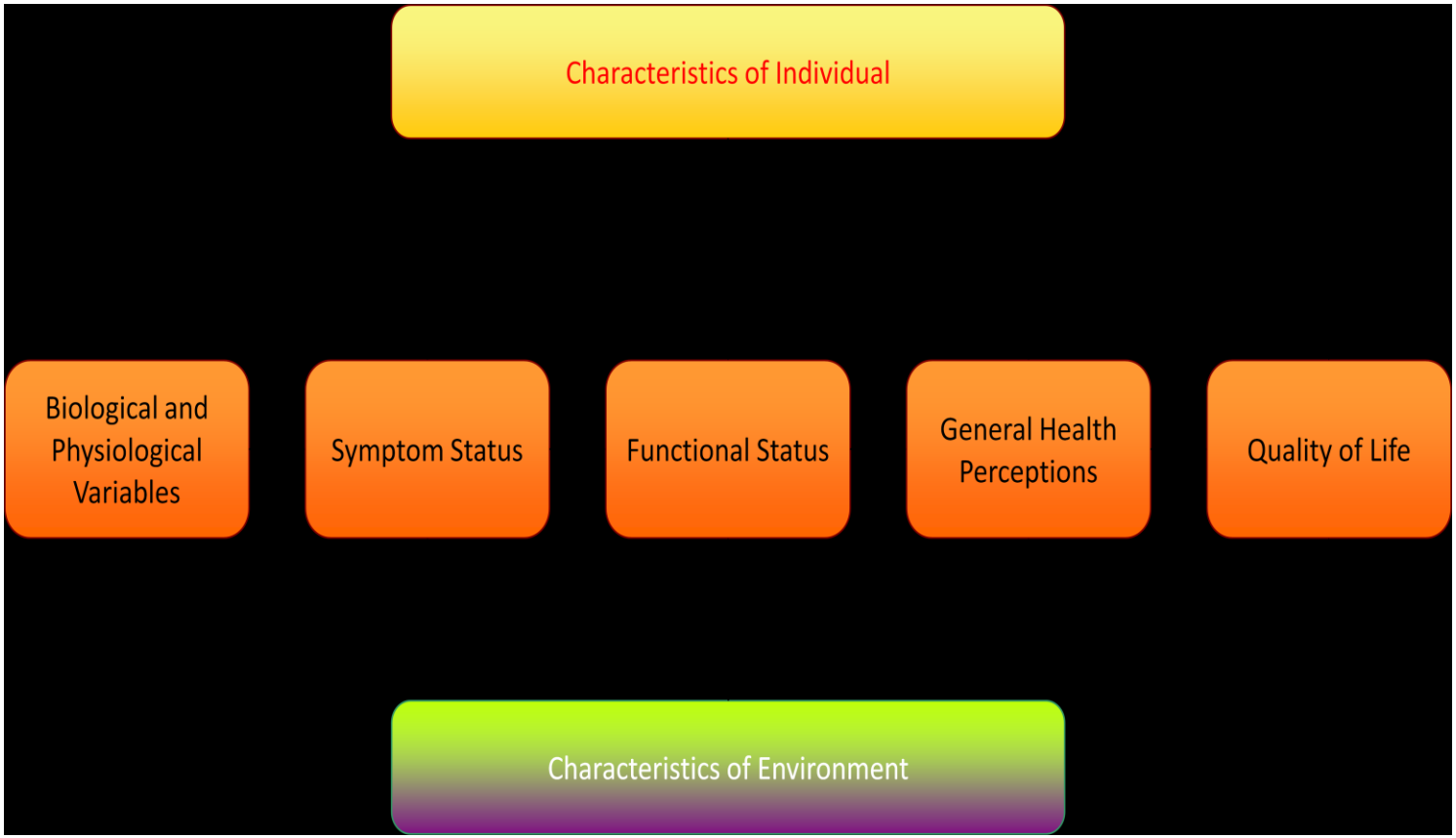


Figure 11.1 The Wilson-Cleary health related quality of life conceptual framework

Taken from: Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. JAMA 1995; 273(1):59-65.

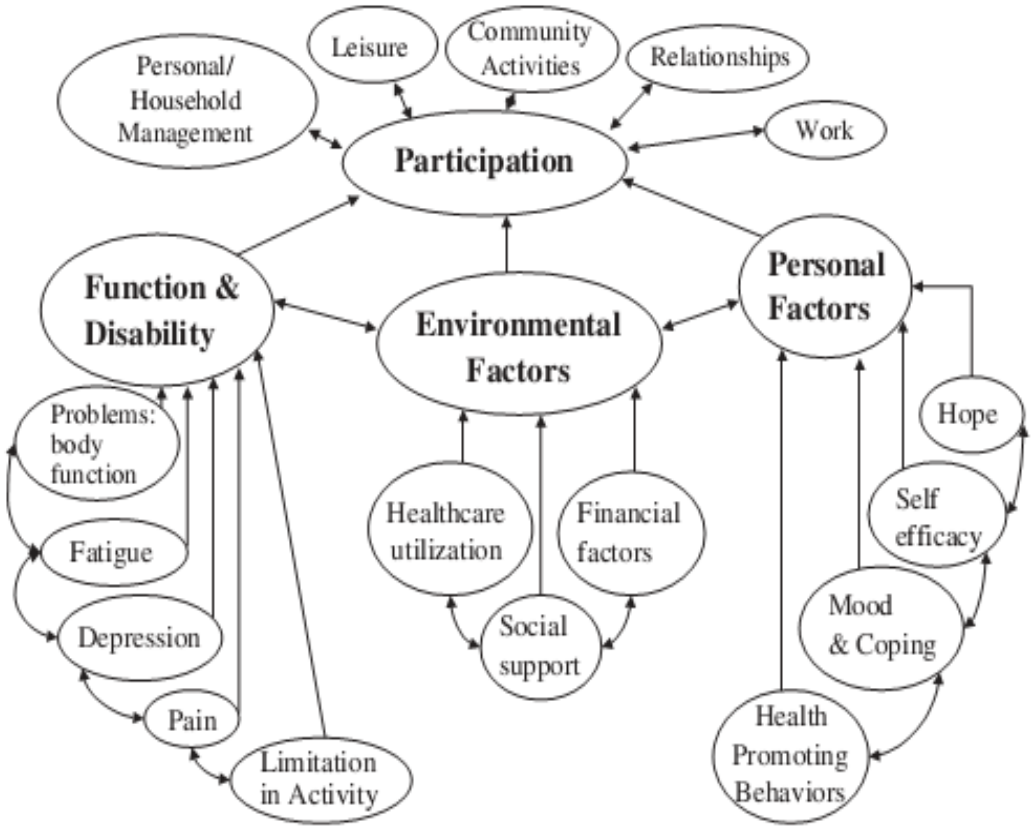


Figure 11.2 A model hypothesizing factors related to participation

Taken from: Yorkston K, Johnson K, Klasner E. Taking Part in Life: Enhancing Participation in Multiple Sclerosis. Phys Med Rehabil Clin N Am 2005 (16): 583–594.

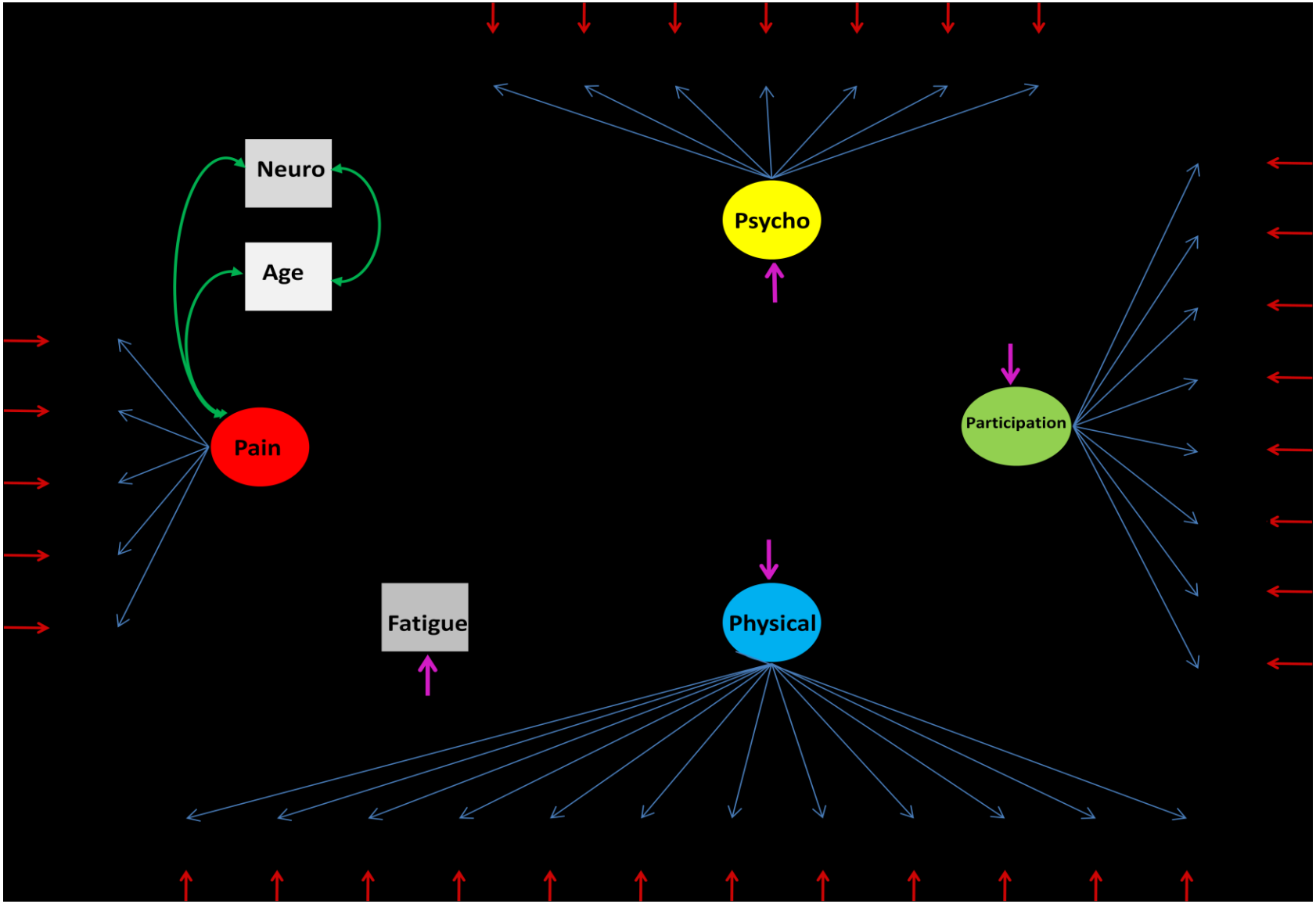


Figure 11.3 The initial hypothesized model

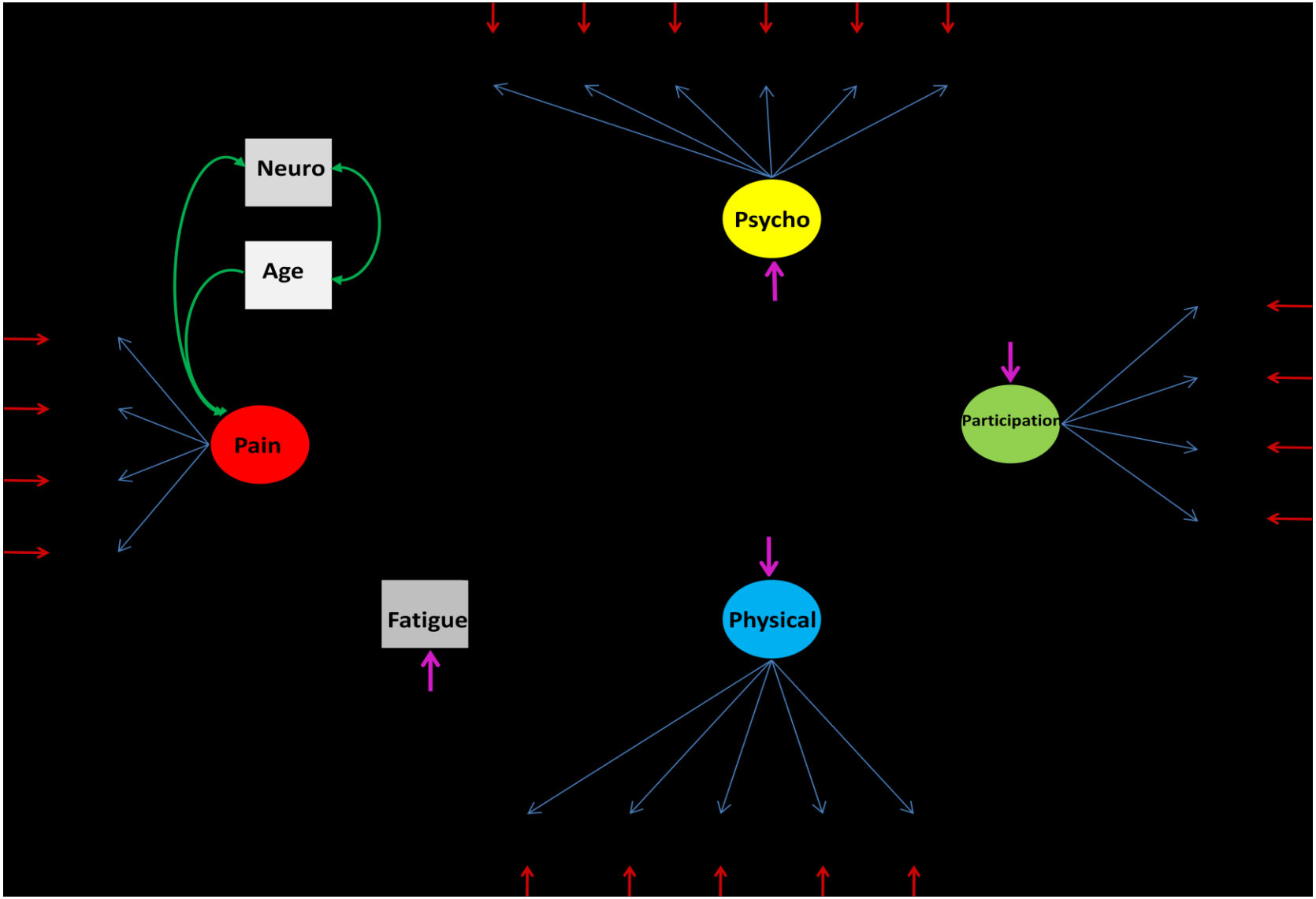


Figure 11.4 Simplified model of relationships

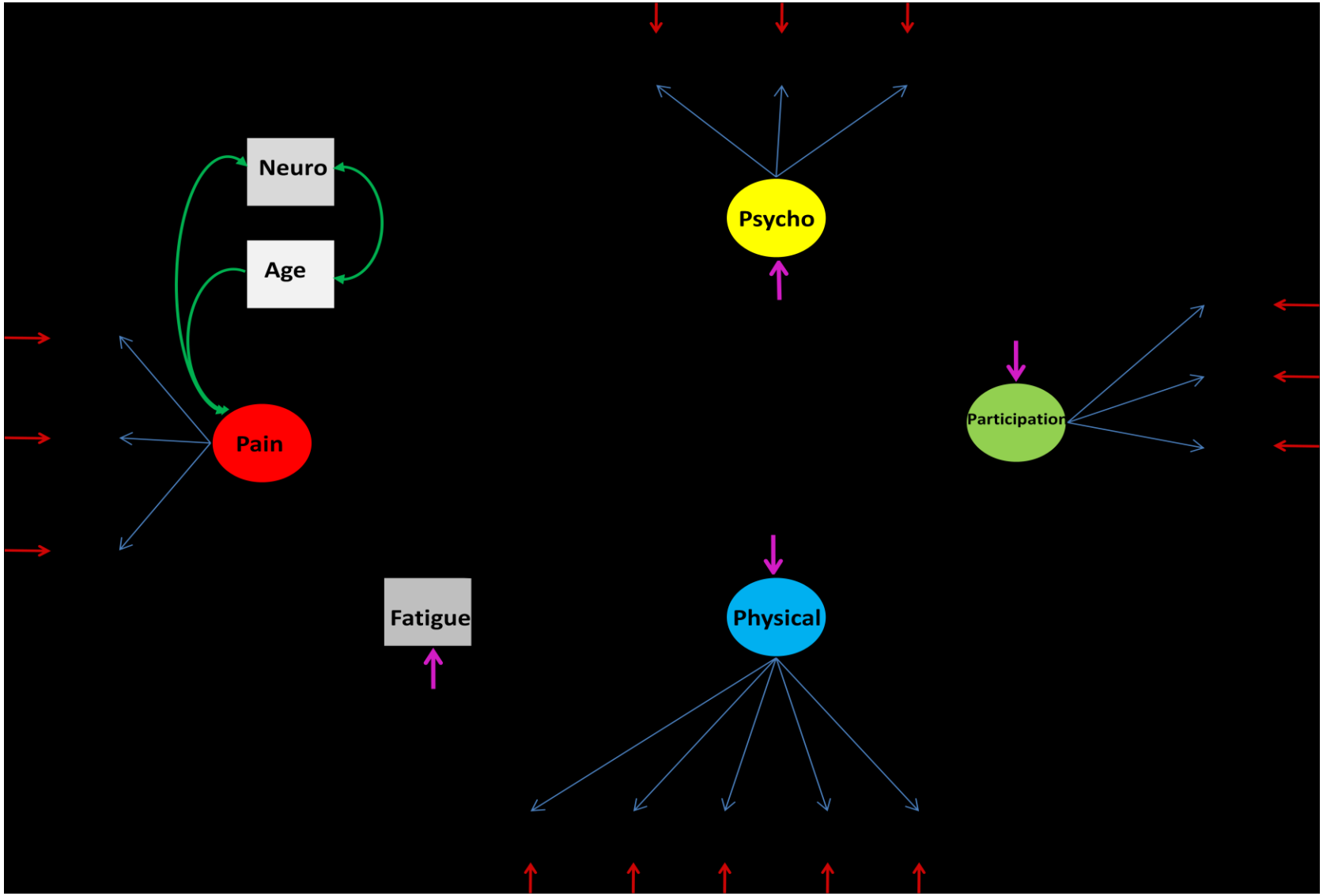


Figure 11.5 Re-specified model of participation

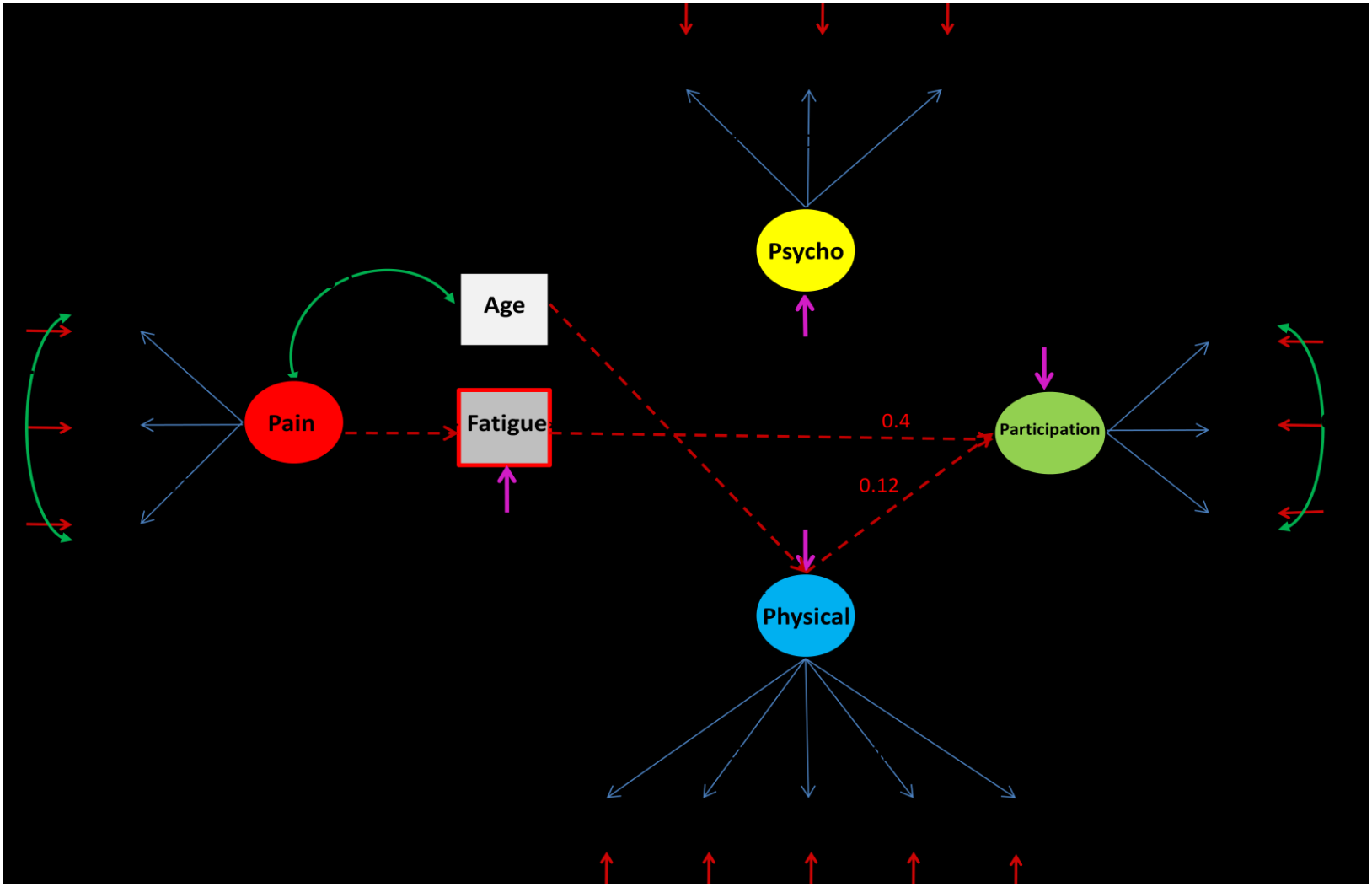


Figure 11.6 The final model

Note: The final model for participation. Black arrows represent a direct relationship and dashed red arrows represent indirect effects. R2 represent the proportion of the variance explained by the model for each endogenous variable. This model explains 88% of the variance seen in participation. All paths displayed in the figure are significant.

CHAPTER 12
CONCLUSION & SUMMARY

12.1 Conclusion

Pain associated with MS is an understudied contributor to MS-associated disability including participation restriction, and also to impaired quality of life (QOL). The global aim of the current study was to contribute to the understanding of the pain experience in people with MS with the context of function, disability, and quality of life. The main objective of this thesis was to contribute evidence as to how the different MS impairments and activity limitations interact to affect participation, a key target of rehabilitation and medical intervention. To achieve this aim, a series of specific objectives/questions were developed and the manuscripts arising from this work form this thesis.

Manuscript 1 was the first systematic review and meta-analysis about the impact of pain on employment status in the MS population. Work was chosen to be the domain of interest in the first manuscript, because work is one of the key aspects of participation and is very important in this relatively young population. Additionally, MS occurs in individuals during peak years of normal productivity, impacting their ability to remain in the work force. Our results indicated that there is an increased risk of unemployment for MS persons who experience pain compared to those who do not have pain. However, the findings also implied that keeping a job depends on a number of factors other than specific symptoms or MS progression. Results are sufficiently encouraging to justify more high quality research efforts in this area. Results suggest that early identification and treatment of pain could potentially keep people with MS employed for a longer time. Stratification of participants based on their initial level of pain and according to whether they are in acute or chronic pain could clarify further the role of pain on work. The effect of pain related treatments such as pain analgesics and muscle relaxants on work status should also be considered as they would further impair cognitive function and enhance fatigue and so limit return to work.

To understand the role of pain in involvement in life roles, naturally the next step was to understand the target population, specifically, their pain characteristics. An essential component

to understanding pain is an adequate assessment of pain. A comprehensive assessment of pain variables, along with its impact and predictors, as well as interpretation of results using appropriate statistical methods help to enhance pain relief. Inadequate treatment of pain is an important public health problem, and can precipitate a progression to chronic pain. The second and third manuscripts, therefore, provided an overall picture of pain in our sample. In the second manuscript, we identified pain prevalence, severity, frequency, duration, quality, location, distribution, treatment, type, impact and interference. Results indicated that pain is a common symptom among people with MS, reinforcing the need to identify the cause of pain and seek out an effective approach to treat pain adequately. Results also indicated that MS severity was a strong predictor for both pain presence and intensity suggesting that some aspects of disease progression contribute to the development and intensification of pain. The results of this study also showed that pain was associated with higher levels of depression, anxiety, sleep problems and cognitive deficit, and lower levels of physical function, general health perception, and ability to work. The identification of factors that diminish or trigger pain is important for clinicians as this knowledge would facilitate the development of targeted rehabilitative interventions to reduce pain.

To further characterize the pain profile of our sample, the third manuscript estimated the extent to which there is stability in pain type and pain severity over time, a feature that has been relatively ignored in the MS pain literature mostly due to the unpredictability of the disease course, as well as the interaction between pain and other symptoms and contextual factors. We found that all ratings of pain severity have been increased; however, neuropathic type pain was stable and only developed in a small percent of the sample. Although this occurrence was rare, of potential interest would be to understand the impact of developing neuropathic pain. Further results of the third manuscript indicated that two individuals, who reported same amount of pain severity on a global pain rating scale may indicate different types of pain sensation, suggesting that a single measure of pain severity alone is inadequate assessment tool as it may not adequately represent the construct of pain. The findings of the third manuscript provided practical applications for chronic pain management programs; serial measures of pain should be included in the visit of every person with MS to provide prognostic information and improve

pain treatment. In addition, it has clinical implications regarding the differences across people in the experience of pain.

While working on manuscripts 2 and 3 several methodological and statistical challenges in measuring pain were brought up. One of the main challenges in measuring pain is that pain can only be measured using self-report tools. These measures vary in terms of what is measured (including duration, severity, and location), and the results are affected by ability to concentrate, memory impairments, fatigue, anxiety, mood, and emotional status at the time of evaluation as well as the time frame in which the pain is reported. In addition, the complexity of pain as a multidimensional construct necessitates a comprehensive multidimensional assessment, and emphasizes that pain should be studied within an interactive framework targeting all contributing factors including different aspects of health from biological, functional, individual and social perspectives.

Another challenge is that pain is susceptible to a phenomenon called response shift. Response shift means a change in an individual's judgment of their pain (or any other self-reported health outcome) over time. This means that persons might give different answers on measures of pain over time, not because of a true change in their pain level, but because they might have changed their perception of pain due to a health state change, or changes in internal standards (recalibration), values (reprioritization), or meaning (reconceptualization) of pain (Schwartz & Sprangers 2013). Recalibration is change in people's evaluation of a target construct due to the change in individuals' perspective or internal standard (Schwartz & Sprangers 2013). For example, a person with MS may rate the intensity of his back pain as 6 out of 10 on a Numeric Rating Scale (NRS). The individual later acquires episodes of intense pain in the face, called trigeminal neuralgia, which are much more painful, the individual realizes that the back pain he rated earlier was probably less than a 6. This phenomenon is known as scale recalibration. Reprioritization is a change in the respondent's values over time (Schwartz & Sprangers 2013). As an example of reprioritization, an individual with MS who originally may value disability over other consequences of MS may later acquire a relapse leading to severe vision problems, which is much more stressful. Although this person may still value disability highly, vision now becomes the most important consequence of MS. Reconceptualization is a redefinition of the

target construct over time (Schwartz & Sprangers 2013). For instance, the factors contributing to an individual's QOL may change after a life-altering event such as a diagnosis of MS, this redefinition of QOL would be an example of reconceptualization (Schwartz & Sprangers 2013).

Increased knowledge of response shift may affect the way in which pain measures are used, both in clinical practice and in research studies. From a theoretical perspective, integrating response shift into pain research would allow a better understanding of how pain is affected by changes in health status. Thus, the assessment of response shift should be part of any longitudinal pain measure because an accurate measure of change in pain could potentially be missed if response shift is not taken into account.

Various methods for response shift detection have been proposed (Ahmed & Mayo 2007, Barclay-Goddard 2009a, b, Schwartz & Sprangers 2013). They mostly involve design approaches (pre- test, post- test), additional administrations of the same questionnaire (e.g., then-test), or additional alternative assessments of the target construct (e.g., interviews, direct assessments of values) (Ahmed & Mayo 2007, Barclay-Goddard 2009a,b, Schwartz & Sprangers 2013). There are also several analytical methods to evaluate response shift such as growth curve analysis, structural equation modeling, and multivariate multilevel models (Barclay-Goddard 2009b). Due to the challenges associated with the design approaches or other methods, the analytical approach is a promising one for evaluating response shift (Barclay-Goddard 2009a). However, statistical methods typically combine data across individuals and give information at the group level, thus they may mask the individual effects (Mayo 2008). A new method called latent trajectory of residuals approach proposed by Dr. Mayo in 2008 is an analytical approach at an individual level (Mayo 2008). In this approach individuals are assigned a residual at each time point depending on how their predicted scores are different from their reported scores. A longitudinal comparison between reported and predicted scores could be used as a method of identifying subjects who potentially experienced response shift. This model has been tested against a data set from a study in which the then-test had been administered and the results support that this methodology identifies the presence of response shift (Mayo 2008). Further empirical research into response shift will be helpful to further our understanding of pain change and adaptation in chronic diseases such as MS.

The fourth manuscript of this thesis provided important information for addressing symptom clusters in MS. While the majority of previous studies on symptom clusters in MS had a small sample size and included mostly women, this is the first application of cluster analysis to gender differences using a well-designed epidemiological study of MS. In addition, while the focus of most previous studies was on a limited number of symptoms, here a broader range of symptoms was included. A strength of this study was the application of different cluster analytical methods such as hierarchical and non- hierarchical clustering, as well as a comparison with exploratory factor analysis enhancing the validity of our results and conclusions. For the first time, predictive ability of different clusters on the downstream disease consequences such as walking capacity, illness intrusiveness, perceived health status and QOL was shown. Interestingly, the physical symptom clusters of pain, fatigue, and sleep disorder proved to be the one with most disabling consequences, affecting all except walking capacity. Nevertheless, there are still many questions in the area of symptom clusters that need more investigation. Future efforts are needed to identify variation in symptom clusters across different MS types, severity, and age groups. Longitudinal studies are also needed to evaluate the change in pattern of clusters over time. However, as illustrated in the third manuscript "Long-term stability of pain type and severity among people with multiple sclerosis" tracking change in even one symptom over time is methodologically and statistically challenging. Tracking of symptoms cluster over time would be even more difficult. For example, to track only one symptom, such as pain type stability over time, we had to consider different pain types (neuropathic, non-neuropathic, and a mixed of both) that could change in any combination; thus not only was time a factor, but so was pain type.

The results of Manuscript 4 provided new insights on the relationship between and among MS symptoms and several important disease consequences. However, analytical methods that we used in Manuscript 4, such as multiple regression analysis, exploratory factor analysis, cluster analysis and principal component analysis, could only determine the direct relationship among symptoms. Nevertheless, the primary aim of this thesis was to contribute evidence to support a multidimensional theoretical framework to conceptualize the construct of participation in the context of MS and simultaneously target and evaluate the complex interrelationships among all contributing factors. Therefore, the fifth and final manuscript of this thesis used Wilson- Cleary

Model (WCM), as a theoretical framework (Wilson & Cleary 1995) to explain these relationship, and SEM, as an advance statistical method. Although a first model, overall our results provided support for fatigue, physical function, and psychological status as most important direct contributors for participation in persons with MS. Fatigue was found to be not only the major reason for participation restriction in this study, but was in relationship with all other variables in the model, thus confirming its role as the most disabling symptom of MS.

Results of the fifth manuscript further indicated the indirect effects of pain on participation. Pain is often considered as one of the MS symptoms that may contribute to problems with participation. It is reasonable to think that in the presence of pain, people may be reluctant to engage in physical and social activities. The results of the current study, however, showed no direct effect of pain on participation. The only effect of pain on participation was through fatigue, indicating that participants with higher levels of pain, who experienced higher levels of fatigue, reported lower levels of participation.

One important message of this study for clinicians is that in persons with MS, a careful assessment of fatigue, psychological status, and physical function would provide a much better guide to a patient's participation than any combination of biologic and physiologic variables or contextual factors. Although this conclusion will not surprise experienced clinicians, it does support the value of a thorough assessment and management of those specific types of symptoms. The role of fatigue in driving the path to participation indicates that its overall effect cannot be underestimated. Reducing fatigue may be the central treatment target and given that pain impacts on fatigue identifies the need for a thorough assessment and treatment of pain type and intensity. These findings have another important implication for clinical practice, as it emphasizes the strong need for health, activity, and social roles promotion in persons with MS.

The findings of this research can play an important role for recommendation to health policy makers to ensure that appropriate resources and adequate supports are available for people with MS to maximize their participation at the life pursuits. Providing convenient facilities where people with MS can go to attend social and recreational activities for free or for a low price, as well as the possibility of providing an appropriate transportation system for patients, would

increase their participation. Employers need to provide reasonable support so that people with disabilities remain in the workforce. Giving appropriate information to patients about the advantage of participating in leisure, exercise, and social activities, and guiding them to do these safely is also suggested.

The results of this study can also be used to conceptualize participation due to the appropriate selection of participation parameters and measurement scales, adequate research method, and complex statistical methods used. However, a limitation of this study was that the measures for participation missed several components that should be included.

Edwards and Bagozzi highlight the importance of distinguishing between different conceptual models when developing a measure (Edwards & Bagozzi 2000). There are two conceptual models: reflective and formative. Under a reflective conceptual model the items reflect the construct, if the construct changes, the items change (De Vet 2011). A reflective conceptual model is a latent model, a latent variable represents a construct that cannot be directly measured but is inferred from reactions to several related items or activities (Edwards & Bagozzi 2000). For example, items that reflect anxiety are the representation of worrying thoughts or panic. If there was an intervention to reduce anxiety, the presence of worrying thoughts or panic would decrease (De Vet 2011). Under a formative model, the items form the construct; the resulting total score is a composite value of presented items and a change in the construct will not affect all of the items (De Vet 2011). A classical example is life stress; when a person loses his job, his life stress increases. However if there was an intervention to decrease life stress, the presence of job loss would not necessarily decrease (De Vet 2011). The challenge with the construct of participation is that it can be conceptualized as both a reflective and a formative model (Dijkers 2010). Participation can be conceptualized as a formative model as it is formed by a number of activities and life roles that individuals engage in. Under a reflective model, participation would be reflected by accomplishing designed activities to a level of personal satisfaction with activities valued by the individual or society (Wood-Dauphinee 1988).

12.2 Summary

Pain associated with MS is an understudied contributor to MS-associated disability, participation restriction, and impaired QOL. Participation is an essential component to rehabilitation in chronic conditions as it affects HRQL. Pain and participation are global constructs, so their complexity poses a measurement challenge emphasizing that they should be studied within a multidimensional approach targeting all contributing factors. Given the methodological challenges of classical modeling techniques a novel approach using SEM was performed. The WCM was used as a guiding framework, providing the hypotheses about associations among variables.

Although it is a first model, overall our results revealed that fatigue, physical function, and psychological status do directly affect participation in persons with MS. Although pain was prevalent, pain-related MS in isolation does not adequately impact on individuals' participation. The only effect of pain on participation was through fatigue, indicating that participants with higher levels of pain who experienced higher levels of fatigue reported lower levels of participation.

Results of the current study brought new evidence of the validity of the conceptualization of participation in MS population due to the appropriate selection of participation measures, adequate research method, and complex statistical methods used. Finally, the results of this study proved evidence for the validity of WCM in MS. Further research needs to be done to go beyond role function and participation to health perception and QOL. This study would serve as a model for future research for these important constructs.

References

Ahmed S., Mayo N. Using structural equation modeling to evaluate response shift Journal of Clinical Epidemiology 2007; 60 (4): 427-428.

Barclay-Goddard R, Epstein J, Mayo N. Response shift: a brief overview and proposed research priorities. Quality of Life Research 2009a; 18 (3): 335-346.

Barclay-Goddard R, Lix LM, Tate R, Weinberg L, Mayo N. E. Response shift was identified over multiple occasions with a structural equation modeling framework. Journal of Clinical Epidemiology 2009b; 62 (11): 1181–1188.

De Vet HCW, Terwee CB, Mokkink L, Knol D. Measurement in medicine. Cambridge University Press; 2011.

Dijkers MP. Issues in the conceptualization and measurement of participation: an overview. Arch Phys Med Rehabil 2010; 91(Suppl 1):S5-16.

Edwards JR, Bagozzi RP. On the nature and direction of relationships between constructs and measures. Psychol Methods 2000; 5(2):155-74.

Mayo NE, Scott SC, Dendukuri N, Ahmed S, Wood-Dauphinee S. Identifying response shift statistically at the individual level. Qual Life Res 2008 May; 17(4):627-39.

Schwartz CE, Ahmed S, Sawatzky R, Sajobi T, Mayo N, Finkelstein J, Lix L, Verdam MG, Oort FJ, Sprangers MA. Guidelines for secondary analysis in search of response shift. Qual Life Res 2013 Apr 10 [Epub ahead of print]

Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. JAMA 1995; 273(1):59-65.

Wood-Dauphinee SL, Opzoomer MA, Williams JI, Marchand B, Spitzer WO. Assessment of global function: The Reintegration to Normal Living Index. Arch Phys Med Rehabil 1988; 69(8):583-90.

REFERECE LIST

(1) Acquadro C, Berzon R, Dubois D et al. Incorporating the patient's perspective into drug development and communication: an ad hoc task force report of the Patient-Reported Outcomes (PRO). Harmonization Group meeting at the Food and Drug Administration, Health 2003; 6:522-31.

(2) Ahmed S, Mayo NE, Wood-Dauphinee S, Hanley JA, Cohen SR. Using the Person Generated Index to evaluate response shift post-stroke. Qual Life Res 2005; 14:2247-2257.

(3) Ahmed S, Mayo N. Using structural equation modeling to evaluate response shift. Journal of Clinical Epidemiology 2007; 60: 427-428.

(4) Altman DG. Practical statistics for medical research. London: Chapman and Hall, 1991.

(5) Amato M.P, Ponziani G, Rossi F, Liedl C.L, Stefanile C, Rossi L. Quality of life in multiple sclerosis: the impact of depression, fatigue and disability. Mult Scler 2001; 7: 340–344.

(6) Amato M, Battaglia M, Caputo D, et al. The costs of multiple sclerosis: A cross-sectional, multicenter cost-of-illness study in Italy. J Neurol 2002; 249:152-63.

(7) Anderberg, M. R. Cluster Analysis for Applications, 1973, New York: Academic Press, Inc.

(8) Andresen, E. M., Malmgren, J. A., Carter, W. B., & Patrick, D. L. Screening for depression in well older adults: Evaluation of a short form of the CES-D. American Journal of Preventive Medicine 1994; 10 (2), 77–84.

(9) Andrich D, Sheridan B, Luo G. Rumm2020: A windows interactive program for analysing data with rasch unidimensional models for measurement. 2004

(10) Archibald CJ, McGrath PJ, Ritvo PG, Fisk JD, Bahn V, Maxner CE, Maxner E, Murray TJ. Pain prevalence, severity, and impact in a clinical sample of multiple sclerosis patients. Pain 1994; 58:89-93.

(11) Armstrong TS, Cohen MZ, Eriksen LR, Hickey JV. Symptom clusters in oncology persons and implications for symptom research in people with primary brain tumors. J Nurs Scholarsh 2004; 36: 197-206.

(12) Aronson KJ. Quality of life among persons with multiple sclerosis and their caregivers. Neurology 1997; 48:74-80.

(13) Asano M, Dawes DJ, Arafah A, Moriello C, Mayo NE. What does a structured review of the effectiveness of exercise interventions for persons with multiple sclerosis tell us about the challenges of designing trials? Mult Scler 2009; 15(4):412-21.

(14) Asche CV, Ho E, Chan B. Economic consequences of multiple sclerosis for Canadians. Acta Neurol Scand 1997; 95:268-274.

(15) Ashworth B. Preliminary trial of carisoprodal in multiple sclerosis. Practitioner 1964; 192: 540–42.

(16) ATS statement: guidelines for the six-minutewalk test. Am J Respir Crit Care Med2002 July 1;166(1):111-7.

(17) Auger C, Montplaisir J, Duquette P. Increased frequency of restless legs syndrome in a French-Canadian population with multiple sclerosis. Neurology 2005; 65(10):1652.

(18) Bakas T, McLennon S.M, Carpenter J.S, Buelow J.M. Systematic review of health-related quality of life Models. Health and Quality of Life Outcomes 2012, 10:134.

(19) Bakhsi R. Fatigue associated with MS: diagnosis, impact and amangement. Mult Scler 2003; 9 (3):219-27.

(20) Bamer AM, Johnson KL, Amtmann D, Kraft GH. Prevalence of sleep problems in individuals with multiple sclerosis. Mult Scler. 2008; 14(8): 1127–1130.

(21) Banks MH. Psychological effects of prolonged unemployment: relevance to models of work re-entry following injury. J Occup Rehabil 1995; 5:37–53.

(22) Barclay-Goddard R, Ripat J, Mayo N. Developing a model of participation post-stroke: a mixed-methods approach. Qual Life Res 2012; 21:417–426.

(23) Barclay-Goddard R, Epstein J, Mayo N. Response shift: a brief overview and proposed research priorities. Quality of Life Research 2009a; 18 (3): 335-346.

(24) Barclay-Goddard R, Lix LM, Tate R, Weinberg L, Mayo N. E. Response shift was identified over multiple occasions with a structural equation modeling framework. Journal of Clinical Epidemiology 2009b; 62 (11): 1181–1188.

(25) Baylor C, Yorkston K, Bamer A, Britton D, Amtmann D. Variables Associated with Communicative Participation in People With Multiple Sclerosis: A Regression Analysis. American Journal of Speech-Language Pathology 2010, (19): 143–153.

(26) Beatty W, Blanco C, Wilbanks S, Paul R, Hames K. Demographic, clinical and cognitive characteristics of multi-ple sclerosis patients who continue to work. J Neurol Rehabil 1995; 9:167–173.

(27) Beck CA, Metz LM, Svenson LW et al. Regional variation of multiple sclerosis prevalence in Canada. Mult Scler. 2005; 11:516-9.

(28) Becker H, Stuifbergen AK, Sands D. Development of a scale to measure barriers to health promotion activities among persons with disabilities. Am J Health Promot 1991;5(6):449-454.

(29) Beeson PB. Age and sex associations of 40 autoimmune diseases. Am J Med 1994; 96(5):457-9.

(30) Begg, CB and Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994; 50:1088–1101.

(31) Beiske AG, Pedersen ED, Czujko B, Myhr KM. Pain and sensory complaints in multiple sclerosis. Eur J Neurol 2004; 11:479–82.

(32) Bender CM, Ergyn FS, Rosenzweig MQ, Cohen SM, Sereika SM: Symptom clusters in breas t cancer across 3 phases of the disease. Cancer Nurs 2005; 28:219–225.

(33) Benedict R, Wahlig E, Bakshi R, Fishman I, Munschauer F, Weinstock-Guttman B. Predicting quality of life in multiple sclerosis: accounting for physical disability, fatigue, cognition, mood disorder, personality, and behavior change. Journal of the Neurological Sciences 2005; 231 (1, 2): 29–34.

(34) Benito-Leon J, Morales JM, Rivera-Navarro J et al. A review about the impact of multiple sclerosis on health-related quality of life. Disabil Rehabil 2003; 25:1291-303.

(35) Benito-Leon J., J.M. Morales, J. Rivera-Navarro. Health-related quality of life and its relationship to cognitive and emotional functioning in multiple sclerosis persons. Eur. J. Neurol 2002; 9: 497–502.

(36) Bjelland I, Dahl AA, Haug TT, Neckelmann D,: The validity of the Hospital Anxiety and Depression Scale; an updated review. J Psychiat Res 2002, 52:69-77

(37) Bohannon RW, Schaubert KL. Test-retest reliability of grip-strength measures obtained over a 12-week interval from community-dwelling elders. J Hand Ther 2005; 18(4):426-7.

(38) Bohannon, R. and Smith, M. "Interrater reliability of a modified Ashworth scale of muscle spasticity." Physical Therapy 1987; 67(2): 206-7.

(39) Bouchard V. Illness intrusiveness in multiple sclerosis: An exploration from the perspective of modern outcome measurement theory. McGill University. Master thesis, Rehabilitation Science, 2012.

(40) Boureau F, Doubrere JF, Luu M. Study of verbal description in neuropathic pain. Pain 1990; 42,145-152.

(41) Brass SD, Duquette P, Proulx-Therrien J, Auerbach S. Sleep disorders in patients with multiple sclerosis. Sleep Medicine Reviews 14 (2010) 121–129

(42) Brasure M, Lamberty GJ, Sayer NA, Nelson NW, Macdonald R, Ouellette J, Wilt TJ. Participation after multidisciplinary rehabilitation for moderate to severe traumatic brain injury in adults: a systematic review. Arch Phys Med Rehabil 2013; 94(7):1398-420.

(43) Brazier JE, Harper R, Jones NM, O'Cathain A, Thomas KJ, Usherwood T, Westlake L. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. BMJ 1992; 305:160-164.

(44) Brown M. Participation: The insider's perspective. Archives of Physical Medicine and Rehabilitation, 2010 (91): S34–S37.

(45) Brunet DG, Hopman WM, Singer MA, Edgar CM, MacKenzie TA Measurement of health-related quality of life in multiple sclerosis patients. The Canadian Journal of Neurological Sciences. Le Journal Canadien des Sciences Neurologiques 1996, 23(2):99-103.

(46) Buchanan RJ, Wang S, Ju H. Analyses of the minimum data set: comparisons of nursing home residents with multiple sclerosis to other nursing home residents. Mult Scler 2002; 8:512–22.

(47) Busche KD, Fisk JD, Murray TJ, Metz LM. Short term predictors of unemployment in multiple sclerosis patients. Can J Neurol Sci. 2003; 30:137- 42.

(48) Butland RJA, Pang J, Gross ER, Woodcock AA, Geddes DM. Two-, six- and 12-minute walking tests in respiratory disease. BMJ 1982; 284:1607–1608.

(49) Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989; 28(2):193-213.

(50) Cano S, Barrett L, Zajicek J, Hobart J. Beyond the reach of traditional analyses: Using rasch to evaluate the dash in people with multiple sclerosis. Multiple Sclerosis Journal 2011; 17:214-222.

(51) Cara Brown, Kaitlyn Kitchen, and Kaley Nicoll (2012) Barriers and Facilitators Related to Participation in Aquafitness Programs for People with Multiple Sclerosis. International Journal of MS Care 2012; 14 (3):132-141.

(52) Cardol M, de Haan RJ, van den Bos GAM, de Jong BA, de Groot IJM. The development of a handicap assessment questionnaire: The Impact on Participation and Autonomy (IPA). Clinical Rehabil 1999; 13: 411- 419.

(53) Carletta, Jean. Assessing agreement on classification tasks: The kappa statistic. Computational Linguistics 1996; 22(2): 249–254.

(54) Castro-Borrero W, Graves D, Frohman TC, Flores AB, Hardeman P, Logan D, Orchard M, Greenberg B, Frohman EM.
Current and emerging therapies in multiple sclerosis: a systematic review. Ther Adv Neurol Disord 2012; 5(4):205-20

(55) Cella DF, Dineen K, Arnason B, Reder A, Webster KA, Karabatsos G, et al. Validation of the functional assessment of multiple sclerosis quality of life instrument. Neurology 1996; 47:129-139

(56) Chau JP, Thompson DR, Twinn S, Chang AM, Woo J. Determinants of participation restriction among community dwelling stroke survivors: a path analysis. BMC Neurol 2009; 9:49.

(57) Chen ML, Lin CC: Cancer symptom clusters: a validation study. J Pain Symptom Manage 2007; 34:590–599.

(58) Cheng S.F, Foster R.L, Huang C.Y. Concept Analysis of Pain. Tzu Chi Nursing Journal 2003; 2:3, 20-30.

(59) Cieza A, Geyh S, Chatterji S et al. ICF linking rules: an update based on lessons learned. J Rehabil Med 2005; 37: 212-8.

(60) Cleeland CS. Symptom Burden: Multiple Symptoms and Their Impact as Person-Reported Outcomes Cancer and its treatm. J Natl Cancer Inst Monogr 2007; 37: 16 – 21.

(61) Clifford DB, Trotter JL. Pain in multiple sclerosis. Arch Neurol 1984; 41:1270–2.

(62) Compston A, Confavreux C, Lassmann H. McAlpine's Multiple Sclerosis. Philadelphia: Elsevier, 2005.

(63) Compston, Alastair Journal of Neurology, Neurosurgery & Psychiatry. 62(6):553-561, June 1997.

(64) Confavreux C, Vukusic S, Moreau T et al. Relapses and progression of disability in multiple sclerosis. N.Engl.J.Med. 2000; 343:1430-8.

(65) Cruccu G, Anand P, Attal N, Garcia-Larrea L, Haanpää M, Jorum E, Serra J, Jensen TS. EFNS guidelines on Neuropathic pain assessment. Eur J Neurol 2004; 11:153–62.

(66) CSEP Health & Fitness Program's Health-Related Appraisal & Counselling Strategy. The Canadian Physical Activity, Fitness and Lifestyle Approach. 3rd ed. Ontario: Canadian Society for Exercise Physiology; 2004.

(67) Culp D. Illness intrusiveness and sexual satisfaction among women with multiple sclerosis. Master of Arts Thesis in Psychology, Ryerson University, 2010.

(68) D'Alisa, S., Miscio, G., Baudo, S., Simone, A., Tesio, L., & Mauro, A. Depression is the main determinant of quality of life in multiple sclerosis: A classification-regression (CART) study. Disability 2006, 28(5), 307 Y314.

(69) da Silva A M, Vilhena E, Lopes A, Santos E . Depression and anxiety in a Portuguese MS population: Associations with physical disability and severity of disease. Journal of the Neurological Sciences 2011; 306, Issues (1–2, 15): 66–70.

(70) De Vet HCW, Terwee CB, Mokkink L, Knol D. Measurement in medicine. Cambridge University Press; 2011.

(71) DeLuca, J. (). What we know about cognitive changes in multiple sclerosis. In: N.L. LaRocca & R. Kalb (Eds.), Multiple sclerosis: Understanding the cognitive changes 2006, pp:17 – 39. New York: Demos Medical Publishing.

(72) Deriu M, Cossu G, Molari A, Murgia D, Mereu A, Ferrigno P, Manca D, Contu P, Melis M. Restless legs syndrome in multiple sclerosis: a case-control study. Mov Disord 2009; 24 (5):697.

(73) Desrosiers J, Hebert R, Bravo G, Dutil E. Comparison of the Jamar dynamometer and the Martin vigorimeter for grip strength measurements in a healthy elderly population. Scand J Rehabil Med1995; 27(3):137-43.

(74) Desrosiers J, Noreau L, Rochette A, et al. Predictors of handicap situations following poststroke rehabilitation. Disabil Rehabil 2002; 24(15):774–85.

(75) Devins GM, Binik YM, Hutchinson TA, Hollomby DJ, Barré PE, Guttmann RD. The Emotional Impact of End-Stage Renal Disease: Importance of Persons' Perceptions of Intrusiveness and Control. The International Journal of Psychiatry in Medicine 1983; 13 (4): 1983-84.

(76) Devins GM, Edworthy SM, Paul LC, Mandin H, Seland TP, Klein G, Costello CG, Shapiro CM. Restless sleep, illness intrusiveness, and depressive symptoms in three chronic illness conditions: rheumatoid arthritis, end-stage renal disease, and multiple sclerosis. J Psychosom Res 1993a; 37(2):163-70.

(77) Devins GM, Edworthy SM, Seland TP, Klein GM, Paul LC, Mandin H. Differences in illness intrusiveness across rheumatoid arthritis, end-stage renal disease, and multiple sclerosis. J Nerv Ment Dis 1993b; 181(6):377-81.

(78) Devins GM. Illness intrusiveness and the psychosocial impact of lifestyle disruptions in chronic life-threatening disease. Adv Ren Repl Ther 1994; 1: 251-263.

(79) Devins GM, Styra R, O'Connor P. Psychosocial impact of illness intrusiveness moderated by age in multiple sclerosis. Psychol Hlth Med 1996; 1: 179-191.

(80) Devins GM, Dion R, Pelletier LG, Shapiro CM, Abbey S, Raiz LR, Binik YM, McGowan P, Kutner NG, Beanlands H, Edworthy SM. Structure of lifestyle disruptions in chronic disease: a confirmatory factor analysis of the Illness Intrusiveness Ratings Scale. Med Care 2001 October; 39(10):1097-104.

(81) Devins GM. Using the illness intrusiveness ratings scale to understand health-related quality of life in chronic disease. J Psychosom Res 2010; 68(6):591-602.

(82) Dijkers MP. Issues in the conceptualization and measurement of participation: an overview. Arch Phys Med Rehabil 2010; 91(Suppl 1):S5-16.

(83) Dodd, M.J., Miaskowski, C., & Paul, S.M. Symptom clusters and their effect on the functional status of persons with cancer. Oncology Nursing Forum 2001; 28: 465 – 470.

(84) Dodd M, Miaskowski C, West C, et al. The prevalence of symptoms clusters and comorbidities in oncology out-persons. Paper presented at the 27th Oncology Nursing Society's Annual Congress, Washington, DC, 2002.

(85) Dorman PJ, Dennis M, Sandercock P. How do scores on the EuroQol relate to scores on the SF-36 after stroke? Stroke1999; 30 (10):2146-51.

(86) Dorman PJ, Slattery J, Farrell B, Dennis MS, Sandercock PA. A randomised comparison of the EuroQol and Short Form-36 after stroke. United Kingdom collaborators in the International Stroke Trial. BMJ1997; 23; 315 (7106):461.

(87) Douglas C, Wollin JA, Windsor C. Illness and demographic correlates of chronic pain among a community-based sample of people with multiple sclerosis. Arch Phys Med Rehabil 2008; 89:1923-32.

(88) Drew M, Tippett L.J, Starkey N.J, Isler R.B. Executive dysfunction and cognitive impairment in a large community-based sample with Multiple Sclerosis from New Zealand: A descriptive study. Archives of Clinical Neuropsychology 2008; 23: 1–19.

(89) Dubuisson D, Melzack R. Classification of clinical pain descriptions by multiple group discriminant analysis. Exp Neurol 1976; 51: 480–7.

(90) Duncan, T. E., Duncan, S. C., Strycker, L. A., Li, F., & Alpert, A. (1999). An introduction to latent variable modeling: Concepts, issues, and applications. Mahwah, NJ: Lawrence Erlbaum Associates, Publishers.

(91) Dyck I and Jongbloed L. Women with multiple sclerosis and employment issues: A focus on social and institutional environments. Can J Occup Therapy 2000; 67: 337–346.

(92) Edgley K, Sullivan M, Dehoux E. A survey of multiple sclerosis: determinants of employment status. Can J Rehabil 1991; 4:127–132.

(93) Edwards JR, Bagozzi RP. On the nature and direction of relationships between constructs and measures. Psychol Methods 2000; 5(2):155-74.

(94) Egger M , Smith GD , Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629–624.

(95) Egner A., Phillips V.L., Vora R., Wiggers E. Depression, fatigue, and health-related quality of life among people with advanced multiple sclerosis: results from an exploratory telerehabilitation study. Neurorehabilitation 2003; 18: 125–133.

(96) Ehde DM, Gibbons LE, Chwastiak L, Bombardier CH, Sullivan MD, Kraft GH. Chronic pain in a large community sample of persons with multiple sclerosis. Mult Scler. 2003; 9:605–11.

(97) Ehde DM, Osborne TL, Hanley MA, Jensen MP, Kraft GH. The scope and nature of pain in persons with multiple sclerosis. Mult Scler 2006; 12:629–38.

(98) Ehde DM, Osborne TL, Jensen MP. Chronic Pain in Persons with Multiple Sclerosis. Physical Medicine and Rehabilitation Clinics of North America 2005; 16: 503-512.

(99) Elbers RG, Rietberg MB, van Wegen EE, Verhoef J, Kramer SF, Terwee CB, Kwakkel G. Self-report fatigue questionnaires in multiple sclerosis, Parkinson's disease and stroke: a systematic review of measurement properties. Qual Life Res 2012 Aug; 21(6):925-44. doi: 10.1007/s11136-011-0009-2. Epub 2011.

(100) Enright P. The six-minute walk test. Respiratory care 2003; 48(8):783-5.

(101) Esper P, Heidrich D. Symptom clusters in advanced illness. Semin Oncol Nurs 2005; 21:20-8.

(102) EuroQol-a new facility for the measurement of health-related quality of life. Health. Policy 1990;16:199-208.

(103) Everitt BS, Landau S, Leese M. Cluster analysis. New York: Oxford University Press; 2001.

(104) Feinstein A. An examination of suicidal intent in patients with multiple sclerosis. Neurology 2002; 59:674-8.

(105) Fernandez E, & Milburn TW. Sensory and affective predictors of overall pain and emotions associated with affective pain. Clinical Journal of Pain 1994; 10:3-9.

(106) Fisk JD, Pontefract A, Ritvo PG, Archibald CJ, Murray TJ. The impact of fatigue on patients with multiple sclerosis. Can J Neurol Sci 1994; 21:9-14.

(107) Fleiss JL. The statistical basis of meta-analysis. Statistical Methods in Medical Research 1993; 2:121–45.

(108) Forbes A, While A, Mathes L, Griffiths P. Health problems and health-related quality of life in people with multiple sclerosis. Clin Rehabil 2006; 20:67–78.

(109) Ford H, Trigwell P, Johnson M. The nature of fatigue in multiple sclerosis. J Psychosom Res 1998; 45:33–8.

(110) Fougeyrollas P, Noreau L, Bergeron H, Cloutier R, Dion SA, St-Michel G. Social consequences of long term impairments and disabilities: conceptual approach and assessment of handicap. International Journal of Rehabilitation Research 1998; 21:127-141.

(111) Fox SW, Lyon DE. Symptom clusters and quality of life in survivors of lung cancer. Oncol Nurs Forum 2006; 33:931–936.

(112) Fraser RT, Clemmons DC, Bennett F. Multiple sclerosis: psychosocial and vocational interventions. New York: Demos Medical Publishing Inc, 2002, p. 45–82.

(113) Freeman, J.A., Hobart, J.C., Langdon, D.W., & Thompson, A.J. Clinical appropriateness: A key factor in outcome measure selection: the 36 item short form health survey in multiple sclerosis. Journal of Neurology and Neurosurgery 2000; 68, 150-156.

(114) Frohman EM, Brannon K, Alexander S et al. Disease modifying agent related skin reactions in multiple sclerosis: prevention, assessment, and management. Mult Scler 2004; 10:302-7.

(115) Garratt AM, Ruta DA. The person generated index. In: Joyce CRB, O'Boyle CA, McGee H, eds. Individual quality of life: Approaches to conceptualization and assessment. Amsterdam: Harwood Academic Publishers; 1999; 105-118.

(116) Garrett, M., & Coote, S. Multiple sclerosis and exercise in people with minimal gait impairment—A review. Physical Therapy Reviews 2009, 14, 169 – 180.

(117) Gerald M. DevinsUsing the Illness Intrusiveness Ratings Scale to understand health-related quality of life in chronic disease. Journal of Psychosomatic Research 2010, 68 (6):591–602.

(118) Gift AG, Stommel M, Jablonski A, Given W. A cluster of symptoms over time in persons with lung cancer. Nurs Res 2003; 52:393-400.

(119) Gift AG, Jablonski A, Stommel M, Given CW. Symptom clusters in elderly persons with lung cancer. Oncol Nurs Forum 2004; 31:202-12.

(120) Given C, Given B, Azzouz F, et al. Predictors of pain and fatigue in the year following diagnosis among elderly cancer persons. J Pain Symptom Manage 2001; 6:456-466.

(121) Given B, Given C, McCorkle R, et al. Pain and fatigue management: results of a nursing randomized clinical trial. Oncol Nurs Forum 2002; 29:949-956.

(122) Glad SB, Aarseth JH, Nyland H, Riise T, Myhr K-M. Benign multiple sclerosis: a need for a consensus. Acta Neurol Scand 2010; 122: 44–50.

(123) Glad SB, Nyland H, Aarseth JH. How long can you keep working with benign multiple sclerosis? J Neurol Neurosurg Psychiatry 2011; 82: 78-82.

(124) Gold MR. Cost-effectiveness in health and medicine. New York: Oxford University Press. 1996.

(125) Goldman MD, Marrie RA, Cohen JA. Evaluation of the six-minute walk in multiple sclerosis subjects and healthy controls. Mult Scler 2008 April; 14 (3):383-90.

(126) Gómez-Choco MJ, Iranzo A, Blanco Y, Graus F, Santamaria J, Saiz A. Prevalence of restless legs syndrome and REM sleep behavior disorder in multiple sclerosis. Mult Scler 2007; 13(6):805.

(127) Goodin DS. Survey of multiple sclerosis in northern California. Northern California MS Stud y Group. Mult Scler 1999; 5: 78-88.

(128) Grasso MG, Clemenzi A, Tonini A, Pace L. Pain in multiple sclerosis: a clinical and instrumental approach. Mult Scler 2008; 14: 506 -13.

(129) Grima D, Torrance G, Francis G, Rice G, Rosner A, Lafortune L. Cost and health-related quality of life consequences of multiple sclerosis. Mult Scler 2000; 6:91-8.

(130) Gronwall DM. Paced auditory serial-addition task: a measure of recovery from concussion. Percept Mot Skills 1977 April;44(2):367-73.

(131) Grudzinski A, Hakim Z, Cox E, Bootman J. The economics of multiple sclerosis: Distribution of costs and relationship to disease severity. Pharmacoeconomics 1999; 15:229-40.

(132) Grytten N, Maseide P. 'When I am together with them I feel more ill.' The stigma of multiple sclerosis experienced in social relationships. Chronic Illn 2006; 2:195-208.

(133) Hadjimichael O, Kerns RD, Rizzo MA, Cutter G, Vollmer T. Persistent pain and uncomfortable sensations in persons with multiple sclerosis. Pain 2007; 127:35–41.

(134) Hallström H, Norrbrink C. Screening tools for neuropathic pain: can they be of use in individuals with spinal cordinjury? Pain 2011; 152 (4):772-9.

(135) Hammel J, Jones R, Gossett A & Morgan E. Examining barriers and supports to community living and par-ticipation after a stroke from a participatory action research approach.Topics in Stroke Rehabilitation 2006, 13, 43–58.

(136) Hammond SR, McLeod JG, Macaskill P. Multiple sclerosis in Australia: socioeconomic factors. J Neurol Neurosurg Psych 1996; 61: 311–313.

(137) Hanley JA, Negassa A, Edwardes MD, Forrester JE. Statistical Analysis of Correlated Data Using Generalized Estimating Equations: An Orientation. Am J Epidemiol 2003; 157:364- 375.

(138) Harrell, Frank E., Jr. Regression modeling strategies. “Sections 9.2, 10.5”. New Yor: Springer-Verlag. ISBN 0387952322.

(139) Hatcher L. A step-by-step approach to using the SAS system for factor analysis and structural equation modeling. Cary NC: SAS Institutes Inc; 1994.

(140) Hawkes CH, Fawcett D, Cooke ED, et al. Dorsal column stimulation in multiple sclerosis: effects on bladder, leg blood flow and peptides. Appl Neurophysiol 1981; 44(1–3): 62–70.

(141) Hays RD, Sherbourne CD, Mazel RM. The RAND 36-Item Health Survey 1.0. Health Econ 1993 October; 2(3):217-27.

(142) Hays Ron D, Morales Leo S. The RAND-36 measure of health- related quality of life. Ann Med 2001; 33:350-7.

(143) Hays R, Revicki D, Coyne K. Application of Structure Equation Modeling to Health Outcome Research. Evaluation & The Health Profession 2005; 28 (3): 295-309.

(144) Heckman-Stone C, Stone C: Pain management tech-niques used by patients with multiple sclerosis. J Pain 2:205-208, 2001.

(145) Heinemann, A. Putting outcome measurement in con-text: A rehabilitation psychology perspective. Rehabilitation Psychology 2005; 50(1), 6–14. doi:10.1037/0090-5550.50.1.6

(146) Hermann C: International experience with the Hospital Anxiety and Depression Scale A review of validation data and clinical results. J Psychosom Res 1997, 42:17-41

(147) Herr K. Neuropathic pain: a guide to comprehensive assessment. Pain Manag Nurs. 2004; 5 (4 Suppl 1): 9-18.

(148) Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-560.

(149) Honarmand K, and Feinstein A. Validation of the Hospital Anxiety and Depression Scale for use with multiple sclerosis patients. Multiple Sclerosis; 2009 15(12): 1518–1524.

(150) Hopman W.M, Towheed T, Anastassiades T, Tenenhouse A, Poliquin S. Canadian normative data for the SF-36 health survey. Canadian Medicine Association Journal 2000; 163 (3) 265- 71.

(151) Hoyle RH. Structural equation modeling. Thousand Oaks (CA): SAGE Publications; 1995.

(152) Hu L, Bentler PM. Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. Structural Equation Modeling: A Multidisciplinary Journal. 1999; 6:1 – 55.

(153) Ilfeld FW Jr. Further validation of a psychiatric symptom index in a normal population. Psychol Rep 1976; 39:1215-1228.

(154) Indaco A, Iachetta C, Nappi C, Socci L, Carrieri PB. Chronic and acute pain syndromes in patients with multiple sclerosis. Acta Neurol Scand 1994; 16:97-102.

(155) International Labour Organization: Resolution concerning statistics of the economically active population, employment, unemployment and underemployment, adopted by the 13th International Conference of Labour Statisticians. http://www.ilo.org/public/english/ bureau/stat/download/res/ecacpop.pdf (2007).

(156) Iris M.R.Weller, Scott G.Thomas, Norm Gledhill, Don Paterson, Art Quinney. A study to validate the modified canadian aerobic fitness test. Canadian Journal of Applied Physiology1994 14; 20(2):211-21.

(157) Italian REMS Study Group. Multicenter case-control study on restless legs syndrome in multiple sclerosis: the REMS study. Sleep. 2008; 31(7): 944.

(158) Jacobs LD, Wende KE, Brownscheidle CM. A profile of multiple sclerosis: The New York State Multiple Sclerosis Consortium. Mult Scler 1999; 5: 369–376.

(159) Jacobs LD, Beck RW, Simon JH, Kinkel RP. Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. CHAMPS Study Group. N Engl J Med 2000; 343 (13):898-904.

(160) Jamison R.N, Brown G.K. Validation of hourly pain intensity profiles with chronic pain patients. Pain 1991; 45: 123-128.

(161) Janssens A.C, van Doorn P.A, de Boer J.B, Kalkers N.F, van der Meche F.G, Passchier J. Anxiety and depression influence the relation between disability status and quality of life in multiple sclerosis. Mult Scler 2003; 9:397–403.

(162) Jensen MP, Karoly P, Braver S. The measurement of clinical pain intensity: a comparison of six methods. Pain 1986; 27:117-126.

(163) Jensen MP, Karoly P, Harris P. Assessing the affective component of chronic pain: development of the Pain Discomfort Scale. J Psychosom Res 1991; 35:149-154.

(164) Jensen MP, Turner JA, Romano JM, et al. Comparative reliability and validity of chronic pain intensity measures. Pain. 1999; 83: 157–162.

(165) Jensen MP, Karoly P. Self-report scales and procedures for assessing pain in adults. In: Handbook of Pain Assessment, 2nd. 2001. Turk DC, Melzack R. eds. Guilford Press, New York.

(166) Jensen MP. Review of Measures of Neuropathic Pain. Current Pain and Headache Reports 2006, 10:159–166.

(167) Jensen MP, Chodroff MJ, Dworkin RH. The impact of neuropathic pain on health-related quality of life: Review and implications. Neurology 2007; 68; 1178-1182.

(168) Jette M, Campbell J, Mongeon J, Routhier R. The Canadian Home Fitness Test as a predictor for aerobic capacity. Can Med Assoc J 1976; 17; 114(8):680-2.

(169) Johnson KL, Amtmann D, Yorkston KM, Klasner ER, Kuehn CM. Medical, psychological, social and programmatic barriers to employment for people with multiple sclerosis: A review of the literature. J Rehab 2004; 70: 38-49.

(170) Johnston MV, Miklos CS. Activity-related quality of life in rehabilitation and traumatic brain injury. Arch Phys Med Rehabil 2002; 83(Suppl 2):S26–38.

(171) Julian L, Vella L, Vollmer T, Hadjimichael O, Mohr DC. Employment in multiple sclerosis. Exiting and re-entering the work force. J Neurol. 2008; 255:1354-60.

(172) Juni P, Altman DG, Egger M. Systematic reviews in health care: assessing the quality of controlled clinical trials. BMJ 2001; 323:42–46.

(173) Kalia LV, O'Connor PW. Severity of chronic pain and its relationship to quality of life in multiple sclerosis. Mult Scler2005; 11:322–7.

(174) Karampampa K, Gustavsson A, Miltenburger C, Kindundu CM, Selchen DH. Treatment experience, burden, and unmet needs (tribune) in multiple sclerosis study: The costs and utilities of MS patients in Canada. J Popul Ther Clin Pharmacol 2012; 19:11-25.

(175) Kassirer MR, Osterberg DH (1987). Pain in multiple sclerosis. Am J Nurs 87:968–969.

(176) Katz JN, Larson MG, Phillips CB, Fossel AH, Liang MH. Comparative measurement sensitivity of short and longer health status instruments. Medical Care 1992; 30:917-925.

(177) Keeney S, Hasson F, McKenna HP. A critical review of the Delphi technique as a research methodology for nursing. Int.J.Nurs.Stud. 2001; 38: 195-200.

(178) Kelley KW, Bluthé RM, Dantzer R, Zhou JH, Shen WH, Johnson RW, Broussard SR. Cytokine-induced sickness behavior. Brain Behav Immun. 2003 Feb; 17 Suppl 1:S112-8.

(179) Kempen JCE, de Groot V, Knol DL, Lankhorst GJ, Beckerman H. Self-reported fatigue and energy cost during walking are not related in patients with multiple sclerosis. Archives of Physical Medicine and Rehabilitation 2012; 93 (5): 889–895.

(180) Kerns R, Kassirer M, Otis J. Pain in multiple sclerosis: a biopsychosocial perspective. J Rehabil Res Dev 2002; 39:225–32.

(181) Kerns R. Psychosocial aspects of pain. Int J Mult Scler Care 2000; 2(4):35-38.

(182) Khan F, Pallant J. Chronic Pain in Multiple Sclerosis: Prevalence, Characteristics, and Impact on Quality of Life in an Australian Community Cohort. The Journal of Pain 2007; 8 (8): 614-623.

(183) Kielhofner G. Conceptual Foundations of Occupational Therapy. Philadelphia, PA: F.A. Davis Company; 2004.

(184) Kieseier BC, Hartung HP. Current disease: modifying therapies in multiple sclerosis. Semin eurol 2003 June; 23(2):133:46.

(185) Kim, H.J., & Abraham, I.L. Statistical approaches to modeling symptom clusters in cancer persons. Cancer Nursing 2008; 31, 162 – 220.

(186) Kirkova Jk, Aktas A, Walsh D, Davis MP. Cancer Symptom Clusters: Clinical and Research Methodology. Journal of Palliative Medicine 2011, 14 (10), 1149- 1166.

(187) Kline RB. Principles and practice of structural equation modeling. 2011

(188) Kornblith AB, La Rocca NG, Baum HM. Employment in individuals with multiple sclerosis. International Journal of Rehabilitation. 1985; 9: 155–165.

(189) Krupp, L.B. (2004). Fatigue in multiple sclerosis: A guide to diagnosis and management. New York, NY: Demos Medical Publishing.

(190) Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983; 33(11): 1444–1452.

(191) Kuspinar A, Andersen R, Mayo NE. Predicting Exercise Capacity through SubMaximal Fitness Testing in Persons with Multiple Sclerosis. Arch Phys Med Rehabil 2010; 91: 1410-7.

(192) La Mantia L, D'Amico D, Rigamonti, A. Interferon treatment may trigger primary headaches in multiple sclerosis patients. Mult Scler 2006; 12: 476-480.

(193) Lalkhen AG and McCluskey A. Statistics V: Introduction to clinical trials and systematic reviews. Continuing Education in Anaesthesia, Critical Care & Pain 2008; 8: 143-6.

(194) Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977; 33: 159-74.

(195) Lapierre Y, Hum S. Treating fatigue. The International MS Journal 2007; 14:64-71

(196) LaRocca N, Kalb R, Kendall P, et al. The role of disease and demographic factors in the employment of patients with multiple sclerosis. Arch Neurol 1982; 39: 25-6.

(197) LaRocca N, Kalb R, Scheinberg L, Kendall P. Factors associated with unemployment of patients with multiple sclerosis. Journal of Chronic Disabilities 1985; 38: 203–210.

(198) LaRocca N. Employment and multiple sclerosis. New York: National Multiple Sclerosis Society, 1995.

(199) Law MC and MacDermid J. Evidence-based rehabilitation: a guide to practice. Second edition. USA: SLACK Incorporated 2008, p. 127.

(200) Leary S, Thompson A. Current management of multiple sclerosis. Int J Clin Pract. 2000;54:161–169.

(201) Lee H, Park HJ, Park J, et al. Acupuncture application for neurological disorders. Neurol Res 2007; 29 Suppl 1: S49–54.

(202) Lenz, E.R., Pugh, L.C., Milligan, R.A., Gift, A., & Suppe, F. The middle-range theory of unpleasant symptoms: An update. Advances in Nursing Science 1997, 19(3), 14 – 27.

(203) Lenz, E.R., & Pugh, L.C. The theory of unpleasant symptoms. In: M.J. Smith & P.R. Liehr (Eds.), Middle range theory for nursing 2003, pp: 69 – 90. New York: Springer.

(204) Lerdal A, Gulowsen E, Krupp L, Dahl AA. A prospective study of patterns of fatigue in MS. European Journal of Neurology 2007; 14: 1338- 43.

(205) Leslie GC, Muir C, Part NJ, and Roberts RC. A comparison of the assessment of spasticity by the Wartenberg pendulum test and the Ashworth grading scale in persons with multiple sclerosis. Clin Rehabil 1992; 6: 41–48.

(206) Leussink VI, Husseini L, Warnke C, Broussalis E, Hartung HP, Kieseier BC. Symptomatic therapy in multiple sclerosis: the role of cannabinoids in treating spasticity. Ther Adv Neurol Disord. 2012 Sep; 5(5):255-66.

(207) Leussink VI, Husseini L, Warnke C, Broussalis E, Hartung HP, Kieseier BC. Symptomatic therapy in multiple sclerosis: the role of cannabinoids in treatingspasticity. Ther Adv Neurol Disord. 2012; 5(5):255-66.

(208) Li Y, Munger KL, Batool-Anwar S, De Vito K, Ascherio A, Gao X. Association of multiple sclerosis with restless legs syndrome and other sleep disorders in women. Neurology 2012; 78(19):1500-6.

(209) Lidgren L. The bone and joint decade IASP 2000-2010. Bulletin of the World Health Organization, 81 (9) (2003), p. 629.

(210) Lintern T. C., Beaumont J. G., Kenealy P. M., Murrell R. C. Quality of life (HRQL) in severely disabled multiple sclerosis persons: Comparison of three HRQL measures using multidimensional scaling. Quality of Life Research 2001, 10: 371-378.

(211) Litcher-Kelly L, Stone AA, Broderick Joan E, Schwartz Joseph E. Associations among pain intensity, sensory characteristics, affective qualities, and activity limitations in patients with chronic pain: A momentary, within-person perspective. The Journal of Pain 2004; (5) 8: 433- 439.

(212) Lovera, J., Bagert, B., Smoot, K. H., Wild, K., Frank, R., Bogardus, K., I Bourdette, D. Correlations of perceived deficits questionnaire of multiple sclerosis Quality of Life Inventory with Beck Depression Inventory and neuropsychological tests. Journal of Rehabilitation Research and Development 2006, 43(1): 73-82.

(213) Lublin F, Reingold SC. Defining the clinical course of multiple sclerosis: results of an international survey. National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis". Neurology 1996; 46 (4): 907–11.

(214) Lublin F. History of modern multiple sclerosis therapy. J Neurol. 2005 Sep; 252 Suppl 3:iii3-iii9.

(215) MacCallum, R. C. Model specification: Procedures, strategies, and related issues. In Structural equation modeling: Concepts, issues, and applications, R. H. Hoyle (editor). Thousand Oaks, CA: Sage Publications, Inc 1995; pp. 16-29.

(216) MacCallum, R. C., Browne, M. W., & Sugawara, H. M. Power analysis and determination of sample size for covariance structure modeling. Psychological Methods 1996, 1, 130-149.

(217) MacCallum, R. C., Browne, M. W., & Cai, L. Testing differences between nested covariance structure models: Power analysis and null hypotheses. Psychological Methods 2006, 11, 19-35.

(218) Manconia M, Fabbrinib M, Bonannib E, Filippic M, Roccac M, Murrib L and Ferini-Strambia L. High prevalence of restless legs syndrome in multiple sclerosis. European Journal of Neurology 2007, 14: 534–539.

(219) Margolis RB, Chibnall JT, Tait RC. Test-retest reliability of the pain drawing instrument. Pain 1988; 33: 49- 51.

(220) Margolis RB, Tait RC, Krause SJ. A rating system for use with patient pain drawings. Pain 1986; 24: 57-65.

(221) Markovic G, Dizdar D, Jukic I, Cardinale M. Reliability and factorial validity of squat and countermovement jump tests. J Strength Cond Res 2004 August; 18(3):551-5.

(222) Marrie RA, Miller DM, Chelune GJ, Cohen JA. Validity and reliability of the MSQLI in cognitively impaired patients with multiple sclerosis. Mult Scler 2003; 9(6):621-6.

(223) Marrie RA, Chelune GJ, Miller DM, Cohen JA. Subjective cognitive complaints relate to mild impairment of cognition in multiple sclerosis. Mult Scler 2005; 11(1):69-75.

(224) Martens Matthew P. The Use of Structural Equation Modeling in Counseling Psychology Research. The Counseling Psychologist 2005; 33: 269-298.

(225) Massimo Filippi, Rohit Bakshi, Marco Rovaris, Giancarlo Comi. MRI and Multiple Sclerosis: What Happened in the Last 10 Years? Journal of Neuroimagaing 2007; 17:1S:2S.

(226) Mathiowetz V, Weber K, Volland G, Kashman N.Reliability and validity of grip and pinch strength evaluations. J Hand Surg [Am] 1984;9(2):222-6.

(227) Mayo N.; Goldberg,M.S.; Kind,P. Calibrating the EQ-5D for a Canadian Population. Proceedings from 1997 EuroQol Plenary Meeting, Center for Health Policy and Law, Erasmus University, Rotterdam, The Netherlands. pp: 25-40.

(228) Mayo NE, Wood-Dauphinee S, Cote R, Durcan L, Carlton J. Activity, participation, and quality of life six months post-stroke. Arch Phys Med Rehab 2002; 83:1035-1042.

(229) Mayo N. Setting the agenda for multiple sclerosis rehabilitation research. Mult Scler 2008 November; 14(9):1154-6.

(230) Mayo NE, Scott SC, Dendukuri N, Ahmed S, Wood-Dauphinee S. Identifying response shift statistically at the individual level. Qual Life Res 2008; 17(4):627-39.

(231) Mayo N.E, Scott S.C, Bayley M, Cheung A, Garland J, Jutai J, Wood-Dauphinee S. Modeling Health-Related Quality of Life in People Recovering From Stroke. Quality of Life Research, 2013, in press.

(232) McHorney CA, Ware JE, Jr., Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. A psychometric and clinical test of validity in measuring physical and mental health constructs. Medical Care 1993; 31:247-263.

(233) McHorney CA, Ware JE, Lu JFR, Sherbourne CD. The MOS 36-item short-form health survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse person groups. Med Care 1994; 32: 40–66.

(234) McNemar Quinn. Note on the sampling error of the difference between correlated proportions or percentages. Psychometrika 1947, 12 (2): 153-157.

(235) McSweeney JC, Cleves MA, Lefler L, Yang S. Cluster Analysis of Women's Prodromal and Acute Myocardial Infarction Symptoms by Race and Other Characteristics. Journal of Cardiovascular Nursing 2010, 25(4): 311-322.

(236) Melzack R, Wall PD. Pain mechanisms: a new theory. Science 1965; 150 (699): 971–9.

(237) Melzack R. The McGill Pain Questionnaire. In: Melzack R, ed. Pain measurement and assessment. New York: Raven, 1983:41-47.

(238) Melzack R. The short-form McGill Pain Questionnaire. Pain 1987; 30:191-197.

(239) Melzack R, Katz J. The McGill Pain Questionnaire: appraisal and current status. In: Turk DC. New York: The Guilford Press; 1992. p. 152–68.

(240) Melzack R, eds. Handbook of Pain Assessment. 2nd ed. New York: Guilford Press; 2001:15–34.

(241) Merskey H and Bogduk N, Eds. International Association for the Study of Pain (IASP), Part III: Pain Terms, A Current List with Definitions and Notes on Usage, in Classification of Chronic Pain: IASP Press: Seattle; 1994: 209-14.

(242) Merskey H, Albe-Fessard DG, Bonica JJ et al. Pain terms: a list with definitions and notes on usage. Recommended by the IASP Subcommittee on Taxonomy. Pain 1979; 6(3):249–52.

(243) Merskey H. The taxonomy of pain. The Medical clinics of North America 2007 91(1): 13–20.

(244) Miaskowski C. Gender Differences in Pain, Fatigue, and Depression in Patients with Cancer. Journal of the National Cancer Institute Monographs 2004; 32: 139 – 43.

(245) Miaskowski C. Symptom clusters: establishing the link between clinical practice and symptom management research. Support Care Cancer 2006; 14:792-4.

(246) Michalski D, Liebig S, Thomae E, Hinz A, Bergh FT. Pain in patients with multiple sclerosis: a complex assessment including quantitative and qualitative measurements provides for a disease-related biopsychosocial pain model. J Pain Res 2011; 4:219-25.

(247) Miller D.M., Rudick R.A., Baier M., Cutter G., Doughtery D.S., Weinstock-Guttman B. Factors that predict health-related quality of life in persons with relapsing–remitting multiple sclerosis. Mult Scler 2003; 9: 1–5.

(248) Miltenburger C, Kobelt G. Quality of life and cost of multiple sclerosis. Clin Neurol Neurosurg 2002; 104:272-5.

(249) Minden SL, Marder WD, Harrold LN, Dor A. Multiple Sclerosis: a statistical portrait. New York: National Multiple Sclerosis Society, 1993.

(250) Moher D, Liberati A, Tetzlaff J, Altman DG, the PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Annals of Internal Medicine 2009; 151: 65-94.

(251) Mohr DC. Stress and multiple sclerosis. J Neurol 2007; 254 Suppl 2: II 65-II68.

(252) Morales FJ, Martinez A, Mendez M, Agarrado A, Ortega F, Fernandez:Guerra J, Montemayor T, Burgos J. A shuttle walk test for assessment of functional capacity in chronic heart failure. Am Heart J 1999 August; 138(2 Pt 1): 291:8.

(253) Morris LA, Miller DW. The regulation of patient-reported outcome claims: need for a flexible standard. Value Health 2002; 5:372-81.

(254) Motl RW, Snook EM, McAuley E, Gliottoni R. Symptoms, self-efficacy, and physical activity among individuals with multiple sclerosis. Res Nurs Health. 2006; 29:597–606

(255) Motl RW, Arnett PA, Smith MM. Worsening of symptoms is associated with lower physical activity levels in individuals with multiple sclerosis. Mult Scler. 2008a; 14:140–142.

(256) Motl RW, Snook EM, Schapiro RT. Symptoms and physical activity behavior in individuals with multiple sclerosis. Res Nurs Health 2008b; 31:466–475.

(257) Motl R.W & McAuley, E. Symptom cluster as a predictor of physical activity in multiple sclerosis: Preliminary evidence. Journal of Pain and Symptom Management 2009a, 38, 270 – 280.

(258) Motl, R.W & McAuley, E. Pathways between physical activity and quality of life in adults with multiple sclerosis. Health Psychology 2009b, 28, 682 – 689.

(259) Motl RW, Weikert M, Suh Yoojin, Dlugonski D. Symptom Cluster and Physical Activity in Relapsing-Remitting Multiple Sclerosis. Research in Nursing & Health, 2010a, 33, 398 – 412.

(260) Motl RW, Suh Y, Weikert M. Symptom Cluster and Quality of Life in Multiple Sclerosis. Journal of Pain and Symptom Management 2010b; 39 (6): 1025- 32.

(261) Moulin DE, Foley KM, Ebers GC: Pain syndromes in multiple sclerosis. Neurology 1988; 38:1830-1834.

(262) Moulin DE: Pain in central and peripheral demyelinating disorders. Neurol Clin 1998;16: 889-897.

(263) MS Society of Canada. MS Information- Frequently Asked Questions. www.mssociety.ca/en/information/faq.htm? Version 2007.

(264) MS Society of Canada. www.mssociety.ca. 2009. Canada, MS Society of Canada. Ref Type: Generic.

(265) Mullins LL, Cote MP, Fuemmeler BF, Jean VM, Beatty WW, Paul RH. Illness intrusiveness, uncertainty, and distress in individuals with multiple sclerosis. Rehabilitation Psychology 2001, 46 (2): 139-153.

(266) Murphy DF, McDonald A, Power C, Unwin A, MacSullivan R. Measurement of pain: a comparison of the Visual Analogue Scale with a Nonvisual Analogue Scale. Clin J Pain 1988; 3:197-199.

(267) Muthén L.K & Muthén B.O. Mplus User's Guide. Seventh Edition. Los Angeles, CA: Muthén & Muthén, 1998-2012.

(268) Nayak S, Matheis RJ, Schoenberger NE, et al. use of unconventional therapies by individuals with multiple sclerosis. Clin Rehabil 2003; 17(2): 181–91.

(269) Neubeck L, Freedman SB, Clark AM, Briffa T, Bauman A, Redfern J. Participating in cardiac rehabilitation: a systematic review and meta-synthesis of qualitative data. Eur J Prev Cardiol 2012; 19(3):494-503.

(270) Newland PK, Fearing A, Riley M, Neath A. Symptom clusters in women with relapsing-remitting multiple sclerosis. J Neurosci Nurs. 2012 Apr; 44(2):66-71. doi: 0.1097/JNN.0b013e3182478cba.

(271) Ng P, Finch L, Hum S, Lapierre Y, Duquette P, Bartlett S, Mayo N. The Path to Work Capacity in People with Multiple Sclerosis. Submitted to Archives Phys Med Rehabil, Oct 2013.

(272) Ng Pamela. The Path to Work in People with Multiple Sclerosis. Master Thesis. School of Physical and Occupational Therapy, Faculty of Medicine, McGill University, August 2012.

(273) Nocentini U, Pasqualetti P, Bonavita S, Buccafusca M, De Caro M F, Farina D, Girlanda P.Cognitive dysfunction in patients with relapsing-remitting multiple sclerosis. Mult Scler 2006; 12: 77.

(274) Nortvedt M, Riise T, Myhr K, et al. Quality of life in multiple sclerosis: measuring the disease effects more. Neurology 1999;53:1098–103.

(275) Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG. Multiple sclerosis. N Engl J Med. 2000; 343: 938–52.

(276) Noseworthy John H., Claudia Lucchinetti, Moses Rodriguez, Brian G.Weinshenker. Multiple Sclerosis. The New England Journal of Medicine 2008; 343(13):938-52.

(277) Noyes B. Maximize your options. National Multiple Sclerosis Society. 2005, http://www.nationalmssociety.org/Brochures-Workforce-Max.asp.

(278) Nuyens G, Weerdt W De, Ketelaer P, Feys H. Inter-rater reliability of the Ashworth scale in multiple Sclerosis. Clinical Rehabilittaion1994 (8):286- 292

(279) O'Brien JA, Ward AJ, Patrick AR, Caro J. Cost of managing an episode of relapse in multiple sclerosis in the United States. BMC Health Serv Res. 2003 Sep 2; 3(1):17.

(280) O'Brien JA, Ward AJ, Patrick AR, Caro J. Cost of managing an episode of relapse in multiple sclerosis in the United States. BMC Health Serv Res. 2003 Sep 2; 3(1):17.

(281) O'Connor A, Schwid S, Herrmann D, Markman D, Dworkin R. Pain associated with multiple sclerosis: Systematic review and proposed classification. Pain 2008; 137: 96–111.

(282) O'Connor P, Lee L, Ng P.T, Narayana P, Wolinsky J.S. Determinants of overall quality of life in secondary progressive MS: a longitudinal study. Neurology 2001; 57: 889–891.

(283) O'Connor P. Key issues in the diagnosis and treatment of multiple sclerosis: An overview. Neurology 2009; 59: S1-33.

(284) O'Connor RJ, Cano SJ, Ramió TL, Thompson A J, Playford ED. Factors influencing work retention for people with multiple sclerosis Cross-sectional studies using qualitative and quantitative methods. J Neurol 2005; 252: 892–896.

(285) Oken BS, Kishiyama S, Zajdel D, et al. randomized controlled trial of yoga and exercise in multiple sclerosis. Neurology 2004; 62(11): 2058–64.

(286) Orlewska E, Mierzejewski P, Zaborski J. A prospective study of the financial costs of multiple sclerosis at different stages of the disease. Eur J Neurol 2005; 12:31-9.

(287) Orton SM, Herrera BM, Yee IM et al. Sex ratio of multiple sclerosis in Canada: a longitudinal study. Lancet Neurol 2006; 5(11):932-936.

(288) Osborne TL, Jensen MP, Ehde DM, Hanley MA, Kraft G. Psychosocial factors associated with pain intensity, pain-related interference, and psychological functioning in persons with multiple sclerosis and pain. Pain 2007; 127(1-2):52-62.

(289) Osterberg A, Boivie J, Thuomas KA. Central pain in multiple sclerosis prevalence and clinical characteristics. Eur J Pain 2005; 9(5):531-42.

(290) Ostir GV, Granger CV, Black DA. Preliminary results for the PAR-PRO: A measure of home and community participation. Arch Phys Medicine Rehabil 2006; 87: 1043-1053.

(291) Padua L, Briani C, Truini A, Aprile I, Bouhassirà D, Cruccu G, Consistence and discrepancy of neuropathic pain screening tools DN4 and ID-Pain. Neurol Sci 2013; 34(3):373-7.

(292) Padua R, Padua L, Ceccarelli E, Romanini E, Zanoli G, Amadio PC, et al. Italian version of the disability of the arm, shoulder and hand (dash) questionnaire. Cross-cultural adaptation and validation. The Journal of Hand Surgery: Journal of the British Society for Surgery of the Hand 2003; 28:179-186.

(293) Paltamaa J, West H, Sarasoja T, Wikstrom J, Malkia E. Reliability of physical functioning measures in ambulatory subjects with MS. Physiother Res Int 2005;10(2):93:109.

(294) Pandyan AD, Price CIM, Curless RH, et al. A review of the properties and limitations of the Ashworth & modified Ashworth Scales. Clin Rehabil 1999; 13(5):373-83.

(295) Pandyan AD, Price CIM, Rodgers H, et al. Biomechanical examination of a commonly used measure of spasticity. Clin Biomechan 2001; 16:859-65.

(296) Parker KP, Kimble LP, Dunbar SB, Clark PC. Symptom Interactions as Mechanisms Underlying Symptom Pairs and Clusters. Journal of Nursing Scholarship 2005; 37:3, 209-215.

(297) Parkin D, Rice N, Jacoby A, Doughty J. Use of a visual analogue scale in a daily person diary: modelling cross-sectional time-series data on health-related quality of life. Soc Sci Med 2004 July; 59(2):351-60.

(298) Patrick DL, Bergner M. Measurement of health status in the 1990. Annu Rev Public Health 1990; 11:165-83.

(299) Patrick DL, Erickson P. Health status and health policy. New York: Oxford Univ Pr; 1993.

(300) Pearson O.R., Busse M.E. Deursen R.W.M. and Wiles C.M. Quantification of walking mobility in neurological disorders. Q J Med 2004; 97:463–475.

(301) Perenboom RJM, Chorus AMJ, Measuring participation according to the International Classification of Functioning, Disability and Health (ICF). Disabil Rehabil 2003; 25 (11- 12): 577- 585.

(302) Peters M.L, Sorbi M.J, Kruise D.A, Kerssens J.J, Verhaak P.F.M, Bensing J.M. Electronic diary assessment of pain, disability and psychological adaptation in patients differing in duration of pain. Pain 2000; 84: 181–192.

(303) Phillips L& Stuifbergen, A. Structural equation modeling of disability in women with fibromyalgia or multiple sclerosis. Western Journal of Nursing Research 2009; 31, 89-109.

(304) Phillips L& Stuifbergen, A. The relevance of depressive symptoms and social support to disability in women with multiple sclerosis or fibromyalgia. International Journal of Rehabilitation Research 2010; 33(2), 142-150.

(305) Piwko C, Desjardins OB, Bereza BG, et al. Pain due to multiple sclerosis: Analysis of the prevalence and economic burden in Canada. Pain Res Manage 2007; 12:259-265.

(306) Ploughman M, Austin MW, Murdoch M, Kearney RN, Godwin M. The Path to Self-Management: A Qualitative Study Involving Older People with Multiple Sclerosis. Physiother Can 2012; 64(1): 6–17.

(307) Plow MA, Finlayson M, Rezac M. A scoping review of self-management interventions for adults with multiple sclerosis. PM R 2011; 3(3):251-62.

(308) Plummer MT, Clayton DG: Measurement error in dietary assessment, an investigation using covariance structure models. Stat Med 1993, 12:925-948.

(309) Poissant L, Mayo NE, Wood-Dauphinee S, Clarke AE. The development and preliminary validation of a preference-based stroke index (pbsi). Health & Quality of Life Outcomes. 2003; 1:43-15.

(310) Pollmann W, erasmus L, Feneberg W et al., Interferon beta but not glatiramer acetate therapy aggravates headaches in MS Neurol 2002. 59(4): 636–9.

(311) Pollman W, Feneberg W, Steinbrecher A, Haupts M, Henze T. Therapy of pain syndromes in multiple sclerosis: An overview with evidence-based recommendations. Fortschr Neurol Psychiatr 2005; 73:268-85.

(312) Portenoy R. Development and testing of a neuropathic pain screening questionnaire: ID Pain. Curr Med Res Opin 2006; 22: 1555–1565.

(313) Poser CM, Brinar VV. Diagnostic criteria for multiple sclerosis. Clin. Neurol. Neurosurg; 2001; 103:1-11.

(314) Rabinstein AA, Shulman LM. Acupuncture in clinical neurology. Neurologist 2003; 9(3): 137–48.

(315) Rae-Grant AD, Eckert NJ, Bartz S, Reed JF. Sensory symptoms of multiple sclerosis: a hidden reservoir of morbidity. Mult Scler 1999; 5: 179 – 83.

(316) Ramagopalan S. Genes and Environmental Factors in Multiple Sclerosis 2010a, 16: 259-259.

(317) Ramagopalan S, Byrnes JK, Orton S-M. Sex ratio of multiple sclerosis and clinical phenotype. European Journal of Neurology 2010b;17, 10.1111/j.1468-1331.2009.02850.x

(318) Rao SM, Leo GJ, Bernardin L, Unverzagt F. Cognitive dysfunction in multiple sclerosis. Frequency, patterns, and prediction. Neurology 1991a; 41(5):685-91.

(319) Rao SM, Leo GJ, Ellington L, Nauertz T, Bernardin L, Unverzagt F. Cognitive dysfunction in multiple sclerosis. II. Impact on employment and social functioning. Neurology 1991b; 41(5):692-6.

(320) Rao S.M. The neuropsychological Screening Battery for Multiple Sclerosis. Milwaukee, WI: Medical College of Wisconsin; 1992.

(321) Redelmeier D, Bayoumi A, Goldstein R, Guyatt G. Interpreting small differences in functional status: the Six Minute Walk test in chronic lung disease persons. American Journal of Respiratory and Critical Care Medicine. 1997; 155:1278 - 82.

(322) Renwick R & Friefeld S. Quality of life and rehabili-tation. In R. Renwick, I. Brown, & M. Nagler (Eds.), Quality of life in health promotion and rehabilitation 1996, pp: 26–37. Thousand Oaks: SAGE Publications.

(323) Richards RG, Sampson FC, Beard SM, Tappenden P. A review of the natural history and epidemiology of multiple sclerosis: implications for resource allocation and health economic models. Health Technol Assess 2002; 6:1-73.

(324) Ried K. Interpreting and understanding meta-analysis graphs: A practical guide. Australian Family Physician 2006; 35: 635-8.

(325) Rio J, Nos C, Bonaventura I, et al. Corticosteroids, ibuprofen, and acetaminophen for IFNbeta-1a flu symptoms in MS: a randomized trial. Neurology 2004; 63(3): 525–8.

(326) Ritvo P, Fischer JS, Miller D, Andrews H, Paty D, LaRocca NG. Multiple sclerosis quality of life: A user's manual. National Multiple Sclerosis Society; 1997.

(327) Rizzo MA. Treatment of pain, paresthesias, and paroxysmal disorders in multiple sclerosis. In: Cohen JA,

(328) Roessler R, Rumrill P, Hennessey ML, Courtney V, Pugsley E, Pittman A. Perceived strengths and weaknesses in employment policies and services among people with multiple sclerosis: Results of a national survey. Work: A Journal of Prevention, Assessment and Rehabilitation 2003; 21: 25-36.

(329) Rosati G. The prevalence of multiple sclerosis in the world: an update. Neurol.Sci 2001; 22:117-39.

(330) Rotstein Z, Hazan R, Barak Y, Achiron A. Perspectives in multiple sclerosis health care: Special focus on the costs of multiple sclerosis. Autoimmunity Reviews 2006; 5 511–516.

(331) Rudick RA, Miller D, Clough JD et al. Quality of life in multiple sclerosis. Comparison with inflammatory bowel disease and rheumatoid arthritis. Arch.Neurol 1992; 49:1237-42.

(332) Rudick RA, editors. Multiple sclerosis therapeutics. 2nd ed. London and New York: Martin Dunitz; 2003.

(333) Rumrill, P. Employment and multiple sclerosis. New York: Demos,1996

(334) Ruta DA, Garratt AM, Leng M, Russell IT, MacDonald LM. A new approach to the measurement of quality of life. The Person-Generated Index. Med Care 1994; 32:1109-1126.

(335) Ruta DA, Garratt AM, Russell IT. Person centred assessment of quality of life for persons with four common conditions. Qual Health Care 1999; 8:22-29.

(336) Salter K, Jutai JW, Teasell R, Foley NC, Bitensky J, Bayley M. Issues for selection of outcome measures in stroke rehabi-litation: ICF Participation. Disabil Rehabil 2005; 27(9):507- 528.

(337) SAS 9.2 [computer program]. Version 9.2. Cary, NC: SAS Institute Inc.; 2008. This is related to the statistical analysis.

(338) Satorra, A. and Saris, W. E. (1993). Power Evaluations in Structural Equation Models, pp 181–204. Newberry Park, CA: Sage.

(339) Savci S, InalInce D, Arikan H, Guclu-Gunduz, Cetisli-Korkmaz, Armutlu, Karabudak. Six-minute walk distance as a measure of functional exercise capacity in multiple sclerosis. 2005, 27 (22): 1365-1371.

(340) Scheinberg L, Holland N, Larocca N. Multiple sclerosis; earning a living. NY State J Med 1980; 80: 1395–1400.

(341) Schwartz CE, Ahmed S, Sawatzky R, Sajobi T, Mayo N, Finkelstein J, Lix L, Verdam MG, Oort FJ, Sprangers MA. Guidelines for secondary analysis in search of response shift. Qual Life Res 2013 Apr 10 [Epub ahead of print]

(342) Seekins T, Shunkamolah W, Bertsche M, Cowart C, Summers JA, Reichard A, White G.A systematic scoping review of measures of participation in disability and rehabilita tionresearch: a preliminary report of findings. Disabil Health J 2012; 5(4):224-32.

(343) Serlin RC, Mendoza TR, Nakamura Y, Eduards KR, Cleeland CS. When is cancer pain mild, moderate or severe? Grading pain severity by its interference with function. Pain 1995; 61:277-84.

(344) Shahrbanian Sh; Auais M; Duquette P; Andersen K; Mayo N. E. Does Pain in Individuals with Multiple Sclerosis Affect Employment? A Systematic Review and Meta-analysis. Journal of Pain Research and Management 2013; 18 (5): e94-e100.

(345) Sharrack B, Hughes RA, Soudain S, Dunn G. The psychometric properties of clinical rating scales used in multiple sclerosis. Brain 1999; 122 (Pt 1):141-59.

(346) Shevil E, Finlayson M. Perceptions of persons with multiple sclerosis on cognitive changes and their impact on daily life. Disabil Rehabil 2006; 30; 28(12):779-88.

(347) Siev-Ner I, Gamus D, Lerner-Geva L, et al. Reflexology treatment relieves symptoms of multiple sclerosis: a randomized controlled study. Mult Scler 2003; 9 (4): 356–61.

(348) Skerrett TN, Moss-Morris R. Fatigue and social impairment in multiple sclerosis: the role of patients' cognitive and behavioral responses to their symptoms. J Psychosom Res. 2006;61(5):587-93.

(349) Smith MM, Arnett AP. Factors related to employment status changes in individuals with multiple sclerosis. Mult Scler 2005; 11, 602-9.

(350) Snook, E.M., & Motl, R.W. (). Physical activity behaviors in individuals with multiple sclerosis: Roles of overall and specific symptoms, and self-efficacy. Journal of Pain and Symptom Management 2008; 36, 46 – 53.

(351) Solaro C, Brichetto G, Amato MP, Cocco E, Colombo B, D'Aleo A. The prevalence of pain in multiple sclerosis: a multicenter cross-sectional study. Neurology 2004; 63:919–21.

(352) Sousa KH, Kwok OM. Putting Wilson and Cleary to the test: analysis of a HRQOL conceptual model using structural equation modeling. Qual Life Res 2006; 15(4):725-37.

(353) Spadoni G F, Stratford P, Solomon P. E, Wishart L. The Evaluation of Change in Pain Intensity: A Comparison of the P4 and Single-Item Numeric Pain Rating Scales. J Orthop Sports Phys Ther 2004; 34 (4):187-192.

(354) Sprangers MA, de Regt EB, Andries F et al. Which chronic conditions are associated with better or poorer quality of life? J.Clin.Epidemiol. 2000; 53:895-907.

(355) Stanton BR, Barnes F, Silber E. Sleep and fatigue in multiple sclerosis. Mult Scler 2006; 12 (4):4 81–6.

(356) Stark SL, Edwards DF, Hollingsworth H, Gray DB. Validation of the reintegration to normal living index in a population of community-dwelling people with mobility limitations. Arch Phys Med Rehabil 2005; 86:344-5.

(357) Stenager E, Knudsen L, Jensen K. Acute and chronic pain syndromes in multiple sclerosis. Acta Neurol Scand 1991; 84:197-200.

(358) Stenager E, Knudsen L, Jensen K. Acute and chronic pain syndromes in multiple sclerosis: a 5-year follow-up study. Ital J Neurol Sci. 1995; 16:629–32.

(359) Sterne JA, Gavaghan D, Egger M. Publication and related bias in meta-analysis: Power of statistical tests and prevalence in the literature. J Clin Epidemiol 2000; 53:1119-1129.

(360) Stuifbergen A, Rogers S. Health promotion: an essential component of rehabilitation for persons with chronic disabling conditions. Adv Nurs Sci 1997; 19(4):1–20.

(361) Suhr Diana D. SEM for Health, Business and Education. Statistics and Data Analysis. 1: 243-27.

(362) Sullivan MJL, Edgley K, Mikail S, et al. Psychological correlates of health care utilization in chronic illness. Can J Rehabil 1992; 6:13–21.

(363) Sullivan KJ, Cen SY. Model of disablement and recovery: knowledge translation in rehabilitation research and practice. Phys Ther 2011; 91(12):1892-1904.

(364) Svendsen KB, Jensen SJ, Overvad K, Hansen HJ, Kock-Henriksen N, Back FW. Pain in patients with multiple sclerosis. Arch Neurol 2003; 60:1089–1094.

(365) Svendsen KB, Jensen TS, Hansen HJ, Bach FW. Sensory function and quality of life in patients with multiple sclerosis and pain. Pain 2005; 114:473–8.

(366) Tachibana N, Howard RS, Hirsch NP, Miller DH, Moseley IF, Fish D. Sleep problems in multiple sclerosis. Eur Neurol 1994; 34 (6):320–3.

(367) Tarsy D & Sheon R.P. Restless legs syndrome. Up To Date. Accessed: March 2009. Available at http://www.uptodate.com/contents/restless-legs-syndrome.

(368) Teng SY, Bartlett S, Koski L, Chamelian L, Duquette P, Grand'Maison F, Lapierre Y, Mayo NE. Self-perceived and tested cognition in multiple sclerosis: Differences across gender. Journal of Multiple Sclerosis Clinical and Laboratory research, 2009; 15 (2).

(369) Tesio L, Perucca L, Franchignoni FP, Battaglia MA. A short measure of balance in multiple sclerosis: validation through Rasch analysis. Funct Neurol 1997; 12(5):255-65.

(370) Trapp BD, Nave KA. Multiple Sclerosis: An immune or neurodegenerative Disorder? Annu Rev Neurosci 2008; 31:247-269.

(371) Turpin KV, Carroll LJ, Cassidy JD, Hader WJ. Deterioration in the health-related quality of life of persons with multiple sclerosis: the possible warning signs. Mult Scler 2007 Sep; 13(8):1038-45.

(372) Tyson S, Connell L. The psychometric properties and clinical utility of measures of walking and mobility in neurological conditions: a systematic review. Clin Rehabil 2009; 23(11):1018-33.

(373) Tyszka AC, Farber RS. Exploring the relation of health-promoting behaviors to role participation and health-related quality of life in women with multiple sclerosis: a pilot study. Am J Occup Ther. 2010 Jul-Aug; 64 (4):650-9.

(374) Van Agt HME, Essink-Bot ML, Krabbe PFM, Bonsel GJ. Test-retest reliability of health state valuations collected with the EuroQol questionnaire. Social Science Medicine. 1994; 39(11): 1537-1544.

(375) van Kessel K, Moss-Morris R. Understanding multiple sclerosis fatigue: a synthesis of biological and psychological factors. J Psychosom Res. 2006; 61(5):583-5.

(376) Vendrig A.A, Lousberg R. Within-person relationships among pain intensity, mood and physical activity in chronic pain: A naturalistic approach. Pain 1997; 73: 71–76.

(377) Verdier-Taillefer MH, Sazdovitch V, Borgel F, Cesaro P, Kurtz A, Millet MF, Roullet E, Marteau R. Occupational environment as risk factor for unemployment in multiple sclerosis. Acta Neurol Scand 1995; 92:59–62.

(378) Vermote R, Ketelaer P, Carton H. Pain in multiple sclerosis patients: a prospective study using the McGill pain questionnaire. Clin Neurol Neurosurg 1986; 88:87–93.

(379) Victor TW, Jensen MP, Gammaitoni AR, Gould EM, White RE, Galer BS. The dimensions of pain quality: factor analysis of the Pain Quality Assessment Scale. Clin J Pain 2008; 24(6):550-5.

(380) Vollmer T, Ni W, Stanton S, Hadjimichael O. The NARCOMS Patient Registry: a resource for investigators. Int J Mult Scler Care 1999; 1:12–15.

(381) Von Korff M, Jensen MP, Karoly P. Assessing global pain severity by self-reports in clinical and health services research. Spine 2000; 25:3140–3151.

(382) Walsh D, Rybicki L. Symptom clustering in advanced cancer. Support Care Cancer2006; 14:831-6.

(383) Warnell P. The pain experience of a multiple sclerosis population: a descriptive study. Axon 1991; 13: 26–8.

(384) Weinshenker BG, Bass B, Rice GPA, Noseworthy J, Carriere W, Baskerville J, et al. The natural history of multiple sclerosis: A geographically based study. Brain 1989; 112:133-146

(385) Weller IM, Corey PN. A study of the reliability of the Canada Fitness Survey questionnaire. Med Sci Sports Exerc 1998 October;30(10):1530-6.

(386) Whetten-Goldstein K, Sloan F, Goldstein L, Kulas E. A comprehensive assessment of the cost of multiple sclerosis in the United States. Mult Scler 1998; 4:419-25.

(387) White LJ, Dressendorfer RH. Exercise and multiple sclerosis. Sports Med 2004; 34(15):1077:100.

(388) Whiteneck GG, Charliefue SW, Gerhart KA, et al. Quantifying handicap: a new measure of long-term rehabilitation outcomes. Arch Phys Med Rehabil 1992;73:519–26.

(389) Willer B, Rosenthal M, Kreutzer JS, Gordon WA, Rempel P. Assessment of community integration following rehabilitation for traumatic brain injury. J Head Trauma Rehabil 1993; 8(2):75- 87.

(390) Willke RJ, Burke LB, Erickson P. Measuring treatment impact: a review of patient-reported outcomes and other efficacy endpoints in approved product labels. Control Clin.Trials 2004; 25:535-52.

(391) Wilmoth MC, Coleman EA, Smith SC, Davis C. Fatigue, weight gain, and altered sexuality in persons with breast cancer: exploration of a symptom cluster. Oncol Nurs Forum 2004; 31: 1069-75.

(392) Wilson CR, VoorhisV, Morgan BL. Understanding Power and Rules of Thumb for Determining Sample Sizes. Tutorials in Quantitative Methods for Psychology 2007, 3 (2): 43-50.

(393) Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. JAMA 1995; 273(1):59-65.

(394) Wood-Dauphinée SL, Opzoomer MA, Williams JI, Marchand B, Spitzer WO. Assessment of global function: The reintegration to normal living index. Arch Phys Med Rehabil 1988; 69:583-90.

(395) World Health Organization. International classification of impairments, disabilities, and handicaps: a manual of classification relating to the consequences of disease. Geneva: WHO; 1980.

(396) World Health Organization (WHO). ICIDH-2: international classification of functioning and disability. Beta-2 draft. Geneva: WHO; 1999.

(397) World Health Organization (WHO). International classification of functioning, disability and health.Available at: http://www3.who.int/icf/icftemplate.cfm. Second revision ed. Geneva: 2001.

(398) Yorkston K, Johnson K, Klasner E. Taking Part in Life: Enhancing Participation in Multiple Sclerosis. Phys Med Rehabil Clin N Am 2005 (16): 583–594.

(399) Yorkston K, Kuehn C. M, Johnson K, Ehde D. M, Jensen M. Measuring participation in people living with multiple sclerosis: A comparison of self-reported frequency, importance and self-efficacy. Disability and Rehabilitation, 2008; 30(2): 88- 97.

(400) Zigmond, A.S., & Snaith, R.P. The Hospital Anxiety and Depression Scale. Acta Psychiatrica Scandinavica1983; 67, 361 – 370.

APPENDICES

Appendix A: Psychometric Properties of Measures Included in Analyses

Variable	Construct*	Measure	Description of measure	Scale	Psychometric Properties
Pain					
Pain Severity	Symptom	Numeric Rating Scale (NRS)	To measure worst pain severity over the previous week we used 0–10 NRS, with 0 indicating 'No pain' and 10 indicating 'the most imaginable pain'.	Quasi-continuous	Psychometric properties of NRS have been documented (Sharrack 1999, Jensen 1986, 1991, 1999, 2001).
Muscle Pain Intensity	Symptom	Visual Analogue Scale (VAS)	Muscle pain was measured with a 0–10 VAS with anchors of no pain to worst pain imaginable. VAS has been widely used in studies of different chronic conditions including MS.	Quasi-continuous	The VAS has several good qualities in terms of practicality, reliability and adaptability (Parkin 2004).
Bodily Pain	Symptom	RAND- 36 Health Survey Pain Subscale (BPS)	The two-item BPS was used as a measure of bodily pain intensity during the past 4 weeks. First item of BPS asks about pain intensity, and the second item grades the impact of pain on work. These two items are combined into a single composite score from 0 to 100, with higher scores indicating lower pain severity.	Continuous	Internal consistency of this scale in the MS population has been reported to range from 0.77 to 0.94 (Brunet 1996, Freeman 2000).
Pain Location	Symptom	Margolis Rating System	Participants were instructed to shade areas that were painful at the time of the evaluation on a pain diagram showing the front and back of the whole body consisting of 45 anatomical areas.	Continuous	The test-retest and inter-rater reliability of scale has been established (Margolis 1988).
Pain Distribution	Symptom	Margolis Drawing Rating System	Pain distribution was measured using the Margolis drawing rating system which has 45 anatomical areas each with a corresponding percentage value of body surface in order to compute a total weighted score, indicating body pain distribution.	Continuous	The test-retest and inter-rater reliability of scale has been established (Margolis 1988).

Variable	Construct*	Measure	Description of measure	Scale	Psychometric Properties
Psychological variables					
Depression/ Anxiety	Symptom	Hospital Anxiety and Depression Scale (HADS)	The HADS has 14 items, 7 of them relate to anxiety and 7 relate to depression. Each item on the questionnaire is scored from 0 'most of the time' to 3 'not at all', and the total score ranges between 0 and 21 for either anxiety or depression (Bjelland 2002); higher scores indicate worse depression/ anxiety symptoms.	Quasi-continuous	The HADS is a reliable and valid tool and has been used in a number of MS studies (Bjelland 2002, Da Silva 2009, Herrmann1997, Honarmand 2009, Zigmond 1983).
Psychological health	Functional Status	RAND Short Form-36 Health Survey Mental Health Index (MHI-5)	MHI has 5 items that ask questions on major mental health dimensions about both the positive feelings (calm, peaceful, happy) and negative feeling (downhearted, blue) (Hays 1993, 2001). For each question the subjects were asked to rate on a 6-point scale with five response categories from all of the time to none of the time. The questions of MHI are combined to produce a continuous measure from 0 (worst) to 100 (best mental health).	Continuous	MHI correlate highly with the General Health Questionnaire which is a well-established indicator of psychic distress (McCabe 1996). MHI is equal to a longer version, MHI-18 (.93-.96) and GHQ (30 items) in detecting the mental disorders (Weinstein 1989).
Mood	Symptom	Visual Analogue Scale (VAS)	Feeling of mood such as sadness and impatient during the past 4 weeks was measured with a 0-10 visual analogue scale (VAS). Participants were asked to mark the position along a horizontal 10-cm line that best corresponded to their mood.	Quasi-Continuous	VAS has been widely used in research and clinical setting and considered to be as a gold standard in measuring health outcome (Parkin 2004).
Irritability	Symptom	Irritability questionnaire	Irritability was measured using a specific irritability index created from Rasch analysis of Psychiatric Symptom Index (PSI) (Illfeld 1976) which measures the presence of depressive or anger-related symptoms indicating the need for referral to a mental-health professional. It comprised 4 items each with a 4-point Likert response options ranging from 1 'never' to 4 'very often'. Persons were asked to tell how often, during the past week, they lost their temperature, felt critical of others, felt easily annoyed or irritated, and got angry over things that were not too important. A maximum total score of 16 representing the most irritability.	Quasi-continuous	Validity and reliability have been demonstrated by Rasch analysis.

Variable	Construct*	Measure	Description of measure	Scale	Psychometric Properties
Cognitive Impairment	Symptom	Perceived Deficits Questionnaire (PDQ)	The PDQ items assess frequency of difficulties with attention/ concentration, retrospective memory, prospective memory, and planning/organization during the past month on a 5-point Likert scale ranging from 'never' to 'almost always' (Sullivan 1992). PDQ contains 20 items, each scores range from 0 to 4 with a maximum total score of 80, where higher scores indicate greater cognitive impairment (Shevil 2006).	Continuous	The validity and reliability of PDQ in MS persons has been widely accepted (Marrie 2003, Sullivan 1992).
Processing Speed/ Attention	Functional Status	Paced Auditory Serial Addition Test (PASAT)	PASAT is a measure of sustained attention. Subjects listen to a series of numbers presented on audiocassette tape every 3 seconds and are requested to add the number they just heard with the number they heard before. The test score is the number of correct sums given (out of 60 possible); higher is better. This task involves working memory, attention and arithmetic capabilities and so requires a high level of attention, especially if the numbers are presented quickly.	Continuous	The PASAT has become widely used in the testing of people with MS (Rao 1992).
Single Indicator					
Fatigue	Symptom	RAND-36, MFIS, FAMS, MFI	Fatigue was created by Rasch analysis from items of several measures including Vitality Subscale of RAND -36 (Hays 1993, 2001), Functional Assessment of MS (FAMS) (Cella 1996), the Modified Fatigue Impact Scale (Ritvo 1997), and the Multidimensional Fatigue Inventory (MFI) (Weinshenker 1989). This component has already been used in MS population (Bouchard 2012, Ng 2012).	Continuous	Each scale has been used in MS population and their validity and reliability have been determined (Hays 1993, 2001, Cella 1996, Fisk 1994, Larson 2013, Ritvo 1997). Validity and reliability of the new measure has been determined by Rasch analysis (Andrich 2004).
Neurological Impairments	Symptom	Symptom checklist,	The component of Neurological Impairments was created by Rasch analysis (Cano 2011) from items	Continuous	The validity and reliability of the measure has been determined by

Variable	Construct*	Measure	Description of measure	Scale	Psychometric Properties
		Medical chart, Expanded Disability Status Scale (EDSS)	of patient symptom checklist, which included neurological signs and symptoms giving biological information as to lesion location, and clinical information such as EDSS, MS type, the use of Disease modifying therapy (DMT), and disease duration (Ng 2012). This component has already been used in MS population (Ng 2012).		Rasch analysis (Ramp 2009, Andrich 2004).
Participation					
Role Physical	Functional Status	RAND -36 Role Physical Subscale (RP)	RP includes 4 items each with 2- response options (yes/ no) asking subjects if during the past 4 weeks they have had any problems with their work or other regular daily activities as a result of their physical health (Hays 1993). Total scores range from 0 to 100; higher scores indicate no or less problems.	Continuous	Psychometric properties of RAND-36 have been demonstrated (Hays 1993, 2001). Also reliability of the RP subscale has been reported to be high in MS population (ρ=0.81) (Moorer 2001).
Role Emotional	Functional Status	RAND -36 Role Emotional Subscale (RE)	RE includes 3 items each with 2- response options (yes/ no) asking subjects if during the past 4 weeks they have had any problems as a result of any emotional problems. The three items are combined into a single sum score and transformed to a 0- 100 scale, higher scores is better (Hays 1993).	Continuous	Reliability, validity, and responsiveness of RAND-36 have been reported (Hays 1993, 2001). Reliability of RE reported to be high in MS (ρ=0.84) (Moorer 2001).
Social Functioning	Functional Status	RAND -36- Social Functioning Subscale (SF)	This subscale includes two items asking subjects to indicate to what extent their physical health or emotional problems have interfered with their social activities with family, friends, or neighbors during the past 4weeks. Again, items are combined into a single score from 0 to 100; higher scores indicating higher levels of social activity (Hays 1993).	Continuous	Reliability, validity, and responsiveness have been reported in different population (Hays 1993, 2001) and MS (Moorer 2001).
Work	Functional Status	Socio-demographic Questionnaire	Participants were asked to report the year that they stopped working. If they mentioned 2009 it means they still work, if stopped before 2009 it means not employed any more. Then study participants were asked to report hours of paid work per week, which	Continuous	Information obtained from the socio-demographical questionnaire.

Variable	Construct*	Measure	Description of measure	Scale	Psychometric Properties
			called as work time, and the number of hours they took care of people and worked, which called work activity.		
Illness Intrusiveness	Functional Status	Illness Intrusiveness Rating Scale (IIRS)	This self-report measure determines the ratings of the degree to which one's illness interfere with life domains such as work, religious and spiritual expression, recreation, financial situation, relationship with others, and community and civic involvement (Devins 1983). It consists of 13 questions each with a 7-point response option, ranging from 1 'Not very much' to 7'very much' with a maximum total score that can range from 13 to 91; higher scores indicate increased illness intrusiveness (rescored from 0 to 78).	Continuous	The psychometric properties of the scale have been administered across numerous chronic-disease populations including MS (Devins 2001, 2010). Test-retest: Cronbach's α=0.80-0.85 (Hays 1993); Internal consistency: 0.90 (Moorer 2001); Validity (Devins 1994).
Exercise Barriers	Functional Status	Exercise Barriers Scale (EBS)	EBS was modified from the Barriers to Health Activities Among Disabled Persons (BHADP) scale (Becker 1991). This scales asks participants to circle the number which best indicates how much each of these problems keep them from exercising. There were 21 items each with response options from 1 "Never" to 3 "Often", with a total score from 21 to 63; higher is worse (rescored from 0 to 42).	Continuous	The psychometric properties of the original HADP scale have been found to be excellent in many health conditions including MS (Becker 1991, Harrison 2001, Becker 2004, Greenhalgh 2004).
Ability to accomplish work/ social activities	Functional Status	Preference Based MS Index (PBMSI)	PBMSI has been modified from the Preference Based Stroke Index (PBSI) (Poissant 2003) and has item that asks participants to indicate their ability to accomplish work or other activities such as recreational activities and driving considering their own health today. It has 11 items each with 1 to 3 response option with a total score from 11 to 33.	Continuous	Good internal consistency (Cronbach's α=0.84), and good convergent validity compared to the Physical Function subscale of RAND-36 (Poissant 2003) have been reported.

Variable	Construct*	Measure	Description of measure	Scale	Psychometric Properties
Physical Function					
Walking Capacity	Functional Status	6 Six-Minute Walk Test	Walking capacity was measured using the Six-Minute Walk Test (6MWT) in which the maximum distance a person can walk as quickly as over the interval six minutes at their own pace is recorded (Butland 1982). In the present study, standardized instructions and encouragement were used (ATS statement 2002).	Continuous	6MWT has been used widely in MS population (Goldman 2008, Savci 2005), and is correlated with the 12-Item MS Walking Scale (r = 0.81) (Goldman 2007). Reliability (ICC = 0.96) has been reported (Paltamaa 2005).
Walking Speed	Functional Status	Gait speed Test	Comfortable and maximum gait speed based on the performance of individuals on a timed walk test was determined over distances of 5 meters (Tyson 2009). Acceleration and deceleration distances, each of 2 m, were marked. Using a digital stopwatch, the time it takes for the subject to traverse the central 5 m section of the walkway was measured.	Continuous	It has been used in MS population and its test-retest and reliability have been reported (Bergamaschi 2006, Beeson 1994, Compston 2005, Poser 2006, Tremlett 2005, 2006, Tyson 2009).
Lower Extremity Power	Functional Status	Vertical jump Test	First, participant stands side on to the wall and reaches up with the extended hand closest to the wall. The point of the fingertips is recorded. Then, participant stands away from the wall, and jumps vertically while touch the wall at the highest point of the jump. The difference in distance between the standing reach height and the jump height is the scored in centimeter.	Continuous	This test has been widely used in health conditions including MS population (CSEP Health & Fitness Program's Health-Related Appraisal & Counselling Strategy 2004, Markovic 2004, Kuspinar 2010, Bouchard 2012).
Muscle Stiffness and Spasticity	Symptom	Modified Ashworth Scale (MAS)	MAS assigns grades to a manually determined resistance of muscle (elbow flexors, wrist flexors/ extensors, knee extensors /flexors, ankle dorsi flexors) to passive stretching (Bohannon 1987). For each segment scores range from 0 (no increase in muscle tone) to 5 (affected part rigid in flexion or extension) with a maximum total score of 60 for both sides (Pandyan 1999, 2001).	Continuous	Validity and reliability of MAS in a number of MS studies have been examined (Ashworth 1964, Bohannon 1987, Leslie 1992, Nuyens 1994, Pandyan 1999).

Variable	Construct*	Measure	Description of measure	Scale	Psychometric Properties
Balance Capacity	Symptom	EQUI-Scale	EQUI-Scale, is a MS specific balance scale and has been created using Rasch modeling from the items of Tinetti Performance Oriented Balance Scale and the Berg Balance Scale (Tesio 1997). The EQUI-Scale has 10 items that are listed in order of difficulty. Each item scores from 0 to 2 with a maximum total score of 20; higher scores indicate better balance skills. Test starts with question number 7. If the participants pass the test, then they go to the next item with a harder level. If they fail, then they should go back to an easier level.	Continuous	The psychometric validity of the scale in MS population has been administered using Rasch Analysis of the original scale (Tesio 1997).
Upper Extremity Dysfunction	Body Structure and Function	Disabilities of the Arm, Shoulder and Hand (DASH)	Participants were asked to rate their ability to do different activities in the last week by choosing 1 to 5 response options of 21 questions, where 1 means "unable", and 5 means "no difficulty".	Continuous	Good test-retest reliability (ICC=0.89), internal consistency (Cronbach's α=0.90), divergent validity ($r<0.70$ with the MSWS-12), and convergent validity ($r>0.70$ with ABILHAND, and MSIS-29) have been reported (Cano 2011, Padua 2003).
Grip Strength	Functional Status	Jamar TM Dynamometer	Standardized instructions and positioning were used and three consecutive trials for each hand were recorded (Mathiowetz 1984, Desrosiers 1995).	Continuous	Grip strength has excellent reliability (Mathiowetz 1984, Desrosiers 1995, Peolsson 2001, Bohannon 2005).
Aerobic Capacity	Functional Status	The modified Canadian Aerobic Fitness Test (MCAFT)	Subjects were asked to perform a series of stepping sequences on a double 20-cm step in time with a musical cadence (Iris 1993, 1994, Jette 1976). Each stage lasted 3-minutes. Subjects completed all the stages necessary to achieve 85% of their age predicted maximum heart rate. (CSEP Health & Fitness Program's Health-Related Appraisal &Counselling Strategy 2004).	Continuous	The MCAFT has been shown to have a high degree of reliability and validity (Iris 1993, 1994, Jette 1976, Weller 1998, CSEP Health & Fitness Program's Health-Related Appraisal &Counselling Strategy 2004).

Variable	Construct*	Measure	Description of measure	Scale	Psychometric Properties
Upper Limb Muscle Endurance	Functional Status	The push-ups Test	This test evaluates an individual's ability to perform repetitive contractions over time. Subjects were instructed to perform as many consecutive push-ups without any time limit. For anchor points men used their toes, women their knees. The test was terminated when subjects were seen to strain forcibly or using compensatory techniques.	Continuous	This test has been widely used in MS population (CSEP Health & Fitness Program's Health-Related Appraisal & Counselling Strategy 2004, Kuspinar 2010).
Abdominal Muscle Endurance	Functional Status	Partial Curl-ups Test	This test evaluates one's ability to perform as many consecutive curl-ups as possible at a rate of 25/min for a maximum of 1 minute. From a supine position with knees bent at 90 degree, subjects were asked to curl-up the upper spine until the middle finger tips of both hands have reached the 10cm mark on the mat, and then to slowly return to the mat.	Continuous	Test has been widely used in health conditions including MS population (CSEP Health & Fitness Program's Health-Related Appraisal & Counselling Strategy 2004, Kuspinar 2010).
Physical Functioning	Functional Status	RAND -36 Physical Functioning Subscale (PFI)	The Physical Functioning Subscale includes 10 items each with 3- response options asking subjects if their health limit them in the activities they might do during a typical day (Hays 1993). Total scores range from 0 to 100; higher scores indicate no or less problems with physical activities as a result of their health problems.	Continuous	In sample of 352 people with MS reliability of this subscale was found to be high (ρ=0.94) (Moorer 2001). Internal consistency estimated from the MOS is also high (α=0.93) (Hays 1993, 2001).

* Construct of each variable has been chosen based on the components of Wilson- Clearly Model (WCM) (Wilson & Cleary 1995).

Appendix B: Questionnaires

PAIN QUESTIONNAIRE

Name /ID: Date: / /
month day year

Hospital: _____

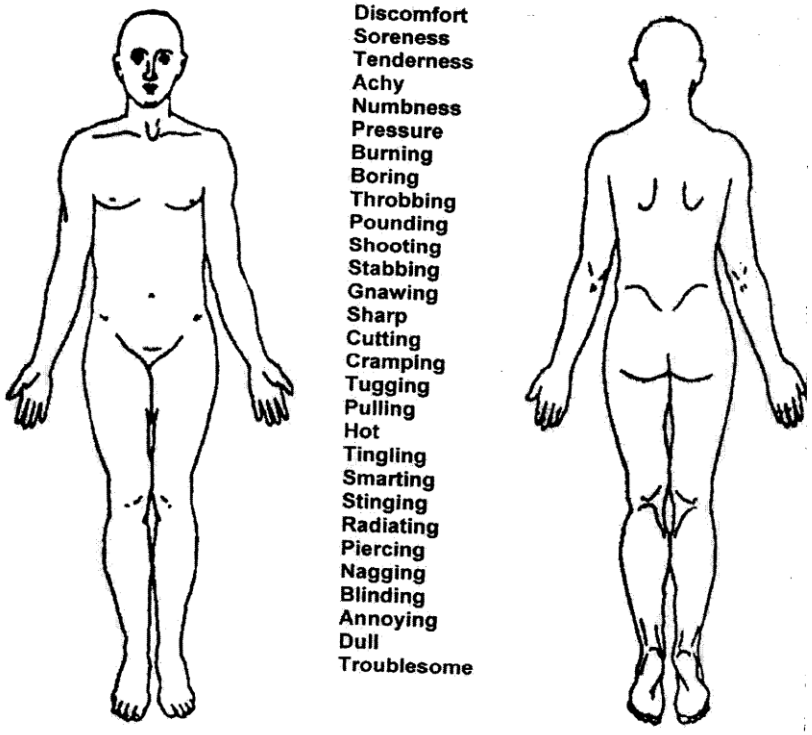
Instructions:

1.

a). On the diagram below, please shade in all the area(s) where you felt pain **during the past week.**

b). Put an "**X"** on the area that hurt the most

c). Please describe the quality of your pain by **circling all the words** listed below that apply.



Discomfort
Soreness
Tenderness
Achy
Numbness
Pressure
Burning
Boring
Throbbing
Pounding
Shooting
Stabbing
Gnawing
Sharp
Cutting
Cramping
Tugging
Pulling
Hot
Tingling
Smarting
Stinging
Radiating
Piercing
Nagging
Blinding
Annoying
Dull
Troublesome

2. Does your pain come and go?

☐ Yes ☐ No, it is constant

3.
a) If yes, how frequently does it occur?

☐ At least once a day ☐ 2-3 times a week ☐ Weekly ☐ Monthly ☐ Irregularly

b) How long does it last?

☐ Minutes ☐ Hours ☐ Days ☐ Weeks

d) Does it interfere with your sleep?

☐ Yes ☐ No

The following questions refer to your experiences **during the past week**.

5. What was your TYPICAL or AVERAGE pain during the past week?

0 1 2 3 4 5 6 7 8 9 10

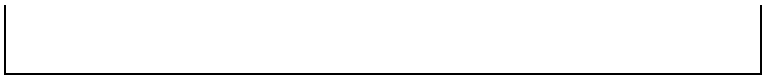
No pain The worst pain imaginable

6. What was your LOWEST level of pain during the past week?

0 1 2 3 4 5 6 7 8 9 10

No pain The worst pain imaginable

7. What was your pain level AT ITS WORST during the past week?



0 1 2 3 4 5 6 7 8 9 10

No pain The worst pain imaginable

8.

a) Do you use anything to relieve pain?

Yes ☐ No ☐

b) If your answer to the above question is yes, what are you using? (medications, substances, products, exercise, massage, acupuncture etc.)

_____

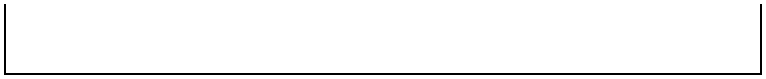
_____

_____

c) Do these help?

Yes ☐ No ☐

9. RIGHT NOW, what is your pain?



0 1 2 3 4 5 6 7 8 9 10

No pain The worst pain imaginable

NEUROPATHIC PAIN QUESTIONNAIRE

Name /ID: Date: / /
Day / Month/ Year

Hospital: _____

We need a clear description of what you are feeling about your pain and sensation to make the correct diagnosis. By completing this questionnaire, you will help to ensure the correct diagnosis.

1. During the past week, did you experience any form of pain?

◯ YES ◯ NO

If you answer YES, continue.

2. Do you experience pain other than a headache or a migraine?

◯ YES ◯ NO

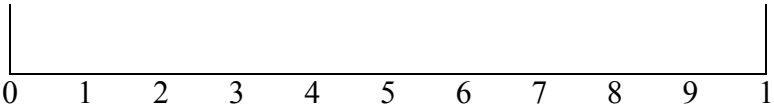
If you answer YES, continue.

Pain severity

3. What was your **LOWEST level of pain** during the past week?

0 1 2 3 4 5 6 7 8 9 10
No pain The worst pain imaginable

4. What was your **pain level AT ITS WORST** during the past week?



0 1 2 3 4 5 6 7 8 9 10
No pain The worst pain imaginable

5. RIGHT NOW, what is your pain?

0 1 2 3 4 5 6 7 8 9 10

No pain The worst pain imaginable

The ID-Pain questionnaire

6. Have you ever been diagnosed by your physician or health care provider for neuropathic pain?

◯ YES ◯ NO

7. Do you feel pain in more than one site of your body?

◯ YES ◯ NO

If you answer yes: complete the questionnaire for that pain site which is subjectively most troublesome.

8. Type of pain

This section will help you describe the type of pain you are feeling. Please complete the questions below. Consider the most painful area when answering these questions (Insert star under yes or no column or just simple type yes or no).

Questions	Score	
	Yes	No
a) Did the pain feel like pins and needles?		
b) Did the pain feel hot / burning?		
c) Did the pain feel numb?		
d) Did the pain feel like electric shocks?		
e) Is the pain made worse with the touch of clothing or bed sheets?		
f) Is the pain limited to your joints?		

Total Score:

Minimum total score = -1; Maximum total score = 5

If you score 2 or more, you may have NP.

9. Comorbidity

At this time do you have any other comorbid conditions, including hypertension, diabetes mellitus, cerebrovascular accident, rheumatoid arthritis, and osteoarthritis?

◯ YES ◯ NO

If you answer YES, please specify here ----------

History of symptoms

10. Has your pain changed during the last year? Please specify if it is

◯ **Better** ◯ **Worse** ◯ **Same**

11. Has your fatigue changed during the last year? Please specify if it is

◯ **Better** ◯ **Worse** ◯ **Same**

12. Are you able to walk (without difficulty)?

◯ YES ◯ NO

If you answer YES, please specify here ----------

◯ More than one kilometer ◯ Several blocks (500 meter) ◯ Less than one block