ILLNESS INTRUSIVENESS IN MULTIPLE SCLEROSIS:

AN EXPLORATION FROM THE PERSPECTIVE OF MODERN OUTCOME MEASUREMENT THEORY

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ABSTRACT

Illness intrusiveness is a construct that emerged in the 1980's to describe disease impact or how much disease symptoms and treatments interfere with valued life activities. This thesis presents two manuscripts applying modern outcome measurement theories and models to examine the construct of illness intrusiveness in people with Multiple Sclerosis (MS). The first manuscript presents the result of a codification exercise on the International Classification of Functioning Disability and Health (ICF). Mapping of the 13 items of the original Illness Intrusiveness Rating Scale (IIRS) and 5 new items added by our team to reflect constructs felt to be missing from the original measure was done by a group of nine rehabilitation experts. It also illustrates the composition of the IIRS as a latent construct using Rasch Analysis. The results showed that, using the ICF framework, this construct could be regarded as measuring participation and 14 of the 18 (13 original + 5 new) items formed a unidimensional hierarchical construct.

Manuscript 2, which is a secondary analysis of a sample of 189 subjects with Multiple Sclerosis (MS), presents the steps and results of a path analysis aimed at contributing evidence for the impact of MS related physical and mental impairments on the latent construct of illness intrusiveness. Path analysis showed a complete mediation of the effects of physical symptoms on illness intrusiveness through mainly fatigue and self perceived physical function. Understanding what impacts the life of people living with MS is important for target interventions and to focus the direction of future research.

ABRÉGÉ

L'impact de la maladie est un concept qui a émergé au cours des années 80 afin de décrire

et comprendre à quel point les symptômes et les traitements d'une maladie chronique

créent de l'interférence avec les activités de la vie quotidienne jugées importantes par les

patients. Cette dissertation présente deux manuscrits appliquant les théories modernes sur

les outils de mesure et la modélisation afin d'examiner le concept de l'impact de la

maladie chez les gens atteints de sclérose en plaque (SP). Le premier manuscrit présente

les résultats d'un exercice de codification sur le modèle conceptuel de l'Organisation

Mondiale de la Santé (OMS) nommé la Classification International du Fonctionnement, du

Handicap et de la Santé (CIF). Les 13 items de la mesure originale de l'impact de la

maladie (Illness Intrusiveness Rating Scale, IIRS) ainsi que 5 items ajoutés par notre

groupe afin de combler les concepts apparaissant comme absents de la mesure originale

furent codifiés par un groupe de neuf experts dans le domaine de la réadaptation. En

utilisant une analyse de Rasch, il fut également démontré que la composition du IIRS est

un construit latent. Les résultats ont démontré, que par rapport au modèle conceptuel du

CIF, l'impact de la maladie est un concept du domaine de la participation et que 14 des 18

items testés forment un construit unidimensionnel et hiérarchique.

Le deuxième manuscrit, qui est une analyse secondaire d'un échantillon de 189 patients

atteints de la SP, présente les étapes suivies et les résultats d'une analyse des pistes

causales qui vise à contribuer des indices par rapport à l'effet des symptômes physiques et

mentaux de la SP sur le construit latent de l'impact de la maladie. L'analyse des pistes

causales a démontré une médiation complète de l'effet des symptômes physiques sur

l'impact de la maladie principalement par la fatigue et la capacité physique telle que

perçue par le patient. Comprendre les facteurs qui ont un impact sur la vie des gens atteints

de SP tient un rôle important pour cibler des interventions et focaliser la direction des

futures recherches dans ce domaine.

ACKNOWLEDGEMENTS

I wish to show my appreciation to my family for giving me the love of learning and the strength and support to pursue my goals. To my little sister Élodie who let me practice my presentation skills on her and made me laugh when I was exhausted. I am grateful to Jean-Philippe who provided an attentive ear when I needed it, supported me and encouraged me to keep pushing.

TABLE OF CONTENTS

INDEX OF TABLES

INDEX OF FIGURES

PREFACE

The main author of this manuscript based thesis is Vanessa Bouchard with extensive editing and feedback from Dr Nancy Mayo. Protocol, data collection and analysis for the codification part of Manuscript 1 were done by Vanessa Bouchard. Data collection for the second part of Manuscript 1 and Manuscript 2 were done in 2008 by Dr Nancy Mayo and her colleagues. Path analysis was performed as a secondary analysis by Vanessa Bouchard. Rasch Analysis presented in Manuscript 1 had already been done by Dr Lois Finch before Vanessa Bouchard joined the research team and was incorporated into manuscript 1 through a team effort between Dr Mayo, Dr Finch, Dr Susan Bartlett and Vanessa Bouchard

Organization of the thesis

The global aim of this thesis was to contribute evidence towards the conceptualization of illness intrusiveness in the context of MS using modern outcome models and measurement theory. Three objectives were used to reach this global goal. The first is to estimate the extent to which the items of the Illness Intrusiveness Rating Scale (IIRS) linked to the International Classification of Functioning, Disability and Health. The second was to estimate the extent to which the items in the original IIRS are hierarchical and cover the full range of the theoretical construct and to identify whether related items improve the fit to an underlying unidimensional hierarchical model. The last objective was to identify the direct and indirect effects of the major physical and mental impairments experience by people with MS on illness intrusiveness. The first two objectives are presented together in

Manuscript 1 and the third objective is presented in Manuscript 2. Additional chapters have been included in the thesis to follow the regulations of the Graduate and Postdoctoral Studies (GPS). GPS requires that a literature review and conclusion be included in the thesis, separate from the manuscripts therefore duplication of material and repetitions are unavoidable.

Chapter 1 serves as an introduction and provides an overview of Multiple Sclerosis, including prevalence, types and symptoms.

Chapter 2 presents the construct and measure of illness intrusiveness. It includes a literature review of the use of the scale in Multiple Sclerosis. It also introduces the most common conceptual frameworks used in health care which are used throughout the thesis.

Chapter 3 introduces the specific objectives and hypothesis of the project.

Chapter 4 contains manuscript 1, entitled "A Modern View of the Illness intrusiveness Construct as an Outcome Measure in Multiple Sclerosis". Objectives 1 and 2 are covered in this manuscript.

Chapter 5 links the two manuscripts in regard to their objectives and the logical progression between the two.

Chapter 6 consists of the second manuscript entitled "Path to Illness Intrusiveness: What Symptoms Impact the Life of People Living with Multiple Sclerosis?". It presents a path analysis that answers to objective 3.

Chapter 7 presents a summary of the findings of the two manuscripts and a discussion taking into account all three objectives. A short conclusion is also presented.

CHAPTER 1

Overview of Multiple Sclerosis

1.1 Disease process of Multiple Sclerosis

Multiple Sclerosis (MS) is a life changing chronic disease that affects young adults. It is one of the most terrifying diagnoses as it attacks the central nervous system, which is composed of the brain and spinal cord. It yields a large variety of symptoms that range from fatigue to loss of balance, and also includes difficulty with concentration and pain[1]. MS is believed to affect 55,000 to 75,000 people in Canada and about 1000 new cases are diagnosed each year. This means that, depending on the region, there are 1 to 2 cases for every 1000 persons in Canada[1]. Diagnosis is usually established between the ages of 15 and 40 when the person is at the beginning or the peak of their career and family life. Life expectancy of a person experiencing MS is considered to be about the same as a healthy individual[1]. Consequently, people with MS live at least half their life with the weight of the diagnosis and the burden of the symptoms.

Since 1995, MS has been diagnosed using brain imaging techniques and evoked potentials. For a diagnosis to be confirmed there must be at least two lesions in separate locations and they should have occurred at different times. These lesions may cause temporary or permanent symptoms or may be asymptomatic. Prior to 1995, diagnosis was based on symptoms and neurological examination. As MS is not always symptomatic following the first lesion, a definitive diagnosis could take considerable time. The emergence of brain imaging improved the time line for confirmation of diagnosis by an

average of 7 years[2]. Early diagnosis also changed the big picture of the MS patient in the way society view them and the way they live with their disease. Their symptoms are less severe and are treated earlier. This population is now called the "New MS" as they differ slightly from populations of people diagnosed with MS prior to 1995[3].

Presently, the exact cause of MS is unknown. However, it is believed that the increased risk of developing MS is due to complex interactions between genetic and environmental factors. Currently, there are no cures for MS. At the moment the main course of treatment is symptom management and disease modifying therapies which decrease the number of relapses experienced. A person diagnosed with MS will therefore have to find ways of adapting to minimize the symptom burden of MS while maintaining as normal a life as possible.

Multiple Sclerosis can present itself in four different forms[1]. The most prevalent type is the Relapsing-Remitting form (RRMS) which accounts for about 85% of all cases. People with RRMS experience flare-ups followed by complete or partial remission. About half of RRMS cases will convert to the Secondary Progressive (SPMS) form approximately 10 years following the initial diagnosis. Exacerbations and remissions will become less apparent as there is a steady increase of symptoms. The third type, Primary Progressive (PPMS), consists of a regular slow appearance of symptoms. PPMS is often diagnosed at an older age and forms about 10% of the total number of MS cases. The last form, Progressing Relapsing MS (PRMS), is the most uncommon type and occurs in only 5% of

all cases. PRMS is characterized by a steady worsening of symptoms with occasional flare-ups. Prior to being diagnosed, people who have had a single episode and experienced full remissions are categorized in the probable MS or clinically isolated syndrome (CIS). As time progress, they will be classified into one type or remain in the CIS category if no other episode happens [1].

In the disease process, the myelin sheath of the nerve cells is damaged or destroyed and replaced by scar tissue, which will modify nerve conductivity. The wide variety of possible lesion sites makes multiple sclerosis a very complex disease and its presentation is uniquely individual. Symptoms of multiple sclerosis include, but are not limited to, fatigue, pain, dizziness and decreased balance, weakness, difficulty walking, loss of coordination, absent or abnormal sensation, cognitive impairments, bowel and bladder dysfunction, depression and spasticity. Some symptoms are more prevalent than others. However, they all affect, in one way or another, an individual's ability to function normally and fulfill their life roles.

1.2 Impairments associated with Multiple Sclerosis

1.2.1 Fatigue

Fatigue is the most prominent MS symptom. In comparison to fatigue experienced by healthy people, the fatigue experienced by people with MS differs in several ways [4]. MS fatigue is: 1) more severe and more frequent; 2) a greater impediment to sustained

physical functioning; 3) more often sudden in onset; 4) longer to recover; 5) precipitated or accentuated by heat or humidity. Fatigue affects about 90% of all MS cases. It can be from either a primary or secondary source. Primary fatigue, which produces a form of lassitude, appears to occur as the result of an active inflammatory process. Secondary fatigue is related to sleep deprivation or a lack of good quality sleep secondary to MS symptoms or medication. Both types of fatigue can be overwhelming and impair the person's ability to complete daily life activities [1].Fatigue is thought to be associated with depression [5, 6],a decrease in self efficacy [5] and decreased motivation [6]. However, physical activity has been shown to have a positive effect on fatigue [7].

Another form of fatigue that can be affected in MS is muscle fatigability. It consists of a decrease in strength with repeated use of a muscle group. This is usually considered an aspect of the strength therefore will be addressed in that section

1.2.2 Depression

Depressive symptoms are very common in populations suffering from a chronic disease, and MS is no exception. Life time prevalence of depressive symptoms in MS is estimated to be from 25% to 50%. Some studies propose that in these cases the cause of depression might be physiological and linked to brain lesions [1]. Fatigue and depression can are related and one can lead to or exacerbate the other. Bakshi and colleagues [8] suggested that there may be a common mechanism behind these two MS symptoms. Another common

sign of depression is a loss of interest or a decrease of pleasure in everyday activities which could in turn affect every day functioning.

In MS, most of the literature identifies depression from questionnaires or checklists of depressive symptoms and uses them as diagnostic tools for depression.

1.2.3 Balance Impairments

To achieve balance, an individual needs to use three different systems in their body[9]. The visual system gives information about where the body is in space and if it is positioned correctly. The vestibular system provides information about verticality and direction of movement. Finally, proprioception, measured by internal censors in the joints, provides information on the angle and direction of joint movement. The knowledge provided by these three systems is analysed in the brain and allows the body to make necessary adjustments to maintain a static or dynamic posture[9]. In multiple sclerosis, the pathways between these systems or the brain cells that analyse the information can be altered, resulting in dizziness, vertigo and other difficulties while walking or moving[10]. These impairments put the person affected with MS at higher risk of falling and thus injuring themselves. To prevent falls, adaptations are often suggested such as a walking aid or grab bars in the house[1]. To date, few treatments have proven to be helpful in the treatment of the neurological aspect of balance deficits.

In addition to balance capacity, a person's ability to recognize the presence, or absence, of deficits is important. This concept is called in the case of balance "balance self-efficacy". Self-efficacy is defined as "a person's belief about their capabilities to produce designated levels of performance that exercise influence over events that affect their lives" [11].Judgement, which is required for recognizing limitations and capabilities, is part of cognition and up to 40% of people with MS suffer from cognitive impairments. A mismatch between balance capacity and balance self-efficacy can cause one to adopt risky behaviour that can lead to falls or an overly protective behaviour that can lead to self-restricted life style contributing to general deconditioning.

1.2.4 Pain

About 50% of people diagnosed with multiple sclerosis suffer from MS related pain during the course of their illness. There are different types of pain, all of which can be either acute or chronic. The most common are neurologic, joint and back pain, and headaches. A number of pain types can be treated but the variety needs to be properly identified for treatment to be successful [1]. This symptom can be quite debilitating, especially in the chronic form. Previous research has demonstrated that pain is associated with a reduction in physical activity in multiple sclerosis patients [12].

1.2.5 Strength

Loss of strength is a very common symptom, although its prevalence is unknown. Weakness by itself is not always a problem, but most everyday activities, such as climbing stairs, lifting a child off of the floor or simply walking require a certain level of strength. Decreased strength with repeated movement, or muscle fatigability, is a common presentation of this symptom. People suffering from fatigability often have to stop before completing a task or take numerous breaks while performing the task. However, physical training has been shown to improve strength and fatigability and a recent review has shown that exercise impacts positively on health related quality of life and general fatigue [13]. The same review [13] supports that not engaging in regular physical activity decreases strength.

Kuspinar et al [14] found that muscle power, or the ability to produce strength rapidly is one of the first manifestations of a decrease in strength. Performing activities that require muscle power, such as jumping, becomes difficult for people living with MS at an early stage of the disease.

1.2.6 Spasticity

Spasticity refers to an impairment of muscle tone. It usually manifests itself in the form of an increased resistance to passive stretch of the muscle. It is a sign of an upper motor neuron lesion, that is, an injury to a nerve cell in the brain that is responsible for motor

commands to the muscles that are now disrupted. Spasticity can be taxing when it comes in the form of muscle spasms especially during sleep. Moving a spastic limb requires more energy as more strength is required to fight the resistance. The severity and number of limbs affected by spasticity determines the person's functional abilities. Treatment for spasticity is usually pharmaceutical but certain conservative methods such as stretching and icing have shown some temporary positive effects. Surgical interventions are also available but only in the advanced disabling cases where spasticity prevents proper self care. Severe spasticity can lead to additional serious problems such as contractures of joints and pressure sores. In certain cases with severe muscle weakness, muscle hypertonicity or spasticity can be beneficial as it allows the person to stand up and walk. In such cases, reducing it will mean a decrease in function [1] [15].

1.2.7 Cognition deficits

Cognitive changes affect about 40% of people with MS to varying degrees during the course of their illness. Frequent problems are memory loss, decreased attention and concentration, reduced speed of information processing and difficulties with planning. About 10-15% of the MS population will suffer from cognitive problems that interfere with daily activities [15].

1.3 Activity limitation and Participation restrictions

A person has multiple roles in society. Whether it is family, work, social, or recreational roles, an individual needs to be able to engage in a large variety of activities in order to be an accomplished member of society. Although not every symptom is experienced by every MS patient, the cumulative effect of multiple symptoms results in limited activity. Activities of daily living such as walking and bathing oneself or preparing a meal require a complex interaction between multiple systems that can be impaired. Being unable to complete tasks of different levels of complexity or to carry them out to the desired level of accomplishment could diminish the ability to fulfill one's life roles and subsequently restrict participation.

1.4 Beyond symptoms and function

The World health organization (WHO) provides a classification and framework of terms to describe a person's functioning and disability. It defines the positive construct of functioning as an umbrella term that covers all body functions, activity and participation. The negative term disability is also an umbrella term that describes the negative manifestations of functioning related to a disease; impairments, activity limitations and participation restrictions[16].

Well being is defined by WHO as "*a general term encompassing the total universe of human life domains including physical, mental and social aspects, that make up what can be called a 'good life'* "[16].

The WHO defines quality of life as "*individuals' perception of their position in life in the context of the culture in which they live and in relation to their goals, expectations, standards and concerns*"[17] From the perspective of the health care system, many of the components of quality of life, such as jobs, housing, schooling and neighbourhood are not attributes of health, and are outside the purview of the health care system[18]. As a result, the distinct concept of health-related quality of life (HRQL) has emerged.

"Health domains are a subset of domains that make up the total universe of human life" [16] Under the functioning paradigm, it is possible for a person living with MS to be in a state of well being as many functions are still intact. There is conceptual compatibility between the disability constructs of the ICF and quality of life. According to the WHO [19], the disease/disability constructs refer to objective and exteriorized signs of the individual, while quality of life deals with what people "feel" about their health condition or its consequences; hence it is a construct similar to "subjective well-being".

Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity [16]. A person with MS can still feel healthy under this definition. The consequences of this definition brings up the issue that treating symptoms will not automatically affect quality of life. The ultimate goal of any treatment is to improve quality of life.

Carr et al. [20] have argued that the relation between quality of life and symptoms in patients with chronic diseases is neither direct nor simple. They also added that quality of life is linked with a person's ability to fulfil a normal role. Symptom relief does not necessarily mean an increase in quality of life. The interactions between various MS symptoms and quality of life or disease impact are not yet determined with certainty.

A term that has been increasingly present in the MS literature is illness intrusiveness. Illness intrusiveness is believed to have a direct link to quality of life and to be affected by symptoms. However it has not been situated within the functioning paradigm set by WHO. The next chapter will review the literature on this construct.

CHAPTER 2

Overview of Illness Intrusiveness

2.1 Definition

Illness Intrusiveness was first introduced by Devins in 1983. It is defined as the illness and treatment-related lifestyle disruptions that interfere with continued involvements in valued activities and interests. The construct and its measure were first developed through classical test theory in end stage renal disease patients, but multiple sclerosis was soon to follow [21].

The outcome measure used to capture illness intrusiveness is called the Illness Intrusiveness Rating Scale (IIRS). The questionnaire quantifies the amount that the illness and/or its treatment interferes with 13 life domains (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). Each item is rated on a scale from 1 to 7 (higher being worst), for a total score ranging from 13 to 91. It has been validated in various chronic diseases including MS, end stage renal disease, osteoarthritis, schizophrenia and various types of cancer [22]. See appendix A for full questionnaire.

Illness intrusiveness is often used as a measure of health related quality of life. Although the two constructs are related, more recent research shows that IIRS is considered more as

indicator of the impact on psychological well-being only one piece of health related

quality of life [22, 23]. To date, the IIRS has been used mostly for research purposes and has

very little use in clinical assessments. Figure 2.1 illustrates the conceptual framework for

illness intrusiveness by Devins [22]. The connections between the disease and treatment

factors and illness intrusiveness are presented as well as how illness intrusiveness affect

well-being directly and through perceived control over the disease.
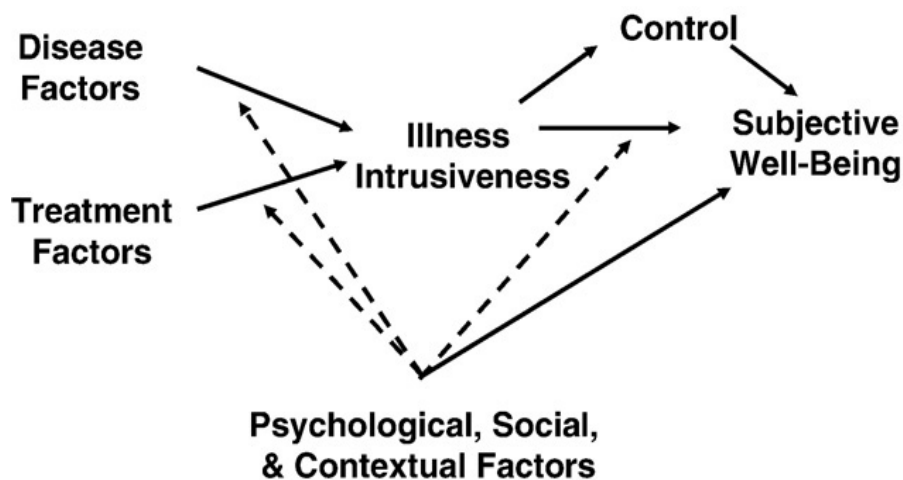
Figure 2.1: Conceptual model of illness intrusiveness by Devins [22]

2.2 Illness intrusiveness in MS

The construct of illness intrusiveness was first introduced in the literature in 1983.

Although this concept has been around for nearly three decades, it was relatively ignored

for the first 20 years of its existence. Before 2001, the IIRS in MS was almost exclusively

used by Devins and his teams. The next section explores the use the IIRS in MS through a structured review.

2.3 Structured review

Searching using the combined keywords of "multiple sclerosis" and "illness intrusiveness" on four well known databases (Pubmed/Medline, PsycInfo, Google Scholar and CINAHL) resulted in 8 articles. After reviewing the articles, five looked specifically at illness intrusiveness in MS. Three articles were eliminated had one that used people with MS as comparison group, one was a confirmatory analysis of the measure and the third tested the perceived control effect on quality of life, also part of Devins' illness intrusiveness theoretical framework [22].

Of the five retained articles the two oldest were published in 1993 by Devins et al.[24] [25]They concluded that people with MS felt greater interference in their daily life than people affected with rheumatoid arthritis (RA) or end-stage renal disease (ESRD). Poor sleep quality was the leading cause of higher intrusiveness in those same diseases (MS, RA, ESRD). In 2001, the same team published a paper that confirmed that the illness intrusiveness rating scale is valid across diseases and confirmed the existence of three subscales: Relationships and Personal Development, Intimacy and Instrumental[26].

That same year, Mullins et al.[27]showed that illness intrusiveness and uncertainty predicted psychological distress in people with MS. They also stated that although illness intrusiveness is highly correlated to distress, it does not mediate or moderate the effect. The next year Shawaryn and colleagues [23] examined the role of illness intrusiveness on different aspects of quality of life. They found correlations between illness intrusiveness and every subset of HRQL: physical, mental, emotional and cognitive. They also showed that illness intrusiveness plays a mediating effect between MS and HRQL. In the light of these findings, they specified that one cannot fully capture HRQL without having a sense of the degree to which the individual perceives the disease to be disruptive of his/her lifestyle and that the IIRS should be used as a screening tool to detect people at risk of an impaired health related quality of life.

The most recent article looking at illness intrusiveness in MS was written by Turpin and colleagues in 2007[28]. This paper discussed the fact that illness intrusiveness is the only MS related construct related to mental health with lack of personal control over the disease as the most important factor affecting the mental and social aspect of the life of patients with MS.

Over the years, the literature has concluded that illness intrusiveness, as measured by the IIRS, is related to health related quality of life in all its subscales and especially the mental and social aspects.

It is important to note that only two of the five studies looked at Illness intrusiveness as an outcome. One of those looked at the effect of different disease on illness intrusiveness as an outcome which does not provide much information about what constitutes illness intrusiveness. Some studies have looked at illness intrusiveness as a moderating or mediating factor. However the largest number of studies looked at illness intrusiveness as an exposure. Thus far no study has described what affects (increases or decreases) illness intrusiveness.

2.4 Terminology issue

One of the main concerns when reviewing the literature is the inconsistency in the use of certain terms. The words mediating and moderating are often used in a vague way and in some cases even interchangeably. A very attentive reading of the methods is necessary to confirm the interpretation of the findings. Figure 2.2 illustrates the mediating and moderating effects.

A mediating effect, also described as an indirect effect, is observed when the outcome is affected by a variable through a second variable. The mediation can be either partial or complete. It is said to be complete if there are no direct effects between the said exposure and the outcome and the only effect it has is through the intermediary variable. If on the contrary there are both a direct and an indirect effect, then the mediation is said to be partial.

A moderating effect happens when an outcome can be explained by two exposure variables. The amount of variance in the outcome explained becomes even larger when the interaction between the 2 variable is added to the list of predictors.

Simple Mediation Model	Simple Moderation Model
Mediator Exposure ⟶ Outcome	Exposure 1 Exposure 2 ⟶ Outcome E1*E2
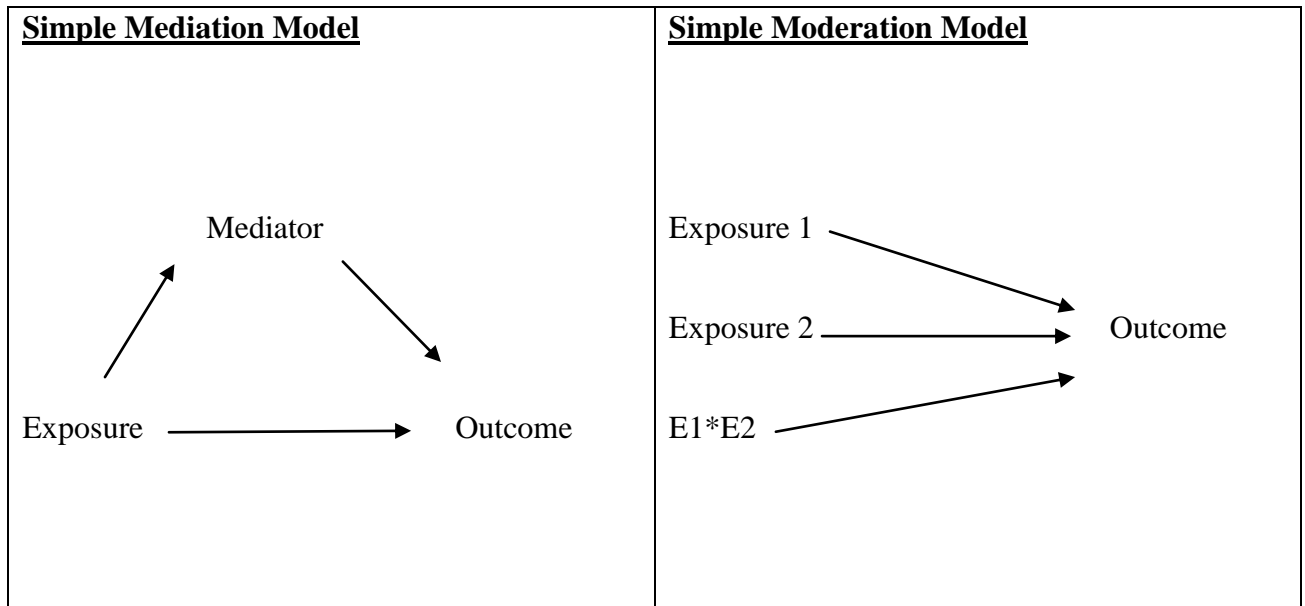
Figure 2.2: Mediating versus moderating effect

2.5 Choosing a theoretical framework for illness intrusiveness

There are two main theoretical frameworks in the field of rehabilitation. The first is called the International Classification of Functioning Disability and Health (ICF) and is promoted by the World Health Organization (fig 2.3). The second is the Wilson Cleary model (fig 2.4)

17

2.5.1 ICF framework

To have a common international language to classify health and health related domains, the World Health Organization created a framework that applies to all people. Launched in 2001, this framework called the International Classification of Functioning, Disability and Health or ICF [16] describes and measures health and disability. It was used for international and national surveys in 71 countries and now helps with the creation of new measures in rehabilitation and other fields. Clinically, it is used for goal setting and treatment planning in various countries, including Canada [29].

The main difference between the ICF and its predecessor, the International Classification of Impairments, Disabilities and Handicaps (ICIDH) created in 1980, is that the ICF focuses on the positive or people's health rather than disability. Therefore, what now constitutes a person is a list of functions and structures of the body, activity and ability to participate in various life situations. All these aspects are inevitably affected by various personal and environmental factors. When a person encounters problems in a sphere it can be described as an impairment in body function or structure, or as an activity limitation or participation restriction. Personal and environmental factors are also recognized to influence the final outcome. The clinical diagnosis is not included in the ICF but is the health condition or event that impacts on the ICF framework. Diseases are classified in another classification system called the International Classification of Disease, 10th revision (ICD-10). In the ICF paradigm, the entire model will reflect health related well-being and takes into account environmental and personal factors.
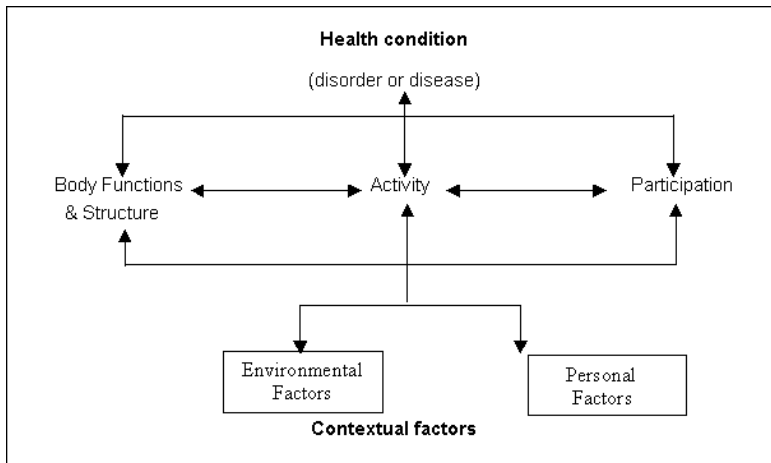
Figure 2.3: The International Classification of Functioning, Disability and Health conceptual framework[16].

2.5.2 Wilson-Cleary Model

The second framework used to conceptualize health is the Wilson-Cleary model (fig 2.4)[30]. It describes the path to quality of life starting from biological/physiological factors. It was developed in 1995 to provide a perspective on the relation between the biological research world, the clinical world and the social science world. This model's relationships are more linear than the ICF with the end effects on quality of life through a domino effect or through a direct relation. The model also takes into account the effect of individual and environmental characteristics on each step.
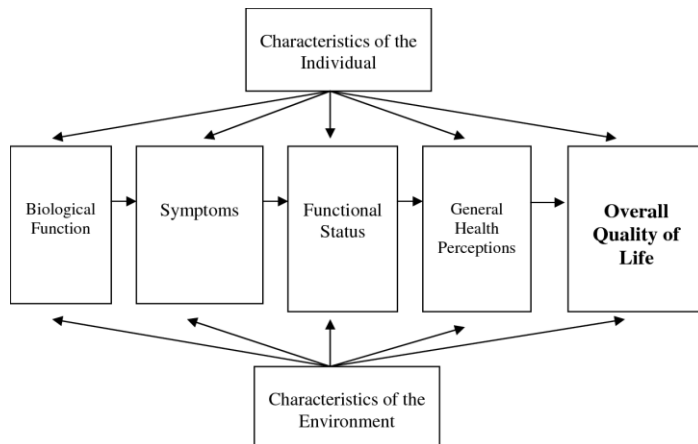
Figure 2.4: The Wilson-Cleary health related quality of life conceptual framework[30].

At this moment, it remains unclear where illness intrusiveness fits within these two models that will be used here to conceptualize health-related quality of life (HRQL) as it was previously done by others [31]. Valderas & Alonso [32] showed that the two models can be superposed and that the two models complete each others to some extent.

This thesis aims to understand the illness intrusiveness construct and its measure, the IIRS, in the context of MS. It will use modern day thinking and methods of outcome measurement research to look at it in a new perspective.

CHAPTER 3

Objectives and Hypothesis

3.1 Objectives

The global aim of this research is to contribute evidence towards the conceptualization of illness intrusiveness in the context of MS using modern outcome models and measurement theory.

The specific objectives are:

1) To estimate the extent to which the items of the illness intrusiveness rating scale (IIRS) link to the International Classification of Functioning, Disability and Health. This exercise will test whether illness intrusiveness is distinct from function or if it is within the function framework as defined by the ICF.

2) To estimate the extent to which the items in the original IIRS are hierarchical and cover the full range of the theoretical construct and identify whether related items improve the fit to an underlying unidimensional hierarchical model.

3) To identify the direct and indirect effects of the major physical and mental impairments experienced by people with MS linked through activity and participation to illness intrusiveness, where:

- physical impairments include balance, strength, pain, tone and physical capacity;

- mental impairments include mood, energy, balance confidence and cognition;

- activities include walking capacity, self-reported physical function, and role participation.

3.2 Hypothesis

The main hypotheses are that illness intrusiveness will map on to the ICF more closely in the participation domain and that the ICF model will fit as a path to illness intrusiveness and support it as a participation-related outcome.

CHAPTER 4

Manuscript 1

A Modern View of the Illness intrusiveness Construct as an Outcome Measure in Multiple Sclerosis

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Running Title: A Modern View of the Illness intrusiveness Construct as an Outcome Measure in Multiple Sclerosis

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4.1 Introduction

The construct of illness intrusiveness arose from work carried out by Devins in the 1980s to describe the emotional impact of chronic diseases. It depicts how chronic disease or its treatment interfered with various valued life activities [1].   The Illness Intrusiveness Rating Scale (IIRS) was first developed and tested in end stage renal disease (ESRD) and multiple sclerosis (MS) and has been validated in various other chronic diseases [2]. It queries how much the disease and treatment interferes with 13 domains of life: 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. A higher IIRS score reflects greater interference and impairments in health related quality of life (HRQL) [3] [4].

A literature search using the keywords of "multiple sclerosis" and "illness intrusiveness" on Pubmed/Medline, PsycInfo, Google Scholar and CINAHL was carried out to identify studies that queried IIRS in MS since its creation in 1983 through May 2011. The search returned eight articles of which five reported research results using this outcome to describe the impact of MS (see Table 4.1). The search revealed that even though illness intrusiveness had been used as an exposure to predict health related quality of life [3] [4], very little work had been published on IIRS as an outcome therefore a lot of work remains to be done to identify specific disease factors that predict variation in illness intrusiveness.

When factors associated with illness intrusiveness have been studied, most literature focuses on disease related factors. There is little research on modifiable aspects of disease (impairments and limitations) related to illness intrusiveness in MS. Without a clear conceptual model of illness intrusiveness in the context of health outcomes, it would be difficult to identify those factors that are part of a causal pathway and distinguish these from factors which may be a consequence of illness intrusiveness. For example, quality of life could be conceptualized as arising from the extent to which the disease sequelae are intrusive. Given that the content of the measure may be relevant to understanding the impact of chronic disease and its treatment on psychosocial and emotional well-being and that it has a proven effect on HRQL (and perhaps quality of life (QOL)), further conceptual work is warranted to identify the areas for intervention which would have the greatest potential for reducing intrusiveness.

The two predominant theoretical frameworks used in health outcomes research are the World Health Organization's International Classification of Functioning, Disability and Health (ICF) [5] and the Wilson-Cleary (WC) model [6]. The ICF classifies functioning and its antithesis, disability. Functioning includes two components, body which comprise function of body parts and body structures, and activities and participation, while disability refers to impairments of body structures and functions, limitations of activities and restrictions to participation [5] The WC model links biological and physiological variables, symptoms, functional status, to general health perception and ultimately to overall quality of life [6]. Both frameworks share many common components. Biological and physiological variables in the WC model correspond roughly to Body Structure and

Function domain of the ICF. The activity and participation domain of the ICF is under the construct of functional status in the WC model. Both models differentiate between health related variables and contextual factors or characteristics of the individual and of the environment. These contextual elements interact with the main components of the model [7]. One of the intent of ICF is the coding of different health and health states and of measurement tools. It is done through a process called a mapping exercise. The codes provide an international conceptual understanding and can help the development or improvement of measures of health status or disability[5, 8] Valderas and Alonso showed that ICF can be linked to the WC [7]. We therefore decided to link the scale to the ICF framework by mapping it and then compare the results to the WC [7].

The overall aim of this study is to contribute to the understanding of how illness intrusiveness fits into the current perspective of outcomes research in the field of MS by (i) linking it to the ICF, and (ii) testing if the items of the IIRS fit a unidimensional, hierarchical construct using Rasch measurement theory.

4.2 Methods

Objective 1: Linking the content of the IIRS to the ICF

The Illness Intrusiveness Rating Scale attempts to quantify the amount that the illness and/or its treatment interferes with 13 life domains (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). Each item is rated on a scale from 1 to 7 (higher scores reflect greater interference), with total scores ranging from 13 to 91. It has been validated in various chronic diseases including rheumatoid arthritis, ESRD and various forms of cancer. Those items were developed in the 1980s in people with ERSD. Clinical and research experience with people with MS of the team members allowed to identify potential gaps in the measure. Therefore, five additional items were added by our research team to reflect constructs possibly missing from the original measure, using a similar stem and response format as the original 13 items. They cover driving ability and confidence, career choice, family planning and making plans for the future.

In the ICF, the World Health Organization WHO identifies 1424 health status codes at the highest level of precision which are divided in three large classifications chapters Body Functions and Structures, Activities and Participation, and Contextual Factors[5]. Body Functions and Structures refer to physiological and psychological functions and the anatomical parts associated with them. Problems with body function and structures are classified as impairments. Activity refers to the execution of a task or action by an individual and participation is involvement in a life situation. Activity limitations and participation restrictions are indicators of difficulties and problems in those domains. Contextual factors are divided in two components: environmental and personal factors. Environmental factors make up the physical, social and attitudinal environment in which people live and conduct their lives while personal factors are the particular background characteristics of an individual's life and living, other than their health state. Each ICF

domain is divided into chapters and the chapters are subdivided into smaller components upwards of three times. Each subdivision increases the level of precision [5].

Each code of the ICF is assigned a letter (b, s, d, e) followed by numeric code. The letter codes are: b for "body function", s for "body structure", d for "activity and participation" and e for "environmental factors"[5]. The letter codes are followed by up to 4 digits. The first digit represents the chapter number (for example, relevant chapters for describing MS would include mental functions, sensory functions and pain, learning and applying knowledge, mobility, domestic life, and community and social life). Subsequent digits represent greater precision within that chapter e.g. mobility includes walking and climbing. Coding can be used to classify the level of granularity of an item in a measure or to link that function to an electronic data base of disease codes. Typically, items can only be classified at the second or third level of precision. The WHO suggests that a three-digit level of precision should be used for surveys and clinical outcome evaluations[5]. Multiple methods are suggested by WHO to separate activity from participation codes. We decided to use chapters D7, D8 and D9 to represent participation and chapters of the D section to reflect activity limitations [5].

To map the content of the IIRS items to ICF components, we used a standardized protocol [9]. Nine experts in the assessment and treatment of disabilities (4 physiotherapists, 1 occupational therapist, 2 exercise therapists, 2 MS clinic workers) mapped the items of the IIRS to the ICF. Six of the raters had clinical and/or research experience in the field of

MS; they also had expertise in mental health, cancer, stroke and hip fractures. The raters were trained on the ICF framework, definitions, coding structure, and coding following the protocol suggested by Cieza et al.[10]. Then each rater independently selected the ICF code that they believed best represented the underlying intent of each item.

Once all of the first set of ratings was collated, a Delphi consensus process was used to reach consensus on the optimal code for each item. After each rounds, each mappers received a list of all the codes endorsed with the percentage each of them got as well as the code they chose. They were asked if they wished to change their choice. This process was repeated until 70% of raters agreed on the code or until no further revision opportunities were likely to yield the target agreement level.

Objective 2: Validation of the IIRS with Respect to the Rasch Measurement Theory

The Rasch Measurement Theory provides a method of estimating the extent to which items relating to a latent construct form a unidimensional linear continuum. Rasch Measurement Analysis transforms ordinal observations onto an interval scale. Modern psychometrics stress the importance of item response models in which people or patients with a particular level of ability have a probability of responding positively to different questions. While termed "modern" the mathematical assumptions emerged from work as far back as the 1920s [11] through to the 1960s [12, 13]. In contrast, traditional psychometrics is based on the premise that a total score can be derived as summative (or linear, in the case factor analysis) function of the items scores with some random error [14]. The outcome

of a Rasch analysis, when the data fit the model, is a unidimensional measure with items

and people organized hierarchically, by difficulty and ability respectively, on the same

measurement scale. Items that fit a Rasch model form a measure with a total score that is

sufficient to determine that person's ability on the underlying construct [15].

Items that do not fit the model are evaluated further to identify potential reasons for their

lack of fit and to explore the relationship between the misfitting items and the construct.

Adjustments to the response options or item deletions may be necessary to improve the fit

of the data to the model[16] .The extent to which the items of the IIRS are arranged along a

continuum provides evidence for construct validity with respect to the how the items fit

together conceptually and where they fit along a linear continuum [17].

The analysis used a sample of 189 people randomly selected, in 2008, from the

computerized databases maintained in the three largest MS clinics in the greater Montreal

area. Detailed methods on selection and characteristics of the sample have been published

previously [18].

Data from 189 respondents on 18 items were analyzed using the Rasch Unidimensional

Measurement Model program (RUMM 2020) [19]. After the initial test of data fit, each

item's response category or threshold was examined to determine if 1–7 responses were

as the developers intended. An item threshold is the point at which the likelihood of

endorsing an item's response option becomes the likelihood of not endorsing it; i.e.,

choosing between 0 and 1, or 1 and 2 [20]. Disordered threshold were re-categorized based on both graphical and statistical data by collapsing adjacent categories that were not able to discriminate between response options[20].

Once the item responses were adequate, overall model fit was re-examined and misfitting items were deleted iteratively to optimally fit the data to the model. Criteria for fit were: item and person standardized fit residuals between ± 2.0 and a global model non-significant χ^2 [21]. To evaluate the precision, a Person or Item Separation Index (equivalent to a Cronbach's alpha) was provided by the program. Model assumptions of unidimensionality and response dependency were also verified via by a principle component analysis (PCA) of the standardized residuals from the Rasch analysis [22] and examination of the item residual correlation matrix with the criterion for dependency set at <0.30.

4.3 Results

ICF Mapping

Four rounds were necessary to reach agreement on all 18 items. Due to the length and complexity of some items, in certain cases two codes were endorsed for the same question. About half the items were endorsed at the three digit level and the other half were endorsed at the four digit level. Only one item was not covered by the ICF (15. Family planning), one item was defined as a personal factor (11. Self-

expression/improvement and one item was considered non definable because it represented general health (1. Health). Table 4.2 presents the codes endorsed and the number of rounds necessary to reach consensus on all items evaluated.

The ICF chapters represented in the IIRS were from body functions B1 Mental Functions (2 items), from activity D4 Mobility (2 items), D5 Self Care (1 item), from participation D7 Interpersonal Interactions and Relationships (4 items), D8 Major Life Areas (3 items) and D9 Community, Social and Civic Life (4 items). 14 items mapped to the activity and participation domains but 11 items mapped specifically to chapters which relate to participation (D7 Interpersonal Interactions and Relationships, D8 Major Life Areas, and D9 Community, Social and Civic Life).

Rasch Analysis

The ranking of the items according to their life impact (item difficulty) is also presented in Table 4.2 along with the number of response thresholds that could be discriminated for each question. Fourteen items were retained in the final model (10 original and 4 new). The respondents were able to distinguish between the original 6 thresholds (n response options − 1) for only 1 item; 5 items were reduced to 2 scoring thresholds, 4 items were reduced to 3 thresholds; and 2 items used 4 thresholds (see table 4.3). The final item list yields scores that range from 0 to 44.

Out of the 14 items that remained in the transformed scale, 15 ICF codes were endorsed. Twelve codes were from the activity and participation categories of the ICF. Two pertained to a body function and one was a personal factor. Two codes were associated with more than one question. Of the 11 items that mapped to participation, 2 of these items did not fit the Rasch Model (sex life, and other social relationships).

Three subscales existed in the original IIRS [23]: Relationships and Personal Development, Intimacy, and Instrumental. With the loss of one or two items from each of the three subscales, the dimensionality of the construct represented by IIRS was also reduced to a single dimension. All the remaining items and all persons fit the model (person residual mean-0.17 ± SD 1.1; item residuals mean 0.18 ± SD 0.85) forming a unidimensional hierarchy.

4.4 Discussion

The results of the mapping indicate that IIRS likely reflects a construct in the participation domain of the ICF. Of the original 13 items, 10 mapped predominantly to the participation component of ICF. Of the 5 added items, only 1 mapped to participation but the items referring to planning for the future and driving a car as an activity did reflect aspects of participation. The planning item could be interpreted as planning for future participation. Driving as coded in the ICF may only represent the process of driving not the intention of the question which is to know the impact of the disease on driving and could be interpreted as driving to participate in desired activities by affecting choices for recreation, social engagement, travel, and work. Of the 18 items, 14 fit a unidimensional,

hierarchical construct (10 original and 4 new) and of these 9 mapped to participation with an additional 3 if we consider plans for the future and driving to be within the participation domain.

Three items of the IIRS (original 13 + 5 new) did not map to the ICF, health, self-expression/improvement, and family planning. This does not mean they are unimportant; of these only self-expression/improvement fit the Rasch model indicating that a broader latent construct of illness intrusiveness could include this item.

The Rasch measurement latent construct did not include the item relating to sex life possibly because it overlapped with spousal relationships; both mapped at the same 3-digit level (D770: intimate relationships). Also excluded was the item for other social relationships. The item "other social relationships" was also excluded as its vague wording had the potential of setting up a situation for inconsistent response.

It was noted, during the mapping exercise, that some of the items from the original IIRS are written with wording consistent with the ICF. For example, "How much does your illness and/or its treatment interfere with your family relationships?" was matched to the code under family relationship. Other questions which were linked to the ICF were debated more requiring more rounds to determine an adequate code. These items appeared to be worded that was farther away from the ICF terminology. For example,

"How much does your illness and/or its treatment interfere with your self-expression/self-improvement?" was coded as a personal factor as all the mappers appeared to have a different interpretation of the wording. Although the original IIRS had three subscales after the Rasch analysis it formed a unidimensional latent construct.

The items of the IIRS relate to participation as defined by the ICF codes. Edwards and Bagozzi [24] emphasize the importance of distinguishing between reflective and formative conceptual models when developing measures. In a reflective model, the items reflect the construct. This is the classic definition of a latent variable, one that cannot be directly measured but is reflected in the items. Changing the construct will show changes at the item level. In a formative conceptual model, the items form the construct and the resulting total score is a composite rather than a latent variable; altering the construct will not change the items.

In looking at the items in the IIRS, most of them would be considered formative and hence as it stands the total score of the IIRS is a composite of all the areas impacted upon by MS. If a participation measure was desired, a decision would need to be made as to whether it would best be a composite or a latent. Based on the results it appears that participation is best expressed as a composite of the number of and satisfaction with activities valued by the individual or society.

Clearly capturing the impact of a disease and its treatment on valued activities and interests is important and fits directly into the conceptual framework of the ICF as

participation. The lens of the ICF would improve the degree to which these important areas are identified for people with MS and would then lead to clinical or self-management strategies. While the ICF extensively used input from people with disabilities in defining the ICF content and granularity, future conceptualization and scoring would need to include the person's voice along with clinical expertise. When the mapping exercise was done, people with MS did not participate in the rating exercise-their voice is not as crucial in choosing an administrative code, as it is in devising items and appropriate wording.

4.5 Conclusion

Placing the construct of illness intrusiveness within the continuum of function and quality of life enriches our understanding of how the lives of people are affected by chronic disease. Valderas & Alonso [7] showed that the ICF model can be superposed on the Wilson-Cleary model and that the two models complete each others to some extent. Defining the construct as participation fits it within a broader model of health related quality of life such as the Wilson-Cleary model. Based on this model, the next step will be to determine what drives the new construct that has emerged from these methods. As the construct seems to fit a formative conceptual framework, the items provide information on how to reduce illness intrusiveness. In particular several items are amenable to modification through interventions of rehabilitation professionals and psychologists and through improved drug therapy and care.

4.6 Tables for Manuscript 1

Table 4.1: Summary of the literature on the use of IIRS in MS

Author (Year)	N	Exposure	Outcome
Devins (1993) [25]	94 MS, 110 RA, 101 ESRD, 176 controls	Restless Sleep	Illness Intrusiveness (Ill Int)
Conclusion. Ill. Int. was reported to be higher in individuals who experience restless sleep. The impact of restless sleep on depressive symptoms is mediated by Ill. Int.			
Devins (1993) [26]	94 MS, 110 RA, 101 ESRD	Disease (MS,RA, ESRD)	Illness Intrusiveness
Conclusion: MS is more intrusive than RA or ESRD. Diet and religious expression were the less affected and work and active recreation was the most affected.			
Mullins (2001) [27]	78	Ill. Int. Uncertainty	Psychological distress
Conclusion: Ill. Int. and uncertainty predicts psychological distress after controlling for demographic and disease variables. Ill. Int. is highly correlated to uncertainty but does not mediate or moderate it			
Shawaryn (2002)	90	Ill. Int.	HRQL (SF-36 subscales)
Conclusion: Ill. Int. is related to all physical, mental, emotional and cognitive measures of HRQL. Measures of Ill. Int. could serve as a screening for those at risk of having HRQL problems rather and a substitute. Ill. Int. was found to have a mediating effect between MS and HRQL. Disease severity appears to be related to self-report of MS-related fatigue impact via Ill. Int. There is a direct relation between Ill. Int. and HRQL.			
Turpin (2007) [4]	292	Ill. Int. Disability Depression Fatigue	HRQL (SF-36 subscales)
Conclusion: Ill. Int. is the only MS specific factor found to be related to mental health. Lack of personal control/increased dependency has been reported as being one of the most important factors relating to the mental and social aspects of MS patients' lives			

N: sample size, MS: Multiple Sclerosis, RA: Rheumatoid Arthritis, ESRD: End-Stage Renal Disease, HRQL: Health related Quality of life, Ill Int: Illness Intrusiveness

Table 4.2: Results of the ICF Mapping and Rasch Analysis

Question	ICF Code*	Number of rounds	Rank** in final Rasch	Number of thresholds
How much does your illness and/or its treatment interfere with your...				
Original items				
1- health?	ND-GH	3	X	0
2- diet?(for example, the things that you eat and drink)?	D5701	1	10	2
3- work (including school work)?	D840 - 859	4	3	4
	D820			
4- active recreation (for example, sports)?	D920	3	2	5
5- passive recreation (for example, reading, listening to music)?	D920	3	12	3
6- financial situation?	D870	3	6	2
7- relationships with your spouse?	D7701	1	7	3
8- sex life?	D7702	1	X	0
9- family relationships?	D760	1	9	4
10- other social relationships?	D750	1	X	0
11- self-expression/self-improvement?	PF	4	4	6
12- participation in spiritual or religious activities?	D9300	3	14	2
	D9301			
13- community and civic involvement?	D910	1	8	3
New items				
1- career choice?	D8450	1	5	3
2- family planning?	NC	3	X	0
3- making plans for the future?	B1641	4	1	3
4- confidence in driving a car?	B1266	2	11	2
	D4751			
5- ability to drive a car?	D4751	2	13	2
Number of Thresholds: number of response options differentiated by Rasch Analysis; ND: Not definable; GH: General Health; D: activity and participation chapter of ICF; B: Body function chapter of ICF; PF: personal factor; X: was excluded during Rasch analysis, NC: not covered.				

* Shading indicates a participation code

** Higher ranks represent more impact.

Table 4.3: Recoding of the item responses following Rasch Analysis.

Item #	Item Mean Location	Item: How much does you disease or its treatment interfere with...	Original response codes						
			1	2	3	4	5	6	7
16	-0.901658	Making plans for the future		1 (-2.196)		7 (-0.961)			33 (0.452)
3	-0.704983	Work		3 (-1.466)	6 (-0.994)	20 (-0.231)			26 (-0.129)
4	-0.653277	Active recreation		2 (-1.522)	4 (-1.071)		12 (-0.616)	21 (-0.198)	29 (0.142)
6	-0.510886	Financial situation		9 (-0.732)			17 (-0.29)		
14	-0.482269	Career choice		8 (-0.83)			14 (-0.462)		23 (-0.154)
11	-0.112406	Self expression/improvement		5 (-1.059)	13 (-0.5)	24 (-0.137)	28 (0.112)	32 (0.325)	35 (0.585)
2	0.201971	Diet		16 (-0.333)			38 (0.737)		
17	0.206299	Confidence in driving a car		18 (-0.262)			37 (0.674)		
7	0.212741	Relationship with your spouse		10 (-0.694)		31 (0.21)		41 (1.123)	

9	0.423717	Family relationships		15 (-0.437)	19 (-0.248)	34 (0.574)	42 (1.806)
18	0.425482	Ability to drive a car		25 (-0.136)		39 (0.987)	
13	0.461442	Community and civic Involvement		11 (-0.622)	30 (0.175)		43 (1.831)
5	0.584082	Passive recreation		22 (-0.187)	27 (-0.017)		44 (1.957)
12	0.849747	Participation in spiritual or religious activity		36 (0.63)		40 (1.069)	

Items are ordered by level of illness intrusiveness from least to worst, top to bottom. Darker shading indicates higher level of intrusiveness or impact. Scores range from 0-44, blank spaces are scored as "0". The numbers in parenthesis below the score represent the logit location of each item on an interval-like scale. The item numbers are as in the original IIRS [2] numbers above 13 were items added by our team.

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CHAPTER 5

Integration of Manuscript 1 and Manuscript 2

5.1 Research Objectives

The global aim of this research is to contribute evidence towards the conceptualization of illness intrusiveness in the context of MS and in the context of modern outcome models and measurement theory.

Objective Manuscript 1: The objective is to contribute to the conceptualization of the construct of illness intrusiveness. The specific objectives are to: (i) estimate the extent to which the content of ILLRs is captured within the ICF; and (ii) estimate the extent to the items of the ILLRs align hierarchically to produce a measure with interval-like properties.

Objective Manuscript 2: The objective of this study is to determine the direct and indirect effects of mental and physical multiple sclerosis impairments on illness intrusiveness.

5.2 Integration of Manuscript 1 and 2

There are multiple ways of contributing evidence towards the conceptualization of a construct. Manuscript 1 and 2 present some of them and form a logical continuum. The first step to understanding a construct is to have it compared to a universal framework. In health research that framework comes from the World Health Organization and is called

the International Classification of Functioning Disability and Health. That is what the first part of Manuscript 1 described.

Another way to contribute to conceptualization is to verify how well the individual items that build the construct hold together through modern statistical methods. The second part of Manuscript 1 presents one of those modern methods. Also, by this method, namely Rasch analysis, the items that did not fit within the construct were eliminated and the new items added to fill the gaps were shown to have a place within this construct. The measure of illness intrusiveness that emerged now has interval properties suited for mathematical manipulations.

The first two steps were important in achieving the ultimate goal of this thesis which is to develop a model that could explain illness intrusiveness based on MS impairments. With an overview of where the construct sits within the large framework of the ICF and a measure strong enough to support modern statistical analysis, a hypothesized model could be designed and tested. The development and testing of the model is presented in Manuscript 2.

CHAPTER 6

Manuscript 2

Path to Illness Intrusiveness: What Symptoms Impact the Life of People Living with Multiple Sclerosis?

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6.1 Introduction

Multiple Sclerosis (MS) is a disease that is diagnosed at a relatively young age and can bring a wide array of symptoms, notably fatigue, pain, muscle weakness, spasticity, balance impairment, and slowness of thinking and difficulty with concentration. The impact ranges from a single impairment to major participation restrictions. Some of these impairments and restrictions continue for a lifetime while others will wax and wane as people with MS experience relapses and remissions. As a result of the large variation in disease manifestation, MS will have an impact on the life of people living with it; ultimately, on their quality of life.

Illness intrusiveness is a concept that emerged in 1983 by Devins. It is defined as illness and treatment-related lifestyle disruptions that interfere with continued involvements in valued activities and interests [1]. People living with chronic illnesses are at risk of major disruptions in their lives which would then affect their quality of life. Beyond psychometric improvements to the measure, very little conceptual work to understand the construct of illness intrusiveness has been done [2, 3].

The sparse literature available on illness intrusiveness in MS has shown that there is a strong association between illness intrusiveness and health-related quality of life, in both the mental and physical domains [4-6]. The single study using illness intrusiveness as an outcome concluded that poor sleep quality increased the perceived lifestyle disruptions [7].

We have previously shown (Chapter 4 of the present thesis) that illness intrusiveness is very close to what would be conceptualized using modern models of health as participation. Participation is defined by the World Health Organization (WHO) as involvement in a life situation [8] and in many other health conditions it has been shown to be strongly related to quality of life [9-11].

Knowing what drives illness intrusiveness would be very valuable as it would enable researchers and professionals to design interventions to target it and could possibly allow clinicians to prioritize clinical interventions. The objective of this study is to determine the direct and indirect effects of physical, emotional, and cognitive impairments on illness intrusiveness in people with MS.

6.2 Methods

Participants

The participants in this project were originally recruited in 2008 to study the gender differences in people living with multiple sclerosis. The recruitment procedure and demographic information has been reported on by Kuspinar et al [12]. A total of 189 patients were recruited from three multiple sclerosis clinics in the greater Montreal area. The main exclusion criterion was a health condition diagnosed prior to the MS that continued to exert an effect on function.

Measures

Illness Intrusiveness

The Illness intrusiveness Rating Scale was created in 1983 by Devins and colleagues [1]. It consists of 13 questions asking participants to rate how much their disease interferes with the various spheres of life on a scale from 1 to 7. The 13 item scores are added to give a total score or subscale scores. Using a classical psychometric approach, the IIRS showed an internal consistency of .87, test- retest reliability of .85 for 9 month and .80 for 18 months[13].The main concern, in the light of modern measurement theories, with this scale is that although the total score is often analyzed as a continuous variable, it is, in reality, ordinal. To add to this difficulty, the total score assumes that each item contributes equally to the underlying construct, and this is unlikely to be true, and if so would indicate that few items would be needed. Rasch analysis is a statistical method of calibrating items to a continuum and aligning them hierarchically in such a way that the score can now be interpreted both mathematically and conceptually as a quantity. Our team performed a Rasch analysis to transform the IIRS ordinal scale into one with interval properties. Appendix A presents the original scale and the new one used following Rasch transformation.

Other measures

Multiple tools and scales were used to measure the impairments that could predict illness intrusiveness. The measures were chosen based on the theoretical framework of the

International Classification of Functioning, Disability and Health from World Health Organization [8].

The depression subscale of the Hospital Depression and Anxiety Scale (HADS) [14] was used for depressive symptoms. Fatigue was a latent variable obtained from fitting items from different fatigue questionnaires to a unidimensional, hierarchical model using Rasch analysis [15]. Subscales of the RAND-36 were used for pain, general health perception, and physical and emotional functioning [16, 17]. Processing speed was assessed through the Paced Auditory Serial Addition Task (PASAT)[18]. For spasticity, the modified Ashworth scale [19] was used and the scores of the main muscle groups were summed up to create a total spasticity score. To approximate general muscle strength, grip strength was measured using a dynamometer [20]. Gait speed [21] and 6 minute walk test [22] were used to represent walking capacity. Balance capacity was measured using the Equi-Scale [23] and self-efficacy using the Activity-specific Balance Confidence Scale [24]. Physical capacity was represented by measures of core strength and muscle power namely number of curl ups and push ups and vertical jump test [25].

6.3 Analysis

The biopsychosocial model underlying the ICF framework indicates a complex relationship between MS impairments, activity limitations and participation restrictions. Because this model and empirical evidence [26-28] indicates both direct and indirect effects, a multiple linear regression model could not be used as it only models the direct effects.

Path analysis is a statistical method that combines regression with correlation and factor analysis. It also accounts for both direct and indirect effects. Finally, it detects mediation of other variables on the outcome. The analysis was conducted using SAS 9.2.

As the number of available variables was large with respect to the available sample size, a set of steps were used to reduce their number.

First the correlation matrix (see Table 6.2) was examined to identify variables with weak connection to the outcome or to any other potential path variable. Variables that did not correlate strongly to other variables or moderately to the main outcome were eliminated. Cohen's scale for strength of correlation was used to decide the cut off points (coefficient $<.3$ = weak, $\geq.3$ and$<.5$ = moderate, $\geq.5$ = strong) [29]. Of the correlated variables with strong correlation to the outcome (depressive symptoms, fatigue, physical function, general health perception, pain, physical and emotional role functioning, balance capacity and self-efficacy, sleep, walking capacity and time worked per week), two (physical and emotional role functioning of the RAND—36) were eliminated as they severely violated the assumption of normality needed for path analysis.

To identify the endogenous variables (variables that both have and are predictors) a series of multiple linear regression models were constructed to explain illness intrusiveness and other potential path variables. The variables that fit the definition of an endogenous variable were fatigue, general health perception, depressive symptoms and physical function. The multiple linear regression model identified an interaction between fatigue

and depression indicating that the effect of fatigue on illness intrusiveness depended on depression and vice versa. In path analysis, it is not possible to fit a bidirectional relationship between two endogenous variables and hence further data exploration was carried out to identify an ordering. The correlation between fatigue and depression is very high as they happen in the same people. It was challenging to identify which one came first. Leaving one out was not an option as the literature points to a strong independent relation between depression and illness intrusiveness and between fatigue and illness intrusiveness [5, 7]. Fatigue arises from two sources, primarily from the actual nerve lesions and secondarily from increased energy expenditure due to other symptoms and decreased sleep quality [30]. Correlation between sleep and fatigue in the sample was 0.35, lower than expected if the cause of fatigue was a lack of a good sleep quality. We concluded that, for this sample, primary fatigue was the main source. Although the debate is still ongoing in the literature [27], fatigue was tested as predicting depression instead of the other way around as fatigue seemed to be more prevalent and appeared earlier than depression.

The final step in designing the model was to determine which variables would be part of the model as exogenous variables (variables that are only predictors). Another series of multiple linear regressions were performed to predict the four endogenous variables discussed previously (fatigue, general health perception, depressive symptoms and physical function). The impairment variables kept following this step were pain, balance capacity, balance self-efficacy, walking capacity and muscle power. The other impairment variables were dropped as they did not appear to fit in the model.

Based on these steps, a model was drawn to be tested. The theoretical framework of the ICF [8] was kept as the underlying model; although, it could not hold completely as illness intrusiveness, while mapping mostly to participation, has items that are impairments and activity limitations. The model presented by Devins[13] was also taken into account while designing the model. Once the model was designed, path analysis was undertaken.

6.4 Results

Table 6.1 presents the demographic information of the participants and shows this sample is representative of the population living with MS in Canada. 74% of the sample is female consistent with the national ratio of women to men of 3:1. Additionally, 78% were of the relapsing remitting type which the MS Society of Canada affirms constitutes 85% of all MS cases [30]. Fifteen (8%) people from the sample (n=189) reported no interference at all on the IIRS. The rest of the sample had various levels of illness intrusiveness.

Figure 6.1 presents the designed and analyzed model. The model was significant (Non-normed fit index (NNFI):0.9913; Normed fit index (NFI):0.9846) with adequate fit of the data to the model (goodness of fit index: 0 .9781; $\chi^{2:}$ 21.41; p=0.2084). The model explained 55% of the variance of illness intrusiveness. Only emotional and physical aspects were represented in the model as no cognitive impairment stayed following variable reduction.

The interesting particularity of this model is the complete mediation effect of fatigue. All physical symptoms except muscle power affect fatigue but have no direct effect on illness intrusiveness. The only four items that have a direct effect on illness intrusiveness are general health perception, fatigue, depression, and perceived physical function. The proportion of the explained variance for each of the endogenous variables was 55% for illness intrusiveness, 43% for general health perception, 50% for depressive symptoms, 78% for physical function, and 47% for fatigue. The effects of sleep and time worked per week were insignificant and neither remained in the model.

Table 6.4 presents non standardized β of the direct, indirect and total effects of various mental and physical impairments on illness intrusiveness. Only fatigue as an impairment variable showed both direct and indirect effects on illness intrusiveness.

6.5 Discussion

This project brings new evidence towards the conceptualization of illness intrusiveness as a construct. Analyses showed that illness intrusiveness can be explained mainly by physical impairments with an important contribution from emotional and mental impairments, namely depression, balance confidence and general health perception. The implications of this proposed model are quite important. The fact that illness intrusiveness predicts health-related quality of life (HRQL) [4-6] means that with a larger sample it would be possible to link impairments to illness intrusiveness and finally to HRQL to provide a better prediction of what symptoms predict HRQL.

From this model, interventions that more specifically target fatigue through physical impairment can be designed that may also impact on other aspects of life such as illness intrusiveness. Exogenous variable in the model (pain, balance confidence, balance capacity, walking capacity and muscle power) could to some extent explain energy expenditure. Worries from pain and fear of falling (balance confidence) could make someone experiencing them a lot more tired at the end of the day. From a rehabilitation perspective, training walking capacity, balance and muscle power, or teaching of good compensatory method to alleviate pain during ambulation could reduce the work of walking. Those are all impairments that can be treated by a multidisciplinary team and could potentially have a positive effect on fatigue and illness intrusiveness.

There appears to be a physical function factor in the model given that 78% of its variance is explained by four of the listed impairments. As the purpose of this study was to explain the variation in illness intrusiveness according to symptoms, it was decided to keep the different physical function components separate to see their different effects therefore no further analysis was done.

The current model is consistent with the previous model of illness intrusiveness by Devins [13] that predicted that illness intrusiveness would be explained by disease and treatment factors. Adding treatment factors to the model could improve the fit and the variance explained however they were not measured in the original study therefore were unavailable. To do so would require a larger sample size and multiple additional

questions. Comparing this model to the ICF framework confirms that illness intrusiveness

sits more on the participation side than the impairment one. It appears that this model also

has some consistency with the Wilson-Cleary model[31] as the physical symptoms all sit on

the left hand side, followed by the consequences of these symptoms on perceptions of

health, physical function and mood, which then all together affect illness intrusiveness.

As in any study there are limitations, this one is no exception. This study was not

originally designed to answer this question. Therefore, we might have missed important

variables such as proprioception, a more complete overview of walking capacity, or a

person's perception of life before being diagnosed with MS. Time since diagnosis and

drug treatment were not added to the model as they are both time dependant variables and

this model is cross-sectional. The use of the Hospital Anxiety and Depression (HAD)

scale might not be the most appropriate to measure depressive symptoms in a sample

from a population with low levels of disability and it appears to have a floor effect in this

sample. It is important to note the HAD scale allows to detect for depressive symptoms

and does not diagnose clinical depression. Therefore the model took into account only the

effect of depressive symptoms and not of clinical depression as a separate diagnosis.

Depression as a diagnosis might have a different relation to illness intrusiveness as the

one presented in figure 6.1. Cognition was probably not adequately captured by the

PASAT which tests only processing speed; a more comprehensive assessment of

cognition was outside the feasibility of this study

As path analysis does not allow for bidirectional relationships between endogenous variables and MS is known for complex interactions between symptoms, some of the interactions might have been missed by the unidirectional arrows.

This analysis used only data from one time point. While this could be considered a limitation, the advantage is that important contributors were identified which would inform a future longitudinal study with a parsimonious data collection.

One of the main limitations of this model is its power. The number of parameters estimated is large and the number of subjects is fairly small. There are 27 parameters (10 variables and 17 paths) and 180 subjects. Kline [32] suggests there should be 10 to 20 subjects per parameter which could indicate that this model is under powered. Although it remains to be tested, due to the richness of the data collected, we are confident that the strength of the relationships in this model would be maintained with a larger sample size. It is possible that other models using this data could have an equal or better fit, but according to the literature review [28] and the multiple tests that were done, this one seems to be the most representative.

6.6 Conclusion

In conclusion, this model of illness intrusiveness brings a new look into what impacts on people's life when living with a chronic disease such as MS and what symptoms causes more interferences with their daily activities. Although it is a preliminary model and it is

slightly underpowered, it shows that fatigue plays a mediating role in how physical

symptoms affect illness intrusiveness and suggests paths to reduce the effect of fatigue.

6.7 Figures for Manuscript 2

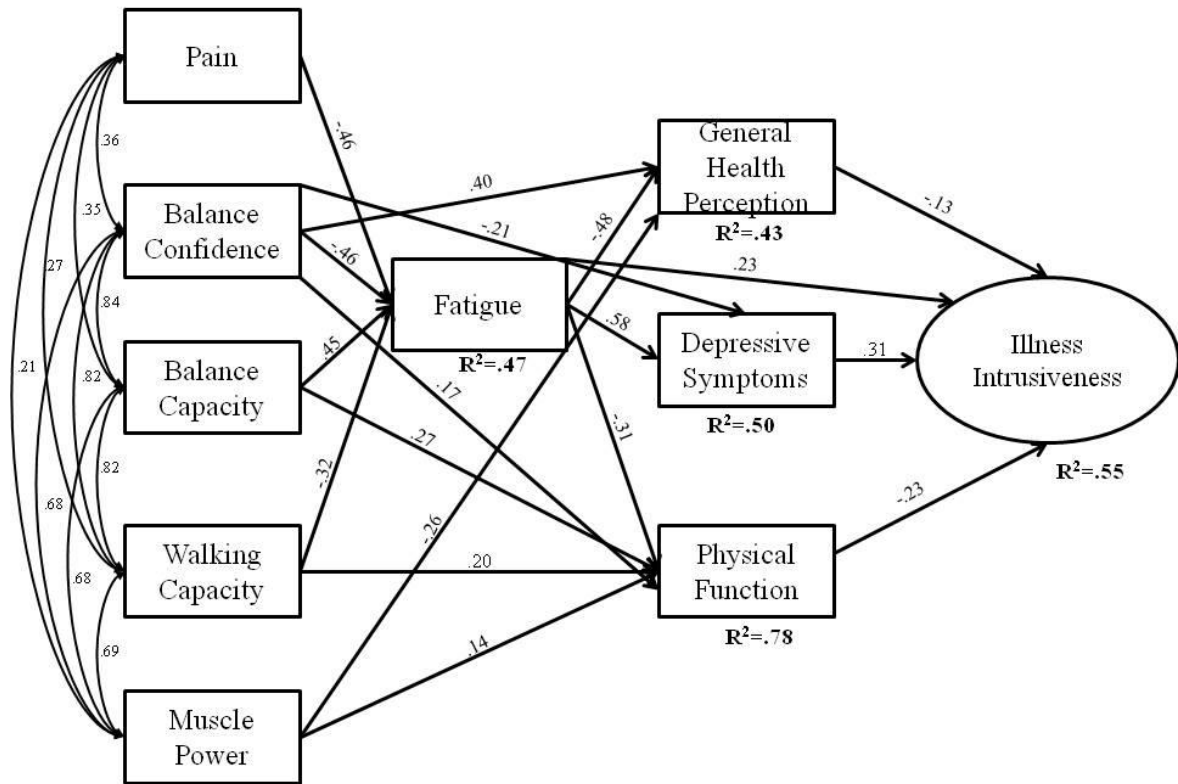Figure 6.1: final path model for illness intrusiveness. Arrows represent a direct relationship. R^2 represent the proportion of the variance explained by the model for each endogenous variable. Numbers on bidirectional arrows between exogenous variables are correlation coefficients. Numbers above unidirectional arrows are standardized path coefficient and represent the strength of the relationship.

6.8 Tables for Manuscript 2

Table 6.1: Demographic characteristics of study participants

Age mean(SD)	43.0(10.2)
Females, n (%)	140(74.7)
Type of MS: RR, n (%)	98(78.4)
PP	8(6.4)
SP	7(5.6)
PR	3 (2.4)
CIS	9 (7.2)
EDSS median(range)	2 (0-8.5)
Working Full time, n (%)	89(47.3)
Part-time	60(31.9)
Not	39(20.7)

Table 6.2: Correlation matrix used to determine possible model parameters

	Depression	Fatigue	Physical function	General health perception	Pain	Balance capacity	Balance self-efficacy	Sleep	Walking capacity
Fatigue	0.68								
Physical function	-0.46	-0.61							
General Health Perception	-0.52	-0.60	0.47						
Pain	-0.33	-0.55	0.40	0.42					
Balance capacity	-0.36	-0.36	0.78	0.36	0.34				
Balance Self-efficacy	-0.49	-0.51	0.80	0.49	0.35	0.84			
Sleep	0.37	0.35	-0.35	-0.25	-0.32	-0.27	-0.41		
Walking capacity	-0.37	-0.45	0.78	0.37	0.25	0.82	0.81	-0.25	
Time worked per week	-0.27	-0.34	0.48	0.24	0.26	0.48	0.46	-0.25	0.44

Outcome measures: depression: HADS depression subscale[14], fatigue: fatigue scale[15], physical function general health perception and pain: RAND-36 subscales[16, 17]., balance capacity: equi-scale[23], balance self-efficacy: ABC scale[24], sleep: sleep questionnaire developed by Rasch analysis, walking capacity: percent predicted on 6 min walk test[22], time worked per week: reported hours worked in a week.

Table 6.3: Direct, indirect and total effects of impairments on illness intrusiveness (non-standardized β)

	Direct	Indirect	Total
Pain	0	-.012	-.012
Balance Confidence	0	-.023	-.023
Balance Capacity	0	.049	.049
Walking Capacity	0	-.012	-.012
Muscle power	0	.0002	.0002
Fatigue	.017	.022	.039
Depression	.100	0	.100
Physical Function	-.0095	0	-.0095
General Health Perception	-.008	0	-.008

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CHAPTER 7

Discussion and conclusion

7.1 Discussion

In view of manuscripts 1 and 2, has the definition and how we see illness intrusiveness changed? It is difficult to determine if the Illness intrusiveness Rating scale (IIRS) is a measure or an assessment. By definition, an assessment has mainly clinical value as it is used for treatment planning and the interest of the scale lies within each individual item. For a measurement scale, the total score is normally of more interest than each of the individual items. A measure has purpose in both clinical practice and research projects.

Since its development, the IIRS has been presented as a tool for researchers to explore the emotional impact of disease [21], therefore its intent was to be a measure rather and an assessment. The fact that Devins presented a conceptual framework for its use (fig 2.1) also supports it as a measure. However, the scale does not appear to form a continuum, a feature required for the total score to be interpretable without considering the responses to the individual items.

As a measure, what does the new IIRS capture? Through the ICF coding exercise, it was shown that the items map to the participation domain. Linking illness intrusiveness to participation adds some evidence to support Devins' theoretical framework [22] (fig 2.1) in which illness intrusiveness influences well being. In addition there is evidence that

participation is strongly associated with quality of life (QoL) in various diseases [33-35]. The effect of treatments factors on illness intrusiveness could not be captured in the model as very little information was available on treatment course in the database used to run our analysis and sample size would not have allowed the addition of new variables. Supporting, its conceptualization as participation, is that the path analysis showed symptoms (impairments) and activity limitations affected illness intrusiveness directly.

The psychometric properties of the new scale have yet to be proven, but some evidence hints at them. The underlying construct has not changed however the instrument's representation of the construct has. Despite the fact that the 5 new items have the same root and response options, the entire scale needs to be tested in a new sample for fit to the Rasch measurement model. Additionally, validity and reliability will require retesting before the new IIRS can be considered a measure. Some evidence for content validity is provided by the mapping exercise although some of the items mapped outside participations (onto the activity and body function domains [31]).

As discussed in manuscript 1, adopting a formative model [36] could help the conceptualization and development of a participation measure. As the items of the IIRS appear to be formative to the construct of illness intrusiveness, we could ask if there was "formative" validity, in that as conceptualized originally? Do the disease related factors contribute formatively to the construct? This we did using path analysis and using the ICF framework as the conceptual mode for linking impairments to activity to participation.

Although this work supports the new IIRS as a potential measure of participation (content, and "formative" validity), there is still a need for rigorous conceptualization and analysis to determine that the items reflect the participation construct and that the total score is a meaningful representation of the "quantity" of participation. Participation is a very important aspect of any chronic disease and efforts to measure participation are emerging [37, 38].

An interesting result of this project is the role that fatigue appears to have on how MS affects one's participation. Fatigue completely moderated the effect of the physical symptoms on illness intrusiveness and on the other self reported psychological variables. Fatigue has always been considered an important symptom in MS but this project demonstrated that it plays a central role in how the disease impacts on the people living with MS.

There is no cure for MS related fatigue although some drug trials are currently underway to try and relieve this problem. However, some non invasive non-pharmaceutical methods have been proven effective [7, 39]. All forms of physical exercise have been shown to be beneficial for people with MS impaired by fatigue. The results of this study should motivate researchers to look more into fatigue as its overall effect on illness intrusiveness and health related quality of life might be larger than previously thought.

7.2 Conclusion

This project has brought new evidence towards the conceptualization of illness

intrusiveness. Placing illness intrusiveness in the context of modern measurement theories

provides guidance for further explorations. It seems to fit well as a construct in the

participation domain of the ICF. However it is not clear whether it is a formative or a

reflective construct. Clearly illness intrusiveness is a construct of importance and it

warrants further conceptualization.

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APPENDICES

The appendices contain the original illness intrusiveness rating scale, in the format administered to subjects. Also included are graphs related to the fit of the persons and items following the Rasch Analysis.

Illness Intrusiveness Ratings Scale

Name / ID: _____   Date: _____

Hospital: _____

The following items ask about how much your illness and/or its treatment **interfere** with different aspects of your life. Please circle the one number that best describes your **current life situation**. If an item is not applicable, please circle the number one (1) to indicate that this aspect of your life is not affected very much. Please do not leave any item unanswered. Thank you.

How much does your illness and/or its treatment **interfere** with your:

1. Health

Not Very Much   1   2   3   4   5   6   7   Very Much

2. Diet (for example, the things that you eat and drink)

Not Very Much   1   2   3   4   5   6   7   Very Much

3. Work (including school work)

Not Very Much   1   2   3   4   5   6   7   Very Much

4. Active recreation (for example, sports)

Not Very Much   1   2   3   4   5   6   7   Very Much

5. Passive recreation (for example, reading, listening to music)

Not Very Much   1   2   3   4   5   6   7   Very Much

6. Financial situation

Not Very Much   1   2   3   4   5   6   7   Very Much

7. Relationships with your spouse

Not Very Much   1   2   3   4   5   6   7   Very Much

8. Sex life

Not Very Much   1   2   3   4   5   6   7   Very Much

9. Family relationships

Not Very Much   1   2   3   4   5   6   7   Very Much

10. Other social relationships

Not Very Much   1   2   3   4   5   6   7   Very Much

11. Self-expression/self-improvement

Not Very Much   1   2   3   4   5   6   7   Very Much

12. Participation in spiritual or religious activities *

Not Very Much   1   2   3   4   5   6   7   Very Much

13. Community and civic involvement

Not Very Much   1   2   3   4   5   6   7   Very Much

* Original item "Religious expression" was modified to fit a more diverse 2010 population

Additional 5 items added by our team

14. Career choice

Not Very Much   1   2   3   4   5   6   7   Very Much

15. Family planning

Not Very Much   1   2   3   4   5   6   7   Very Much

16. Making plans for the future

Not Very Much   1   2   3   4   5   6   7   Very Much

17. Confidence in driving a car

Not Very Much   1   2   3   4   5   6   7   Very Much

18. Ability to drive a car

Not Very Much   1   2   3   4   5   6   7   Very Much

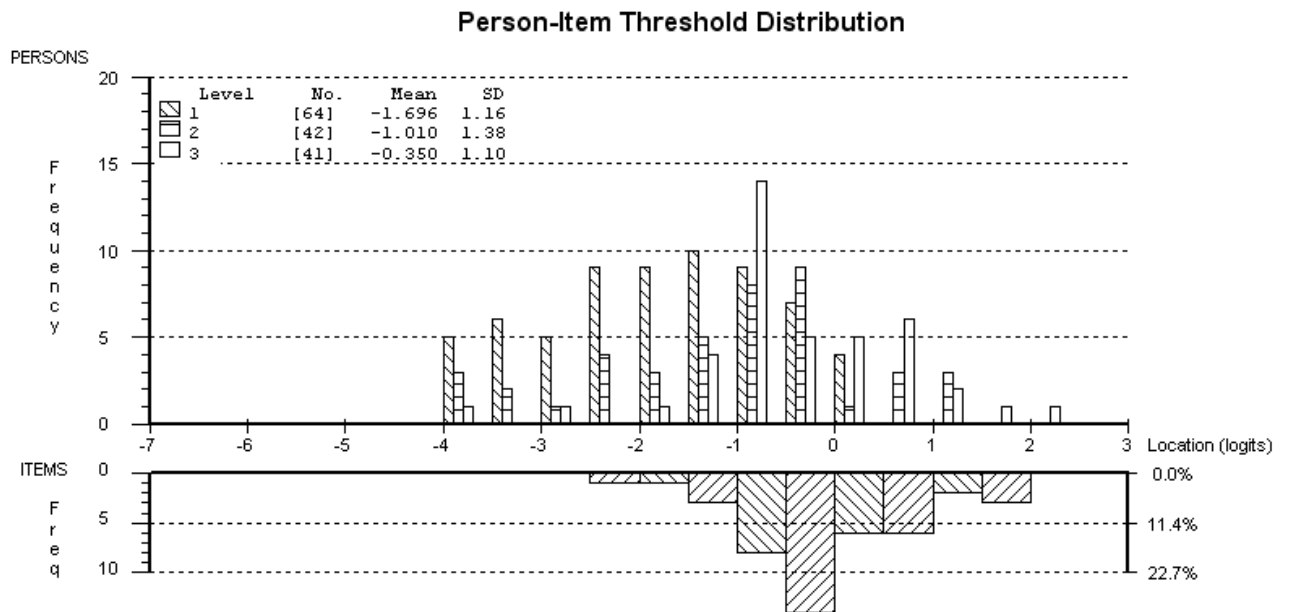**Appendix B: Supplemental Information on Rasch Analysis**

Figure 1a: The Persons and Items Distribution in the IIRS

 The horizontal axes, scaled in logits, denote illness intrusiveness from least at the left to most at the right. The vertical axis denotes the proportion of subjects or items. The bars represent the distribution of subjects (top half of the graph) by EDSS group (1=EDSS 1; 2=EDSS2; 3=EDSS 3) and items (bottom half of the graph) at each location.

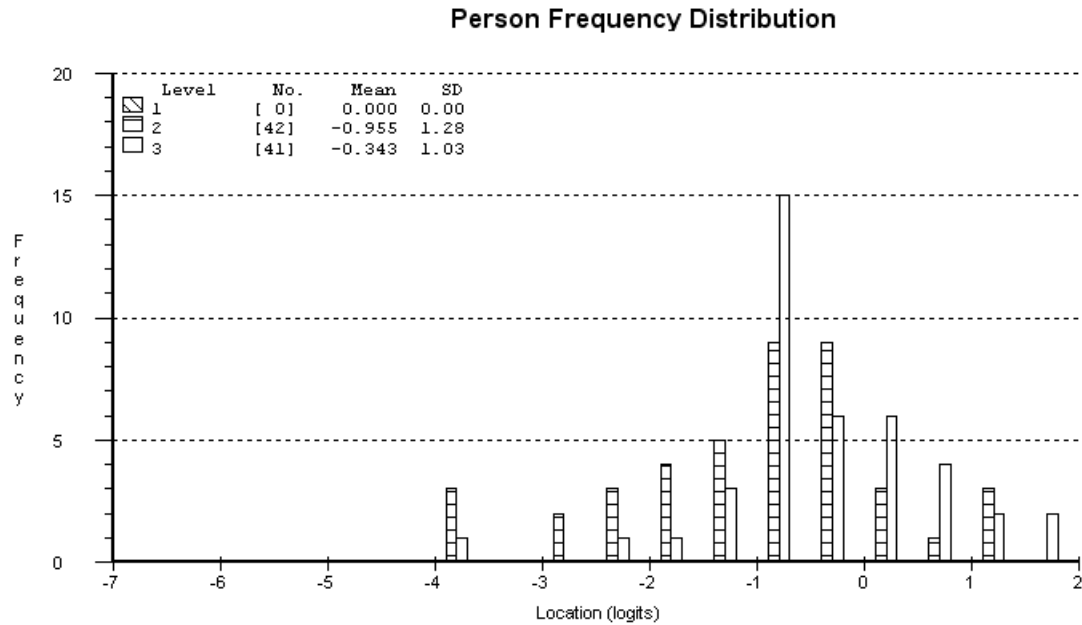## Person Frequency Distribution

Figure 1b: The Persons and Items Distribution in the IIRS without EDSS 1 group

The horizontal axes, scaled in logits, denote illness intrusiveness from least at the left to most at the right. The vertical axis denotes the proportion of subjects or items. The bars represent the distribution of subjects (top half of the graph) by EDSS group (2=EDSS 2; 3=EDSS 3) and items (bottom half of the graph) at each location.

Comparing figure 1a and 1b, people with EDSS= 1 in the top figure represented by the slanted lines have few symptoms other than light sensory deficits and are located to the left of the graph. These people do not report as much intrusiveness from the MS as those people living with more symptoms and categorized with an EDSS of 2 or 3 located towards the right of the graph. As the group with an EDSS of 1 is the largest proportion of this sample the person location is slightly miss-targeted. To improve the targeting of the new IIRs as a measure we would need to add items that reflective of minor MS symptoms to target this group more effectively. Note that when the EDSS group1 are removed from the graph the targeting improves with the EDSS 2 group location changing from -1.69 to -0.95 and the EDSS 3 group location changing from 0.35 to 0.34. Also note that the SE decreased in these two groups