University of Alberta

Factors Associated with the Health-related Quality of life of Persons with Relapsing-remitting Multiple Sclerosis

by

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requirements for the degree of Master of Science

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ABSTRACT

The purpose of this research was to identify factors associated with the health-related quality of life (HRQoL) of adults with relapsing-remitting multiple sclerosis (MS) by conducting a best-evidence synthesis of studies published between 1990 and 2003, and by performing original research with MS participants (N=256). The best published research consistently identified five factors associated with poorer HRQoL: unemployment, fatigue, depression, disability, and relapses. In addition, age was identified as most likely having an association with HRQoL. The original research identified female sex, older age, unemployment due to MS, comorbid conditions, fatigue, disability, and relapses to be associated with poorer physical HRQoL. Illness intrusiveness and comorbid conditions were associated with poorer mental HRQoL. Older age was associated with worse mental HRQoL in men but better mental HRQoL in women. These findings may assist clinicians in identifying patients who may be experiencing poor HRQoL, thereby permitting timely and effective intervention.

DEDICATION

I would like to dedicate this thesis to my family. To my parents, Ken and Jacquie Andersen, for always believing in me and supporting me through every step of my life. I thank you for your care and concern in both the little and the big things of my life. You have loved me and stood beside me through all my trials and triumphs. I am truly blessed to have you as parents.

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1. INTRODUCTION

1.1 Background

Health care researchers and health care providers are concerned with improving both the quantity and quality of life of persons who are suffering from illness. Great strides have been made in decreasing mortality, especially from infectious diseases such as influenza and pneumonia. Measuring improvements in quantity of life (mortality) is relatively straightforward, whereas measuring improvements in quality of life can be difficult because of the subjective nature of the concept. Measuring improvements in quality of life is imperative however when caring for persons with chronic illnesses, such as multiple sclerosis (MS), for which the threat to life is mainly qualitative in nature versus quantitative.

1.2 Multiple Sclerosis

MS is a chronic neuroimmunological disease of the central nervous system (namely the brain, spinal cord, and optic nerves) (O'Connor, 2002). The central nervous system contains billions of nerves that send messages throughout the body. The nerves transmit messages through a part of their cells called axons, and are protected by a coating of insulation called the myelin sheath. In this autoimmune disease, random attacks of inflammation damage the myelin sheath and the nerve axons, causing scarring to occur in multiple areas. The scars in turn interfere with transmission of nerve impulses, resulting in various symptoms.

The symptoms of MS are numerous and variable in degree. Symptoms include ambulation problems (impaired balance, gait disturbance, weakness), bladder and or bowel dysfunction, cognitive dysfunction, depression, fatigue, sensory problems (numbness, tingling, pain), sexual dysfunction, spasticity, speech and or swallowing problems, tremor, vertigo (dizziness and nausea), and visual impairment (optic neuritis – temporary loss or disturbance of vision, double vision, nystagmus – jerking of one or both eyes). Persons with MS may experience some or all of these symptoms during the course of their illness, and may do so to various degrees of severity and time lengths.

The majority of persons with MS experience onset of symptoms such as weakness, numbness, or double vision, between the ages of 20 and 40, with the peak age being 30 years (Vollmer, 1999). There are more women with MS than men by a ratio of about 1.4 to 1.0 (Warren et al., 2001). MS is rarely found amongst non-white populations such as Asians and Africans, but is commonly found amongst Caucasians, and especially those with northern European ancestry. It is also found more commonly in temperate areas compared to tropical areas. The prevalence of MS tends to increase with movement away from the equator in both hemispheres. The highest prevalence rates (> 30 / 100,000 population) in the world are found in Canada, northern United States, northern Europe, Australia, and New Zealand (Warren et al., 2001).

MS is an unpredictable and variable illness. The experience one person will have with the illness will be different from the next. In general however, persons diagnosed with the illness tend to fall into one of two broad types of MS: relapsing-remitting or progressive (O'Connor, 2002). Relapsing-remitting MS is characterized by episodes of relapses (attacks, exacerbations), defined as worsening of old symptoms or appearance of new symptoms lasting greater then 24 hours, occurring without fever or acute illness, followed by a time of complete or partial recovery (remission). There is generally no worsening between attacks. Complete recovery is often achieved during the early stages of the illness, but usually only partial recovery is achieved as the years go by and the scarring becomes permanent (Warren et al., 2001). A subtype of relapsing-remitting MS is benign MS, in which remission after relapses is almost complete, so that in 10-15 years after the onset of the disease there is only minimal disability (O'Connor, 2002).

The definition of progressive MS is slow and continuous disability with or without relapses (O'Connor, 2002). There are two types of progressive MS: primary progressive and secondary progressive. In primary progressive MS, disability increases right from the start of the disease, whereas in secondary progressive MS, the disease only becomes progressive after an initial 5-25 years of relapsing-remitting MS. A rare subtype of primary progressive MS is progressive relapsing, whereby relapses are superimposed upon the steady progression of disability. There is also a rare subtype of secondary progressive MS called relapsing progressive, whereby gradual worsening of disability is supplemented by relapses.

At the time of diagnosis, about 85% of the MS population are classified as having relapsing-remitting MS, 10% primary progressive MS, and the remaining 5% benign or progressive relapsing MS (Vollmer, 1999). Secondary progressive MS develops in 50-75% of those who start with the relapsing-remitting form of MS. Females are more apt to have a relapsing-remitting MS classification than males by a ratio of about 3:1, and persons initially diagnosed at age 40 or older are more apt to have a primary progressive MS classification (Warren et al, 2001). Favourable prognostic factors include younger age at onset, female sex, normal MRI (brain scan) at presentation, complete recovery from first relapse, low relapse rate, long interval to second relapse and low disability at two and four years (Vollmer, 1999).

In a research study conducted by Runmarker et al. (1993), the authors found that indeed about 85% of the MS population has relapsing-remitting disease at the time of diagnosis. However, after 10 years more than 50% will develop progressive disease, and by 25 years over 90% will change to progressive disease. Thus, the sequelae of MS, namely worsening of symptoms and decreased functional ability as time goes by, often means persons with MS are less able to carry out valued activities and roles. Reductions in the quality of life of persons with MS are thus not unexpected.

The Canadian Burden of Illness Study Group (1998) found that quality of life actually decreases substantially in the early stages of MS, i.e., when the majority of persons with MS have the relapsing-remitting form of the disease. Since the majority of persons with MS are diagnosed as young adults, many will live with a reduced, and perhaps reducing, quality of life for 25 years or longer. Determining how the illness impacts the quality of life of persons with MS in the early stages of the illness is critical for effective and efficient patient care. Knowledge of the factors associated with quality of life may assist health care providers to provide targeted programs, services, and treatments early enough in the care of their patients to minimize the negative impact MS may have on the quality of life of their patients.

1.3 Health-Related Quality of Life

Studying the quality of life of a group of persons is not easy given the subjective nature of the concept. The importance of measuring quality of life has come to the forefront of health care research and practice given the changing patterns of mortality and morbidity, and the changing patterns of medical interventions. Chronic diseases are much more prevalent than infectious diseases, as are disabilities and injuries compared to deaths due to illness (Hennekens et al., 1987). As a result, health care providers and researchers are putting more of their resources into improving life versus lengthening life. Measuring the length of a life is relatively straightforward, whereas measuring improvement in a life is much more difficult.

The World Health Organization Quality of Life Group (1991) defined quality of life as "... an individual's perception of their position in life in the context of the culture and value systems in which they live in relation to their goals, expectations, standards, and concerns. It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, level of independence, social relationships, and their relationships to salient features of their environment."[1] This definition of quality of life is very broad in scope, encompassing both health and non-health related dimensions. It reinforces the notion that quality of life is subjective, involving a person's values and environment and his or her reference point, and can be variable over time. The issue arises as to how all the concepts listed in the above definition can be measured in the face of a chronic illness / disability. Persons with chronic conditions such as MS are apt to evaluate their quality of life through colored lenses, as their condition is now a part of their daily lives. Thus, measuring the quality of life of a group of persons with a chronic condition requires a modified definition of quality of life, which acknowledges the influence the condition will have on how these persons will assess their quality of life.

Health-related quality of life (HRQoL) is the term most often used to describe the quality of life of a group of persons affected by illness or injury. HRQoL has been

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[1] World Health Organization. Assessment of quality of life in health care: a working party report. Geneva: World Health Organization; 1991. In Bowling A. Measuring disease: a review of disease-specific quality of life measurement scales. Buckingham; Philadelphia: Open University Press; 1995, p.3.

defined as "… the value assigned to duration of life as modified by the impairments, functional states, perceptions, and social opportunities that are influenced by disease, injury, treatment or policy."[2] HRQoL has also been described as the attributes valued by patients including their resultant comfort or sense of well-being; the extent to which they are able to maintain reasonable physical, emotional, and intellectual function; and the degree to which they retain their ability to participate in valued activities within their family, in the workplace, and in the community (Spilker, 1996). The essential dimensions of HRQoL include physical functioning, psychological functioning, social functioning and role activities, individuals' overall life satisfaction and perceptions of their health status (Spilker, 1996). Other dimensions might be important as well, depending on the person or condition, such as cognitive or neuropsychological functioning, personal productivity, intimacy and sexual functioning, sleep disturbance, fatigue, and pain (Spilker, 1996).

Using the above definitions of HRQoL, researchers and clinicians have worked to develop instruments that would allow for the measurement of HRQoL in various patient populations. The are two types of HRQoL instruments: generic and specific. Generic instruments are those that can be used with any patient population. Some generic instruments can even be used with the general population. They allow for broad comparisons between disease groups, and often between a disease group and general population. They are less responsive to changes in specific conditions however. Specific HRQoL instruments tend to be more responsive, and address the particular symptoms / problems encountered by the instrument's target group. Specific instruments can be

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[2] Patrick DL, Erickson P. Health status and health policy: quality of life in health care evaluation and resource allocation. New York: Oxford University Press; 1993, p.22.

disease, population, or function / problem specific in nature. Both generic and specific instruments usually provide domain specific HRQoL values (e.g. physical, emotional, social HRQoL domain scores), and most also provide summary or overall HRQoL values.

Within the literature studying the HRQoL of persons with MS, both types of instruments have been used. Nortvedt et al. (2003) reviewed 83 studies in English that have presented data on quality of life in MS. Of these, 39 used a generic questionnaire known as the SF-36 Health Status Survey. The SF-36 is a 36-item short-form version of a questionnaire that was designed to survey health status in the Medical Outcomes Study. The Medical Outcomes Study was designed to determine whether variations in patient outcomes are explained by differences in systems of care, clinicians, etc., and to develop practical tools for routine monitoring of patient outcomes in medical practice (Tarlov et al., 1989). The SF-36 has been found to demonstrate the impact of MS on important aspects of functioning and well-being (Balcer, 2001). Other generic HRQoL instruments that have been used amongst the MS population to a lesser extent include the Sickness Impact Profile (SIP), Disability Impact Profile (DIP), Nottingham Health Profile, and Farmer Quality of Life Index.

A subtype of generic HRQoL instruments is a utility instrument. Utility HRQoL instruments summarize HRQoL in a single number along a continuum that usually extends from death (0.0) to full health (1.0), although scores less than zero, representing states worse than death, are possible (Guyatt et al., 1993). Utility measures are useful for determining if persons are, overall, better or worse off then others or after a particular treatment, but they do not show the domains in which improvement or deterioration occurs (Guyatt et al., 1993). A few utility instruments have been used with MS patients including the EuroQoL and Health Utilities Index.

There are a number of HRQoL instruments that have been designed specifically for persons with MS. The most commonly used, as reported by Nortvedt et al. (2003), is the MS Quality of Life-54 (MSQoL-54) questionnaire, developed by Vickery et al. (1995). The MSQoL-54 contains the generic SF-36 questionnaire, along with 18 additional questions specific to MS on fatigue, pain, sexual function, bladder and bowel function, cognitive function, emotional status, social relationships and support. Other common MS specific instruments include the MS Quality of Life Inventory (MSQLI) and the Functional Assessment of MS (FAMS). The MSQLI also uses the SF-36 as its base questionnaire. Nine existing symptom specific scales were added regarding fatigue, pain, sexual function, bladder function, bowel function, visual function, cognitive function, emotional status, and social relationships and support, to compose the MSQLI (Fischer et al., 1999). Cella et al. (1996) developed the FAMS questionnaire. The authors used the Functional Assessment of Cancer Therapy-General as the core measure. Items specific to MS regarding fatigue, pain, sexual function, bladder function, cognitive function, emotional status, and social support and relationships were then added to compose the FAMS. Other MS specific HRQoL instruments include the Leeds MS Quality of Life questionnaire, Quality of Life Index – MS, MS Impact Scale, and Quality of Life Questionnaire for MS.

With the existence of questionnaires such as the SF-36, SIP, MSQoL-54, MSQLI and FAMS, measuring the HRQoL of persons with MS is possible. By converting the subjective nature of HRQoL to an objective measurement, researchers and clinicians can quantify changes in HRQoL and can also compare the impact of different diseases on HRQoL. Further, factors that are associated with HRQoL can also be identified objectively, arming researchers and clinicians with tangible clues as to how they might improve the HRQoL of persons with MS.

1.4 Anticipated Significance of Outcomes

As one of the leading causes of neurological disability in young adults (Warren et al., 2001), MS has enormous implications for the current and future HRQoL of young adult Canadians and their families. Canada, in particular, the provinces of British Columbia, Alberta, and Saskatchewan, has a high prevalence of MS, ranging from 30 per 100,000 to over 200 per 100,000 population (Svenson et al., 1994). Variable progression, multitude of symptoms, unknown cause, and no known cure, makes MS a difficult illness to live with on a daily basis, for both those directly and indirectly affected by it. Health care researchers and health care providers need to maintain their resolve to help those suffering from MS by addressing both the physical and psychosocial needs of MS patients. This study will provide insight into the factors associated with the HRQoL of MS patients in the relapsing-remitting stage of the disease, so that health care providers might identify patients who may be at risk for decline in their perceived quality of life early in their care, and thereby intervene appropriately and timely.

2. OBJECTIVES

2.1 Research Goal

The purpose of this research is to explore the health-related quality of life (HRQoL) of Saskatchewan adults with relapsing-remitting multiple sclerosis (MS).

2.2 Research Objectives and Questions

The research goal will be met through addressing the following research objectives, and the specific research questions relating to each of the objectives:

2.2.1 Best-evidence Synthesis

The first research objective is to produce a best-evidence synthesis of the literature on the HRQoL of persons with MS, by performing a comprehensive search and critical review of all relevant literature. This will identify the factors that have been well established as having an association with HRQoL in the MS population, and the factors that merit further investigation. The best-evidence synthesis will also serve to identify important explanatory variables to be considered in the second research objective.

2.2.2 Research Study

The second research objective is to describe the HRQoL of Saskatchewan adults with relapsing-remitting MS, and to determine the factors associated with their HRQoL. This involves the following research question:

> What are the factors associated with the physical health summary scale and the mental health summary scale of the SF-36 Health Status Survey in persons with relapsing-remitting MS? Possible explanatory factors include:

i. Demographic (sex, age, marital status); socioeconomic status (education, income, employment status); and location of residence (rural vs. urban setting);

ii. Health factors (self-reported depressive symptoms as measured by the Beck Depression Inventory (BDI) (Beck, 1967), body mass index (BMI), fatigue, self-reported comorbid medical conditions); and

iii. MS specific factors (self-reported illness intrusiveness as measured by the Illness Intrusiveness Ratings Scale (IIRS) (Devins et al., 1983), number of MS attacks in the past 6 months; and disability level as measured by the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983)).

3. BEST-EVIDENCE SYNTHESIS

3.1 Background

The concept of researching health-related quality of life (HRQoL) in the MS population is relatively new. Studies specifically designed to investigate factors associated with and predictive of the HRQoL of persons with MS have only regularly begun appearing in the scientific literature in the last ten years. This area of research is imperative however given the chronic nature of MS. It is critical to have an understanding of the factors that have the greatest influence on the HRQoL of persons with MS. Armed with this knowledge, health care providers might begin to identify patients at risk for deteriorations in their quality of life early in their care, and thereby intervene appropriately and timely.

3.2 Purpose

The purpose of the literature review was to produce a best-evidence synthesis of the literature on the HRQoL of persons with MS, by performing a comprehensive search and critical review of all relevant literature. Questions addressed in the synthesis include:

1. What factors are associated with the HRQoL of persons with MS?
2. Which factors have been well established as having an association with HRQoL in the MS population, and which factors merit further investigation?
3. What are the implications of the findings from the synthesis for the following research study examining factors associated with the HRQoL of persons with relapsing-remitting MS?

3.3 Methods

3.3.1 Literature Search

The scientific literature included in the Medline database between January 1, 1990 and October 15, 2003 was systematically searched. This was done by designing an extensive search strategy with the assistance of a library scientist to identify relevant key words and thesaurus terms (medical sub-heading terms) for searching the Medline database. The Medline search strategy included the use of the following thesaurus terms (that is, medical sub-heading terms or MeSH terms): multiple sclerosis; multiple sclerosis, relapsing-remitting; quality of life; and health-related quality of life (as a keyword).

All citations identified in the electronic search were screened for relevance using the following inclusion and exclusion criteria.

Inclusion criteria:

1. Studies published since January 1, 1990. This year was chosen because few studies (N=5) on this topic exist prior to this date. Those that do exist usually looked at HRQoL as a secondary outcome, or were merely descriptive in nature.
2. English language studies.
3. Studies published in a journal. The goal of this synthesis was to identify factors that had been found associated with or predictive of HRQoL through research means.
4. Studies examining the factors associated with or predictive of HRQoL in persons with MS.
5. Studies that include at least 10 participants with MS.

6. Studies were limited to those involving human participants.

Exclusion criteria:

1. Studies in which HRQoL was an outcome for a specific therapy or treatment being studied. For example, studies examining the effect of interferons on the HRQoL of persons with MS taking these medications (positive/neutral/negative effect on HRQoL).
2. Studies in which HRQoL was not the main outcome. For example, studies examining the effect of counseling on bladder management, which may in turn have an indirect effect on HRQoL.
3. Studies in which the HRQoL of persons with MS was only described. For example, studies reporting only the mean values of how the participants scored on a particular HRQoL instrument, or papers that stressed the importance of looking at HRQoL in this population.
4. Studies solely describing the creation of a new HRQoL instrument. For example, studies describing the reliability and validity of a new questionnaire for persons with MS.
5. Studies comparing HRQoL instruments. For example, studies examining the value of one instrument over another in an MS population.

Each citation and abstract (if available) found in the electronic database search was reviewed in order to select relevant literature to include in the review. Each citation was deemed probably relevant, irrelevant, or unknown. A citation was deemed unknown if the abstract was unavailable, where insufficient information was available in the abstract, or where the abstract was not sufficiently clear with respect to the inclusion /

exclusion criteria. A citation was deemed irrelevant if it was clear from the abstract that the study did not meet the inclusion criteria.

For every citation deemed probably relevant or unknown, the entire paper was obtained either through the University of Alberta's library's e-journal on-line access, or from the library. Upon retrieval of the articles classified as unknown relevance, the papers were screened and reclassified as either relevant or irrelevant.

In addition to the electronic search of the Medline database, the reference lists of all the relevant studies were reviewed in order to identify any possible additional relevant studies that were not included in the electronic search. These papers were then obtained and screened as per the inclusion and exclusion criteria and deemed relevant or irrelevant.

3.3.2 Critical Review of the Literature

A critical review of all the relevant articles was then conducted using an available Microsoft Access program designed for assessing the validity, relevance, and clinical applicability of various studies. The program contains critical review forms that allow for abstraction of information about the study, and identification of important methodological flaws and biases, if present. The forms provide opportunity to evaluate study design, study population, issues related to the conduction of the study, participation rates, measurement issues and analysis. Opportunity for recording the primary findings and conclusions of the study is also given. The appraisal criteria used in the critical review forms were derived from fundamental epidemiology principles, measurement and design approaches.

3.3.3 Evidence Tables

Evidence tables were developed for summarizing the findings from the critical review and for ascertaining if studies were sufficiently similar (i.e. similar designs and outcomes) to justify the development of aggregate effect sizes (Table 3.1). The tables outline the findings of those studies that identify factors associated with the HRQoL of persons with MS. Since the overwhelming majority of the studies were cross-sectional in nature, the development of aggregate effect sizes was neither feasible nor appropriate.

3.4 Literature Search Results

A total of 109 citations were identified in the search of the electronic database Medline. Review of the reference lists of all the relevant articles resulted in the inclusion of seven additional relevant studies (Koch et al., 2001; O'Connor et al., 2001; Provinciali et al., 1999; Schwartz et al., 1999; Singer et al., 1999; Stuifbergen et al., 1997; Stuifbergen et al., 2000). The results of the search and the application of inclusion / exclusion criteria for relevance are outlined in Table 3.2. A total of 51 studies (44 from electronic search, 7 from references lists) were found to be relevant and thus were critically reviewed. The findings from these 51 studies (Appendix A) comprise the best-evidence synthesis.

Table 3.2 Number of Citations in Electronic Database Search and Results of Screening

Inclusion / Exclusion Criteria	Number of Citations
1. Included: Relevant studies	44
2. Excluded: Studies in which HRQoL was an outcome for a specific therapy or treatment being studied	24
3. Excluded: Studies in which HRQoL was not the main outcome	6
4. Excluded: Studies in which the HRQoL of persons with MS was only described	17
5. Excluded: Studies solely describing the creation of a new HRQoL instrument	10
6. Excluded: Studies comparing HRQoL instruments	8

3.5 Factors Associated with the Health-related Quality of Life of Persons with MS

3.5.1 Demographic Factors

Of the 51 studies reviewed, only three studies reported any kind of difference between males and females. Pfennings et al. (1999) found men had better scores than women on the SF-36 HRQoL emotional role limitation and mental health subscales. Hakim et al. (2000) found depressed mood to be four times more frequent in men. In a study comparing the quality of life scores of participants with MS, rheumatoid arthritis and inflammatory bowel disease, women had worse quality of life scores than men in each disease group (Rudick et al., 1992).

In all the studies that considered sex as a possible factor associated with HRQoL, sex was not found to have a statistically significant association with HRQoL (Benito-León et al., 2002; Brunet et al., 1996; Chang et al., 2002; Fruehwald et al., 2001; Janardhan et al., 2002; Janardhan et al., 2000; Jønsson et al., 1996; Koch et al., 2001; Miller et al., 2003; Murphy et al., 1998; Nicholl et al., 2001; Nortvedt et al., 1999b; Parkin et al., 2000; Rice et al., 1999; Roberts et al., 1998; Shawaryn et al., 2002; Singer et al., 1999; Solari et al., 1999, Solari et al., 2001; Wang et al., 2000). The majority of the current literature thus suggests that sex does not have a statistically significant relationship with the HRQoL of persons with MS. The three studies that did report a difference between males and females provide limited support to the idea that sex is associated with HRQoL, but do raise a slight possibility.

The current literature regarding the association between age and HRQoL is conflicting. Several studies found no association between age and HRQoL (Amato et al., 2001; Brunet et al., 1996; Cutajar et al., 2000; Fruehwald et al., 2001; Gulick, 1997; Hakim et al., 2000; Janardhan et al., 2000; Janardhan et al., 2002; Jønsson et al., 1996; Miller et al., 2003; Murphy et al., 1998; Nicholl et al., 2001; Nortvedt et al., 1999b; Parkin et al., 2000; Rice et al., 1999; Rudick et al., 1992; Solari et al., 2001; Wang et al., 2000). However, nine studies did find a significant association between age and HRQoL.

Chang et al. (2002) concluded that age and disability contributed most consistently to the various quality of life domains measured by the Functional Assessment of Multiple Sclerosis (FAMS) questionnaire. The greatest contribution of age was in explaining the variance in the FAMS mobility score, with older persons faring worse. Merkelbach et al. (2002), Shawaryn et al. (2002), and Solari et al. (1999) found the physical health summary score of the SF-36 to worsen with increasing age.

Ford et al. (2001) found age to be associated with HRQoL as measured by the LEEDS MS Quality of Life Scale, but found younger persons to fair worse. The LEEDS questionnaire measures HRQoL as a single construct, and does not separate the physical from the mental components of HRQoL. Koch et al. (2001) also found younger persons had worse HRQoL scores using the Quality of Life Scale, which focuses on the psychosocial components of HRQoL (e.g., social and family life, future expectations). Singer et al. (1999) found scores to decline with increasing age for the physical function domain of the SF-36, but found little change in the mental health domain. The authors suggest this finding supports the notion of a psychological adjustment process, as even though older persons are more disabled than younger persons, they have similar mental health scores to younger persons.

Roberts et al. (1998) examined the relationship between various factors and the self-rated health of the MS participants. The authors' found the primary difference between the participants' three age groups of young (18-45), middle-aged (46-60), and old (61-78), was the disability's direct effect for the younger group. The authors speculated that younger persons may become less depressed as they age because older persons appear to protect their self-perceptions of health by relying less on their level of disability even though they are more disabled. Anxiety has also been found to be less common in older persons (Hakim et al., 2000).

The results from the studies that found an association between age and HRQoL suggest that age may have an effect on HRQoL, but that effect may be different for the physical and mental health components. Getting older may have a negative influence on physical HRQoL, but it may have a positive influence on mental HRQoL. Even though the majority of the current literature suggests there is no relationship between age and HRQoL, age and its possible association with the HRQoL of persons with MS is worthy of further investigation given that nine studies did find a relationship.

Marital status has not been widely investigated as a possible factor associated with the HRQoL of persons with MS. Aronson (1997) found that being a spouse of a person with MS was associated with decreased satisfaction with HRQoL as a whole for caregivers. Devins et al. (1993b) found that MS participants scored worse in the "relationship with spouse" and "family relations" domains of the Illness Intrusiveness Ratings Scale questionnaire (IIRS) in comparison with rheumatoid arthritis and end-stage renal disease participants. Solari et al. (1999) reported that lower physical and mental health summary scores of the SF-36 were associated with marriage / cohabitation. The authors suggest this finding might be due to confounding (e.g. patients stay married because their disability makes them unable to live alone). These authors found that marital status did not remain as an explanatory factor in their model when they controlled for other explanatory factors such as age.

Gulick (1997) found living with a spouse to be positively associated with HRQoL as measured by the Life Situation Survey. Aronson (1997) and Jønsson et al. (1996) both found family, relatives, and friends to be thought of as positive factors influencing HRQoL by persons with MS. Schwartz et al. (1999) found that participants who reported their spouses as encouraging towards their well behaviours were significantly less depressed than those who reported their spouses to be more punitive. The authors also found that participants who reported their spouses as encouraging towards their well behaviours were less physically disabled than those who reported their spouses to be punitive towards their well behaviours.

The relationship between marital status and HRQoL is unclear in the current literature, with three studies suggesting a positive association, three studies suggesting a negative association, and the Schwartz study suggesting both types of associations are possible depending on the attitude of the spouse. Thus, further investigation into the nature of the relationship is warranted. Perhaps looking at the relationship between marital status and the physical and mental components of HRQoL separately would be of value to determine if marital status has a different relationship with the physical versus the mental component.

3.5.2 Socioeconomic Factors

Education, employment status, income, and location of residence (urban vs. rural), have been explored to some degree in the current literature. There is evidence in the literature to suggest that employment status might be an important factor. Aronson (1997) found that being unemployed and having a low income were associated with decreased satisfaction as a whole with HRQoL for the MS participants. Devins et al. (1993b) found the MS participants fared worse in the "work" domain on the IIRS questionnaire than the rheumatoid arthritis or end-stage renal disease participants. Being unemployed, and having a low education level, were found to have a negative relationship with HRQoL in a study conducted by Koch et al. (1999), using a primarily psychosocial quality of life scale. Lankhorst et al. (1996) reported that "work" was one of four items ranked with a low HRQoL rating by persons with MS. In the study conducted by Rudick et al. (1992) comparing persons with MS, inflammatory bowel disease, and rheumatoid arthritis, far fewer participants with MS were employed, and the MS group had the worse HRQoL scores. Solari et al. (1999) found that full employment had a positive impact on the physical health summary score of the SF-36, and that the physical and mental health summary scores were lower in the unemployed (Solari et al., 2001). Vickery et al. (1995) found the MS Quality of Life-54 (MSQoL-54) physical role limitation, social function, health distress, and physical and mental health summary scores to worsen with higher numbers of days unable to work due to health.

Thus, there appears to be a strong association between employment status and HRQoL, with those who are employed faring better physically and mentally than those who are not. The ability to remain employed may be linked to the MS person's disability level, duration of disease, and disease progression. As disability, duration, and or progression increases, so does the chance of unemployment. The link between employment and HRQoL therefore might be a reflection of increasing limitations imposed by increasing disability. Hakim et al. (2000) found severity of disease to be negatively associated with employment status. There does not appear to be any association between education, income, location of residence and HRQoL, but these variables have not been investigated as often as employment status.

3.5.3 Health Factors

Fatigue has been implicated as a factor associated with both the physical and mental health components of HRQoL in the MS population, with higher levels of fatigue severity associated with lower physical and mental HRQoL scores (Amato et al., 2001; Aronson, 1997; Janardhan et al., 2002; Jønsson et al., 1996; Merkelbach et al., 2002; Nortvedt et al., 2003). Aronson (1997) and Koch et al. (2001) cite fatigue as one of the most prevalent and distressing symptoms for persons with MS.

Depression has also been implicated as a factor associated with both the physical and mental health components of HRQoL, with depressed persons having lower physical and mental HRQoL scores than persons who are not depressed (Amato et al., 2001; Benito-León et al., 2002; Cutajar et al., 2000; Fruehwald et al., 2001; Janardhan et al., 2002; Kenealy et al., 2000; Merkelbach et al., 2002; Nicholl et al., 2001; Patti et al., 2003; Provinciali et al., 1999; Solari et al., 1999; The Canadian Burden of Illness Study Group, 1998; Vickery et al., 1995; Wang et al., 2000). Depression and fatigue have been found to be significantly correlated (Amato et al., 2001; Janardhan et al., 2002;

Merkelbach et al., 2002), although it should be pointed out that fatigue or low energy levels are also a symptom of depression.

Many authors spoke to the importance of examining the relationship between cognitive and psychological factors and HRQoL for persons with MS. Benito-León et al. (2002) found low cognitive scores, and high depression / anxiety scores to be associated with lower HRQoL as measured by the FAMS. Similarly, Cutajar et al. (2000) found that persons who had impaired frontal cognitive functions and behavioural memory involvement, depression, and diminished perception of well-being (despite good physical functioning), had worse HRQoL SF-36 scores. Ford et al. (2001) also found cognitive problems to have a negative impact on HRQoL. Fruehwald et al. (2001) found depression, anxiety, and emotional state to have high negative correlations to most HRQoL domains as measured by the Quality of Life Index, with depression accounting for 42.6% of the variance in the overall HRQoL score. Shawaryn et al. (2002) also found poor cognitive function to be a predictor of worsening HRQoL and depression.

Kenealy et al. (2000) conducted a study in a long-term care hospital with severely disabled MS patients. It is of interest that the authors found the lowest levels of HRQoL to be reported by depressed participants with normal memory regardless of disability level, while non-depressed participants with impaired memory reported the best levels of HRQoL. Perhaps one could speculate that in the early stages of cognitive impairment, the effect on HRQoL is negative, whereas as the reverse is true in the advanced stages of cognitive impairment.

Nicholl et al. (2001) concluded that mood measures, such as measures of depression, anxiety, and psychological disorders, are more important than disability measures in predicting HRQoL. Changes in emotional well-being and health distress were found to explain a greater proportion of the variance in HRQoL than physical measures in a study conducted by O'Connor et al. (2001). The authors concluded that overall HRQoL is more a measure of mental health than physical disability. This conclusion is further supported by the study conducted by Rothwell et al. (1997) who found that the mental health, emotional role limitation, general health, and vitality domains of the SF-36 were more important to patients. Clinicians, on the other hand valued the physical function, physical role limitation, social function, and bodily pain domains. Solari et al. (1999) also concluded that age and depression have a major influence on HRQoL, with disability having less influence.

3.5.4 MS Specific Factors

3.5.4.1 Disability

Disability goes hand in hand with MS. The type and degree of disability will vary from time to time and from person to person, yet without question it appears to be a factor associated with the HRQoL of persons with MS. Disability is often measured by the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983) amongst the MS population, which gives a numerical value to a person's disability level along a 0.5 point increment scale from 0.0 (normal neurological exam) to 10.0 (death due to MS). The EDSS has poor psychometric properties, and mainly focuses on the ambulation ability of patients, yet despite these limitations, the EDSS is commonly used in clinical and research settings for assessing disability.

Some studies investigated the relationship between disability level and HRQoL by splitting the sample into groups based on their EDSS scores. Henriksson et al. (2001) split the study sample into three EDSS groups: mild (≤ 3.0), moderate (3.5-6.0), and severe (≥ 6.5). HRQoL, as measured by the EuroQoL, decreased with increasing disability. Modrego et al. (2001) had similar EDSS groupings and also found HRQoL, as measured by the FAMS, to be significantly worse in the moderate and severely disabled groups. Solari et al. (2001) found significant differences between the disability groups (< 4.0, 4.0-6.5, > 6.5) and all domains of the MSQOL-54 questionnaire, except for cognitive and sexual function, with the greatest differences being in the physical function and physical role limitation domains. HRQoL scores worsened as the EDSS increased.

Murphy et al. (1998) found physical and social function scores to decrease with increasing disability, but not psychological function (EDSS groups: mild 1.0-3.5; moderate 4.0-6.0; severe 6.5-8.0). The general well-being function scores also decreased from low EDSS to moderate EDSS, but to a lesser extent to high EDSS. Similarly, Rice et al. (1999) found the only significant differences of worsening between the three disability groups (<3.0, 3.0-6.0, >6.0) was in physical function, physical role limitations, and general health, and not in the mental health domains.

Nortvedt et al. (1999b) found that participants with low EDSS scores had lower mean scores than the general population in all dimensions except for mental health, but scored significantly better in all dimensions than the two groups with higher EDSS scores (mild ≤ 2.5, moderate 3.0-6.0, severe ≥ 6.5). Patti et al. (2003) found the EDSS group of < 3.0 had significantly lower scores than the general population in all domains except for bodily pain, but again scored significantly better in all dimensions than the two groups with higher EDSS scores (3.0-6.0, > 6.0). In an Italian study, a significant decrease was found in HRQoL as measured by the FAMS, after participants reached an EDSS of 3.5, but then no further declines in HRQoL were found as EDSS increased (Provinciali et al., 1999). The Canadian Burden of Illness Study Group (1998) found that the mild EDSS group ($\leq$ 2.5) had on average 30% lower scores for all subscales of the SF-36 than the general population. They also found that physical function, physical role limitation, and social function decreased significantly as EDSS increased (3.0 – 6.0, $\geq$ 6.5), but the mental health scales did not significantly increase as EDSS increased. Vermersch et al. (2002) also found their MS sample to score worse in all SF-36 domains than the general population, with the greatest difference existing for the general health domain, and smallest difference existing for the mental health domain. All the above studies support an apparent association between disability and the HRQoL of persons with MS. However, they also raise the possibility that perhaps disability is associated with only the physical aspect of HRQoL.

Several authors have found disability to have a significant association with the physical health component of the HRQoL of persons with MS (Amato et al., 2001; Benito-León et al., 2002; Brunet et al., 1996; Chang et al., 2002; Ford et al., 2001; Fruehwald et al., 2001; Henriksson et al., 2001; Janardhan et al., 2000; Janardhan et al., 2002; Merkelbach et al., 2002; Miller et al., 2003; Modrego et al., 2001; Murphy et al., 1998; Nortvedt et al., 1999b; Nortvedt et al., 2000a; Nortvedt et al., 200b; O'Connor et al., 2001; Patti et al., 2003; Parkin et al., 2000; Pfennings et al., 1999; Rice et al., 1999; Rudick et al., 1992; Shawaryn et al., 2002; Solari et al., 1999; Solari et al., 2001; Stuifbergen et al., 2000; The Canadian Burden of Illness Study Group, 1998; Vermersch et al., 2002; Vickery et al., 1995). In all cases, the physical HRQoL scores of the MS participants worsened with increasing disability.

The relationship between the mental health component of MS patients' HRQoL and disability is less clear however. In those studies in which HRQoL is reported as a whole and not separated into physical and mental health components, the findings were that disability was associated with HRQoL (Benito-León et al., 2002; Ford et al., 2001; Fruehwald et al., 2001; Henriksson et al., 2001; Janardhan et al., 2000; Janardhan et al., 2002; Modrego et al., 2001; O'Connor et al., 2001; Pfennings et al., 1999; Rudick et al., 1992). Amato et al. (2001), Brunet et al. (1996), Merkelbach et al. (2002), Miller et al. (2003), Murphy et al. (1998), Nortvedt et al. (1999b, 2000a), Patti et al. (2003), Rice et al. (1999), Solari et al. (1999, 2001), The Canadian Burden of Illness Study Group (1998), and Vermersch et al. (2002) separately reported the physical from the mental health components of HRQoL and found disability to only be negatively associated with the physical component. Rudick et al. (1992) found EDSS correlated with the functional / economic, medical problems, and overall HRQoL scales, but not the social / recreational and affect / life in general scales. Vickery et al. (1995) stated that global ratings of MS symptoms severity in the prior year and level of ambulation were more highly associated with functioning scales (physical, social, role limitations) than with well-being scales (emotional well-being, energy, pain).

Chang et al. (2002) however, found disability and age to explain 21% of the variance in the emotional well-being scale of the FAMS. Nortvedt et al. (2000b) found that a high score of self-rated health (good, very good, excellent) correlated with a low EDSS (disability) score, and that low scores on the SF-36 mental health scale were significantly correlated with worsened EDSS scores 1 year later. In another study conducted by Nortvedt et al. (2000a), they found no significant correlation between the mental health summary scale of the SF-36 and EDSS, but found the mental health subscales of mental health, emotional role limitations, social function, and vitality to be significantly correlated with EDSS. Nortvedt et al. (1999b) found that those with higher EDSS scores had markedly reduced scores for the SF-36 mental health subscale. Parkin et al. (2000) found the social function and health distress domains of the MSQLI to worsen with increased disability, and Shawaryn et al. (2002) reported EDSS to be one of seven factors explaining 26% of the variance in the mental health component summary score of the MSQLI. The question as to whether disability is associated with the mental health component of the HRQoL of persons with MS thus remains. Further investigation into the existence, strength, and direction of the relationship between disability and the mental health component of MS patients' HRQoL is clearly required.

3.5.4.2 Relapses

Exploring the relationship between number of relapses (attacks, exacerbations) and HRQoL has not been as widely investigated as disability and HRQoL, but in all instances in which it has been studied, the conclusions are the same. Relapses are associated with poorer HRQoL. Chang et al. (2002) found the variable "number of relapses in previous year" to explain part of the variance in the FAMS total score, mobility score, general contentment score, and thinking and fatigue score, with worse scores being associated with a greater number of relapses. Cutajar et al. (2000) found worsening of depression, a factor associated with HRQoL, to be predicted by an increase in the number of relapses in the previous year. Vermersch et al. (2002) reported that 30 out of 106 of their participants had two relapses and or at least a 0.5 increase in their EDSS score during the course of the study. These 30 participants had a significant decrease in their before and after treatment scores for physical and social function.

Participants experiencing a relapse had much lower HRQoL scores as measured by the Health Utilities Index (Grima et al., 2000), EuroQoL (Henriksson et al., 2001), and MSQLI (Parkin et al., 2000) than those in remission. In a qualitative study conducted by Somerset et al. (2002), the participants identified relapses as one factor leading to a decrease in quality of life. Solari et al. (1999) reported that "clinical worsening in previous year" was associated with both the physical and mental health summary scales of the MSQOL-54. Although the authors defined clinical worsening as "absent/mild" or "moderate/severe", and not number of relapses, the results from this study lend support to the notion that relapses are associated with poorer HRQoL for persons with MS. In a study comparing the HRQoL of relapsing-remitting patients taking Betaseron® to reduce the MS attack rate, to historical controls who did not take the medication, the authors speculated that one of the reasons for the better HRQoL reported by the cases might be due to the lower relapse rate amongst the cases despite similar disability levels (Rice et al., 1999). Vickery et al. (1995) assessed participants' "MS symptom severity in the past year", and found that those with mild symptoms scored significantly better than those with extreme symptoms on the physical function, physical role limitations, health perceptions, social function, health distress, overall quality of life, and physical and mental health summary scales.

A greater number of relapses certainly appear to be associated with the poorer HRQoL. Since there are very few studies that have investigated if relapses are associated with only certain components of HRQoL, investigating the relationship between relapses and the physical and mental health components of HRQoL separately might be of some benefit.

3.5.4.3 Other Factors

Several other MS specific factors have been explored in the literature including type or clinical course of MS, duration of disease, and MS related symptoms. The literature tends to report a worsening of HRQoL for those MS participants who have primary or secondary progressive disease compared to those with a relapsing-remitting course (Aronson, 1997; Benito-León et al., 2002; Chang et al., 2002; Janardhan et al., 2000; Janardhan et al., 2002; Modrego et al., 2001; Nortvedt et al., 2003; Pfennings et al., 1999; Shawaryn et al., 2002).

Brunet et al. (1996) however, report that the relapsing-remitting group had lower scores in the emotional role limitation and emotional well-being scales than the other progressive and benign groups. Cutajar et al. (2000) report that HRQoL is affected by diminished perception of well-being despite good physical functioning. Ford et al. (2001) report some interesting results in that they found worse physical functioning to mean worse HRQoL, yet being in a wheelchair meant better HRQoL. The authors speculate the reason for these findings is due to a psychosocial adjustment to the disease. Younger persons with relatively recent onset, who are experiencing difficulty in mobility but are not yet wheelchair users, may perceive their quality of life as poor, compared to older persons who have had the disease for some time and have adjusted to their increasing disability. Vickery et al. (1995) found a non-linear relationship between ambulation status and HRQoL for some scales such as pain and physical role limitations. The pain and physical role limitations scores were significantly lower for participants who needed assistance to walk than for participants who were essentially confined to a wheelchair. Wheelchair users may in fact have a feeling of increased mobility since they may be able to go further and longer than when they were trying to walk.

Having a progressive or secondary progressive disease course generally means having higher disability levels (i.e., EDSS scores of ≥ 6.0 – constant unilateral assistance) than a relapsing-remitting course. Since disability has an association with the physical component of HRQoL, perhaps this would explain the apparent worsening of HRQoL with progressive disease courses. The Canadian Burden of Illness Study Group (1998) found that those SF-36 scales that were unrelated to physical function tended to stabilize with disease progression. The authors speculated that perhaps this was due to adaptation of patients to the disease and adjustment to living with the long-term consequences of MS. The physical health aspects of HRQoL may be worse for those with progressive courses, but the mental health aspects might not.

Duration of the disease has also been investigated as a possible factor associated with the HRQoL of persons with MS. Longer disease duration has been reported to have a negative association with HRQoL (Aronson, 1997; Benito-León et al., 2002; Merkelbach et al., 2002; Miller et al., 2003; Nicholl et al., 2001; Nortvedt et al., 2003; Patti et al. 2003; Pfennings et al., 1999; Shawaryn et al., 2002; Solari et al., 1999). In contrast to all the above studies, Ford et al. (2001) found that having shorter disease duration was actually associated with worse HRQoL, as measured by the Leeds MS questionnaire, perhaps again reflecting a psychosocial adjustment that comes with longer duration. (The Leeds HRQoL questionnaire provides an overall HRQoL score and does not separate physical from mental HRQoL domains.) Vickery et al. (1995) reported duration to be inversely correlated with physical and sexual function scores, but no other significant relationships were found between duration and the MSQoL-54 scores.

In 11 studies which investigated the relationship of both duration and disability with HRQoL, increasing disability was found to have a negative association with HRQoL, but duration of disease was not (Amato et al., 2001; Chang et al., 2002; Fruehwald et al., Hakim et al., 2000; Janardhan et al., 2000; Janardhan et al., 2002; Murphy et al., 1998; Nortvedt et al., 1999b; Parkin et al., 2000; Roberts et al., 1998; Rudick et al., 1992). Duration of disease might be associated with the HRQoL of persons with MS, but it appears that disability level might be a more important factor.

Similar to disease course, disease duration can also be translated into disability terms. The longer the duration, the greater chance the disability level will be greater. As has already been stated, the SF-36 scales unrelated to physical function tend to stabilize with disease progression, which may be due to adaptation of patients to the disease and adjustment to living with the long-term consequences of MS (The Canadian Burden of Illness Study Group, 1998). Again, the physical health aspects of HRQoL may be worse for those with longer durations and progressive courses, but the mental health aspects might not.

There are a few other interesting findings in the literature review worth mentioning. Brunet et al. (1996) found family history of MS to be associated with lower scores in the physical, social, pain, and vitality domains of the SF-36. Abnormalities seen on images taken of the brain (MRI scans) were associated with impaired HRQoL in the areas of sexual function, physical role limitation, emotional role limitation, and overall mental health, but interestingly, not overall physical health (Janardhan et al., 2000). Bladder and sexual dysfunction have been found to be negatively associated with HRQoL (Nortvedt et al., 2001). Stuifbergen et al. (1997, 2000) found health-promoting behaviours (resources, self-efficacy, acceptance) to be positively related to HRQoL, and suggest that health-promoting behaviours may enhance HRQoL regardless of disability level. Stuifbergen's sample, comprised of women with MS, scored significantly higher in the interpersonal and stress management domains than the general population, perhaps once again reflecting a possible psychosocial adjustment to the illness. Further investigation into these apparent associations might be of benefit to determine the strength and influence of these factors on the HRQoL of persons with MS.

3.5.5 Factors Important to Persons with MS

Aronson (1997) used the General Social Survey, a generic HRQoL instrument, to collect information from persons with MS and caregivers. The strongest association with reduced HRQoL for the MS participants was interference by MS with social activities. Devins et al. (1993b) found that MS participants had statistically significant lower scores in the work, passive recreation, relationship with spouse, family relations, social relations, and self-expression / self-improvement domains of the IIRS questionnaire than the rheumatoid arthritis and end-stage renal disease participants. Difficulties with mental/emotional symptoms, motor/sensory symptoms, reduced intimacy / recreation /

socializing activities of daily living were negatively correlated with the Life Satisfaction Survey used by Gulick (1997) to assess HRQoL. Persons with MS gave the lowest HRQoL ratings to the walk, work, clean house, and worry about deterioration items from the Disability Impact Profile (Lankhorst et al., 1996).

Rothwell et al. (1997) reported that patients are more concerned with the less tangible aspects of HRQoL such as mental health and vitality than the physical aspects. Somerset et al. (2002, 2003) report that the two most important quality of life outcomes as prioritized by persons with MS were not being depressed and experiencing good social function, regardless of any impairment or consequences of having MS. Variables that were significantly associated with depression included lower emotional role limitation score and feeling of diminished control / increased dependency (Somerset et al., 2003). Variables that were associated with lower social function included lower emotional role limitation score, lower mental and physical health scores, and feeling of diminished control / increased dependency (Somerset et al., 2003).

The impact of the illness on the mental and social aspects of the lives of those with MS appears to be more of a concern to persons with MS than the physical aspects. Intrusiveness of the illness on HRQoL has been investigated in terms of fatigue, depression, and disability, but examining illness intrusiveness as a variable in and of itself would be of some merit. Shawaryn et al. (2002) explored illness intrusiveness as a mediator between various factors and HRQoL, and found evidence that it does mediate relationship between factors. For example, if illness intrusiveness is high, mobility limitations and learning and memory impairments affect HRQoL. From the work conducted by Devins et al. (1993b) it is certainly apparent that MS is an intrusive disease in many social aspects of life.

Perhaps researchers and clinicians need to concentrate on the mental and social intrusiveness of the illness and less so on the physical intrusiveness in order to best help those living with the disease. Several authors have suggested that perhaps persons with MS are able to accept and adjust psychosocially to their illness in the face of increasing physical disability (Ford et al., 2001; Miller et al., 2003; Patti et al., 2003; Roberts et al., 1998; Singer et al., 1999; Stuifbergen et al., 1997; The Canadian Burden of Illness Study Group, 1998). The sense from the current literature on the HRQoL of persons with MS is that indeed the physical component of their HRQoL is apt to decrease, but the mental and social components have the potential to stabilize or perhaps increase if something is done early enough in the care of MS patients to facilitate improvement in their psychosocial lives.

3.6 Factors with Well Established Associations and Factors Meriting Further Investigation

Fatigue, depression, and relapses clearly have a negative association with the HRQoL of persons with MS, with an increase in any of these factors meaning worse HRQoL. Increasing disability also clearly has a negative association with the physical component of HRQoL. Increasing disability most likely does not have an association with the mental component of HRQoL, but some studies suggested the possibility of a negative association, and thus further research is required regarding the relationship between disability and mental HRQoL. Employment status appears to have a clear association with HRQoL, with those who work faring better than those who do not. Age most likely has an association with HRQoL, with older persons probably faring worse in terms of physical health but better in terms of mental health. Further investigation would certainly help to determine the existence, strength, and direction of the association between age and the HRQoL of persons with MS.

Marital status is a variable meriting further investigation given the conflicting evidence in the literature. Perhaps exploring the whole concept of social support in terms of family, relatives, and friends warrants further investigation to better understand how support systems can help or hinder the HRQoL of persons with MS.

Sex was clearly not found to be associated with HRQoL. Clinically however this might remain an important variable to consider when addressing the HRQoL of male versus female patients, given the differing concerns and roles men and women often have. For example, young females newly diagnosed with MS invariably inquire as to their ability to have children, whereas newly diagnosed males rarely ask this.

Disease course and disease duration most likely do have an association with HRQoL, yet because both these factors are also associated with disability, their relationship with HRQoL might be confounded by the disability factor. Progressive patients and those experiencing longer illness duration probably have poorer physical HRQoL because of increasing disability, yet as the literature suggests, they might have better mental HRQoL.

The concept of illness intrusiveness has been explored to some degree by examining the association of symptoms and HRQoL, but it has not been studied as an independent explanatory factor. The IIRS questionnaire provides a single score measuring the concept of illness intrusiveness and thus would be a useful measure for exploring the possible association between the impact of MS and HRQoL, and is worthy of further investigation.

3.7 Implications of the Findings for the Following Research Study

The following study explores factors associated with the HRQoL of persons with relapsing-remitting MS. Given that the majority of the studies reviewed for the best-evidence synthesis included participants of all types of MS, the following study provides insight into factors that are associated with one particular group of MS participants, those with relapsing-remitting MS. All the demographic, socioeconomic, health, and MS specific factors found to have or possibly have an association with HRQoL in the synthesis were assessed in the following study (age, employment status, fatigue, depression, number of relapses, and disability). The sex of the participants was also assessed given the clinical importance of the factor and ease of collection. Marital status, education, income, and location of residence was also obtained, again given the ease of collection, and because there has not been a lot of research regarding these factors.

Health factors other than fatigue and depression have not been widely investigated. A comorbid condition questionnaire was given to the participants for ascertaining the presence and severity of other conditions amongst the MS participants. Illness intrusiveness as a MS specific factor had also not been investigated, but was through the administration of the IIRS.

3.8 Discussion

This best-evidence synthesis provides a unique look at what is currently known in the English literature about the factors associated with the HRQoL of persons with MS. The main strength of the synthesis is that it provides a critical review and summary of the research that has been conducted thus far to investigate the factors associated with the HRQoL of persons with MS. The synthesis delineates the factors that have consistent evidence supporting their association with the HRQoL of persons with MS, as well as the factors requiring further investigation to determine the existence, strength, and direction of their possible association with HRQoL. The vast majority of the studies were cross-sectional in nature, and had a mixed sample in terms of disability level and type of MS.

Of all the 51 studies reviewed for the best-evidence synthesis, only six did not employ a cross-sectional design (*Case series:* O'Connor et al., 2001; *Cohort studies:* Miller et al., 2003; Rice et al., 1999; *Descriptive studies:* Rothwell et al., 1997; *Reviews:* Nortvedt et al., 2003; *Qualitative studies:* Somerset et al., 2002). Cross-sectional studies provide insight into factors that are associated with one another, but do not allow for inferences as to the influence of one factor on another. The current literature regarding HRQoL and persons with MS is thus fairly descriptive in terms of the factors that might be associated with HRQoL, but it is lacking in ability to determine which factors might directly cause a better or worse HRQoL. Case-control, cohort, and randomized controlled trial study designs provide stronger evidence for determining directions of associations between factors. A longitudinal cohort study to determine factors that are predictive of worsening HRQoL, employing and following newly diagnosed patients, would certainly be of great value.

A possible limitation of the synthesis is that non-English studies were not included. Eleven possible studies, written mainly by Spanish and French authors, were excluded because of this exclusion criterion. Due to the barriers of translation however, it was not possible to include these studies.

Another possible limitation is the restriction of the search to the electronic database Medline. Other databases such as Cinahl, Embase, and PsycINFO might have contained additional studies. Medline was deemed the most appropriate database to search however, due to its vastness in clinical and epidemiological studies. By way of reviewing the reference lists, other studies of relevance were identified that were not included in the Medline database.

3.9 Conclusion

The Medline electronic database was searched to identify citations relating to factors associated with the HRQoL of persons with MS. In addition, the reference lists of all relevant articles were reviewed to identify any further papers regarding this topic. After applying the inclusion / exclusion criteria, 51 articles were found to be relevant. Each article was then critically reviewed. The findings from the studies were then summarized into evidence tables, which formed the basis for the best-evidence synthesis. The synthesis identified factors that are consistently associated with the HRQoL of persons with MS, and factors that require further investigation.

Table 3.1 Evidence Tables

Abbreviations:

ADL = Activities of Daily Living
CES-D = Centre for Epidemiological Studies Depression Scale
EDSS = Expanded Disability Status Scale
FSS = Fatigue Severity Scale
MMSE = Mini-Mental State Examination
MSQLI = MS Quality of Life Inventory
PCS = Physical Health Component Summary Scale of the SF-36
QoL = Quality of Life
RRMS = Relapsing-remitting MS
SPMS = Secondary Progressive MS
BDI = Beck Depression Inventory
DIP = Disability Impact Profile
FAMS = Functional Assessment of MS
MCS = Mental Health Component Summary Scale of the SF-36
MSFC = MS Functional Composite
MSQOL-54 = MS Quality of Life-54 Questionnaire
PPMS = Primary Progressive MS
RCT = Randomized Controlled Trial
SIP = Sickness Impact Profile

Authors / Setting & Subjects	**Explanatory Factors / Outcomes**	**Study Design / Findings**
Amato et al., 2001 In- and outpatients consecutively admitted to the Dept. of Neurology at the Univ. of Florence. Adults, clinically or lab supported MS, not experiencing relapse or on steroid therapy (N=103).	EF: Age, education level, marital status, employment status, disease duration, clinical course, cognition (MMSE), disability (EDSS), depression (Hamilton Rating Scale), fatigue (FSS). Outcome: HRQoL as measured by the MSQOL-54.	Cross-sectional: Depression, disability, fatigue explained 65% of the variance in the PCS. Depression, fatigue explained 67% of the variance in the MCS. Depression & fatigue significantly correlated.
Aronson, 1997 Mail survey of persons with MS and their caregivers – 1993 to 1994. Recruitment via Ontario MS Society and 5 Ontario MS Clinics (N=697 MS, N=345 caregivers). Unclear inclusion / exclusion criteria.	EF: Demographic variables, employment status, income, mobility level, disease course, severity of symptoms, fatigue, duration and frequency of caring, current attitude towards MS, worry and degree of stress, extent that MS has interfered with	Cross-sectional: Fatigue and walking problems most prevalent and distressing symptoms. MS group – family, friends, housing had highest satisfaction rating, health the lowest.

	social activities. Outcome: HRQoL as measured by the General Social Survey (domains – health, job or major activity, housing, finances, family, friendships, HRQoL as a whole).	Caregivers – family, friends, housing had highest ratings, finances the lowest. Being unemployed, household income under $35,000, fatigue, disease course of SPMS or PPMS, associated with decreased satisfaction with HRQoL as a whole in MS group. Being a spouse, longer duration or care giving, moderate or worse symptoms in person with MS associated with decreased satisfaction with HRQoL as whole for caregivers. MS group HRQoL model – strongest association - interference by MS with social activities while controlling for income, employment status, and sex. Caregiver HRQoL model – strongest association - disease course of person with MS (especially SPMS) adjusting for income and spousal status.
Benito-León et al., 2002 Hospitals in Madrid, Spain (13). Random sample of MS patients participating in ongoing study of QoL and social problems of MS. Clinically definite MS, met Poser criteria (N=209).	EF: Sex, disability (EDSS - low 0-5.5, high 6.0+), duration (1-10, 11 years +), clinical course (RRMS and progressive – SPMS, PPMS). Outcomes: HRQoL as measured by the 6 subscales of the FAMS; cognitive functioning (MMSE & clock drawing test); emotional functioning - depression (Hamilton Rating Scale for Depression), anxiety (Hamilton Rating Scale of	Cross-sectional: No differences between the sexes. The more severe EDSS, the more progressive, the longer the illness, the worse the HRQoL. Greater physical disability & progressive course – worse HRQoL, worse cognitive & emotional functioning. Increasing illness duration – worse mobility, symptoms, emotional well-being,

	Anxiety).	general contentment, thinking/fatigue, depression, and anxiety. Low cognitive scores, high depression/anxiety scores – worse HRQoL.
Brunet et al., 1996 MS Clinic in Kingston, Ontario. Clinically or lab supported definite or probable MS, active patients (N=97).	EF: Sex, family history, type of MS, clinical course, age, age at diagnosis, disability (EDSS). Outcome: HRQoL as measured by the SF-36.	Cross-sectional: Highly significant correlation between PCS and EDSS. EDSS correlated significantly with physical function subscale, strong trend with social function. Family history of MS associated with lower scores in physical, social, pain, vitality domains. RRMS group had lower scores in role-emotional and emotional well-being than other progressive and benign groups.
Chang et al., 2002 Hospital outpatient clinics in Spain (58). Met Poser's criteria for MS (N=625).	EF: Disability (EDSS), age, number of relapses in previous year, clinical subtype, sex, years from disease onset. Outcome: HRQoL as measured by the FAMS, Spanish version - 6 subscales and 1 summary scale.	Cross-sectional: EDSS, age, number of relapses in previous year explained 28% of the variance in the FAMS total score. EDSS, age, number of relapses explained 51% of variance in mobility score. Age, EDSS, clinical subtype explained 10% of variance in symptoms score. EDSS, age explained 21% of variance in emotional well-being score. EDSS, age, number of relapses explained 19% of variance in general contentment score.

		Age, number of relapses, EDSS explained 14% of variance in thinking and fatigue score. EDSS explained 3% of variance in family / social well-being score. EDSS and age contributed most consistently – older and higher (worse) EDSS, worse HRQoL.
Cutajar et al., 2000 MS Centre in City of Bolgna. Report of 1st evaluation session of 4 for 3-year longitudinal study on cognitive function & QoL. Definite diagnosis, met Poser criteria, 20-50 yrs of age, EDSS ≤ 3.5, RRMS. Exclusion criteria: positive psychiatric history, language impairments, presence of visual dysfunction, dysfunction of dominant upper limb, presence of any other disabling pathologies (N=40).	EF: Number of relapses during the year prior, age of disease onset, any treatment cycles of neuro-motor re-education, age, sex, discriminating ability (Luria's Frontal Lobe Syndromes Test), behavioural memory (Rivermead Behavioural Memory Test), depression (BDI), anxiety (State-Trait Anxiety Inventory). Outcomes: HRQoL as measured by the SF-36.	Cross-sectional: HRQoL affected by diminished perception of well-being despite good physical functioning. Patients' emotional state influences important dimensions of HRQoL as represented by physical functions, role limitation-physical, social functioning, and mental health. Frontal component of cognitive functions and behavioural memory involvement is related to worsening of HRQoL. Worsening of depression is predicted by increase in number of relapses in previous year.
Devins et al., 1993 Residents of Southern Alberta receiving treatment through University affiliated programs at 1 of 2 local hospitals for rheumatoid arthritis (RA), MS, or end-stage renal disease (ESRD). MS group –	EF: Age, sex, marital status, educational level, duration of illness, disability (EDSS for MS, health assessment questionnaire for RA, intercurrent non-renal illnesses for ESRD). Outcome: Illness intrusiveness (II) as	Cross-sectional: Scores on IIRS (13-91): MS – 42.6, RA – 37.9, ESRD – 38.8. All background characteristics unrelated to II. MS group scored worse in following areas:

Poser criteria for probable or definite MS, 1 of 2 neurologists made diagnosis (N=94). RA group (N=110), ESRD group (N=101).	measured by the Illness Intrusiveness Ratings Scale (IIRS).	work*, passive reaction*, financial situation, relationship with spouse*, sex life, family relations*, other social relations*, self-expression / self-improvement*, religious expression. (*=significant difference)
Ford et al., 2001 Mail survey to population register of 712 people with definite or probable MS in Leeds Health Authority UK (N=180).	EF: Age, disability (SF-36 physical function), symptom checklist, duration, disease course, Barthel Index – extent of physical dependency, bladder, and bowel problems. Outcomes: HRQoL as measured by the Leeds MSQoL scale (measures a single construct).	Cross-sectional: Physical functioning, wheelchair user, difficulty bathing, cognitive problems, age, duration, swallowing problems accounted for 43% of the variation in HRQoL. The worse the physical functioning, not being in a wheelchair, having troubles with bathing, cognition, being younger, having shorter disease duration, and having swallowing problems = worse HRQoL. No significant differences across disease courses (RRMS, SPMS, PPMS, benign).
Fruehwald et al., 2001 Centre for MS treatment. Consecutive MS patients who were MRI confirmed, met Poser criteria, not cognitively impaired (MMSE <25), over 3-month study period (N=60). Healthy controls, matched for age and sex, also recruited (N=60).	EF: Age, sex, duration, disability (EDSS), cognitive function (MMSE), depression (Zung Depression Rating Scale), anxiety (Zung Anxiety Rating Scale), emotional function (von Zerssen Emotional State Scale). Outcomes: HRQoL as measured by the Quality of Life Index (10 questions covering various aspects of QoL and providing for satisfaction rating).	Cross-sectional: No relationship between age, sex, duration and HRQoL. EDSS correlated to depression, anxiety, and most HRQoL domains. Depression, anxiety, emotional state high negative correlation to most HRQoL domains. Depression accounted for 42.6% of the variance in HRQoL, followed by the EDSS at 28.6%.

Grima et al., 2000 MS clinics at Montreal Neurological Institute and London Health Sciences Centre. At least 18 yrs of age, RRMS, ambulatory (EDSS <7), not in clinical trial. In relapse (N=31), in remission (N=147).	EF: Relapse versus remission, disability (EDSS). Outcomes: HRQoL as measured by the Health Utilities Index (sensation – vision, hearing, speech; mobility, cognition; self-care; emotion; pain; discomfort).	Cross-sectional: Utility values for those in relapse lower than those in remission – utility values for patients recalling worse week of their last relapse had lowest values of all. Substantial increases in costs and reductions in utility values observed as EDSS increased. Authors conclude that a patient would have a utility decrease in HRQoL of 0.24 if they progress from 1.0 to 6.0 EDSS score in 15 yrs. – 50% of recently diagnosed patients would experience a decrease in utility that is 25% greater than would normally be expected to occur in 60 yrs from age 25 yrs.
Gulick, 1997 Mail survey to persons with MS involved in a longitudinal study pertaining to self-monitoring of health. 10th year of study (N=153). Study began with 634 participants.	EF: Age, age at diagnosis, educational level, marital status, employment status, duration of MS, symptoms (MS-related Symptoms Scale), activities of daily living (ADL Self-care Scale for MS Persons). Outcomes: HRQoL as measured by the Life Situation Survey (work, leisure, health, love / affection, self-esteem, 10 areas related to MS).	Cross-sectional: Living with spouse, mental / emotional symptoms, motor symptoms, sensory symptoms, intimacy ADL, recreation / socializing ADL correlated significantly with the LSS and explained 61% of the variance in the LSS.
Hakim et al., 2000 Population based survey of patients with MS in county of Hampshire in England, 1986-1989. Definite or probable diagnosis	EF: Age, sex, duration of MS symptoms, disability (EDSS), cognitive status. Outcomes: Psychological well-being (Hospital Anxiety and Depression scale),	Cross-sectional: Marital status not changed due to MS. Severity of disease negatively associated with employment status, recreational and

of MS. List of patients compiled from hospital records, family doctor records, MS Society (N=305). Patients and relatives (N=223) interviewed.	recreational activities, social activities, marital status, employment status.	social activities. Cognitive impairment important factor for patients' inability to remain in paid employment. Severity of disease associated with depressive symptoms. Depressed mood 4 times more frequent in men. Tendency for anxiety to be more common in younger patients.
Henriksson et al., 2001 Mail survey to clinically definite MS patients registered with the Division of Neurology in a Swedish Hospital (N=413).	EF: Disability (EDSS), occurrence of relapse in past month. Outcomes: HRQoL as measured by the EuroQoL.	Cross-sectional: HRQoL was reduced with increased disability – 0.68 in mild group ($\leq$ 3.0), 0.52 in moderate (3.5-6.0), 0.17 in severe ($\geq$ 6.5). Those who were experiencing a relapse had a lower HRQoL score by 0.0635 units.
Janardhan et al., 2000 Community based clinic in Buffalo, NY. Clinically definite MS patients aged 18-60. Excluded those with PPMS, poor MRIs, other major diseases, relapse in past 4 weeks, taking medication that might affect fatigue, mood or cognition (N=60).	EF: Age, sex, duration of illness, disease course, disability (EDSS), MRI lesions & atrophy. Outcomes: HRQoL as measured by the MSQOL-54.	Cross-sectional: SPMS patients had significantly lower HRQoL than RRMS patients, especially physical function. Increased EDSS meant decreased HRQoL. No significant relationship between age, sex, duration and HRQoL. MRI abnormalities associated with impaired HRQoL in areas of sexual function, role limitation due to physical and or emotional dysfunction and overall mental health.

		Overall physical health was not associated with any brain MRI abnormality.
Janardhan et al., 2002 Community based MS clinic in United States. Prospective, consecutive series of clinically definite MS patients over two-year period. Age 18-60, mostly new referrals – newly diagnosed or previously untreated. Exclusion criteria included taking medications that might alter mood, fatigue or cognition, recent relapse, family history of depression (N=60).	EF: Age, sex, disease duration, disability (EDSS), fatigue (FSS), depression (Hamilton Depression Inventory 17). Groups: RRMS or SPMS, MS-associate fatigue (MSF) or MS-nonfatigue (MSNF), and depression (MSD) and MS-nondepression (MSND). Outcomes: HRQoL measured by the MSQOL-54.	Cross-sectional: No significant relationship between HRQoL scores and age, sex, disease duration. RRMS / SPMS & HRQoL: health perception, mental health composite, change in health, satisfaction with sexual function worse in SPMS after accounting for fatigue and depression. MSF / MSNF & HRQoL: health perception, role limitations due to physical dysfunction, social function worse in MSF after accounting for depression and disability. MSD / MSND & HRQoL: health perception, fatigue, pain, sexual function, health distress, mental health composite, overall QOL, emotional well-being, role limitations due to emotional dysfunction worse in MSD after accounting for fatigue and disability. EDSS, fatigue and depression all independently associated with impaired QOL.
Jønsson et al., 1996 MS rehabilitation hospital in Haslev, Denmark. Met Schumacher's diagnostic	EF: Sex, age, disease duration, type of disease, disability (EDSS), fatigue, depression (BDI).	Cross-sectional: LLQ correlated only with BDI. LLQ did not correlate with EDSS.

criteria, no psychiatric disease, younger than 65 years, not of foreign origin, not cognitively impaired (N=43).	Outcome: HRQoL as measured by the Laman and Lankhorst Questionnaire (LLQ), with questions on cognition and fatigue added.	Items that had negative / low HRQoL weightings: readily tired, fatigue, dependence on other people, worry about deterioration, walk. Items that had positive / high HRQoL weightings: home adequate, family relations, relative and friends, financial situation, hear, speak, and read.
Kenealy et al., 2000 Long-term care hospital in England. Severely affected MS patients, partially or completely dependent for their care. Able to communicate sufficiently to complete instruments with assistance (N=30).	EF: Disability – partially dependent (EDSS < 8.5), predominantly dependent (8.5), completely dependent (> 8.5); duration of illness – 22 yrs or less, 23 yrs or more; depression – depressed (Hospital Anxiety and Depression Scales > 7) or not depressed (< 8); autobiographical memory – deficits (Autobiographical Memory Interviews < 13) or normal (> 12). Outcomes: HRQoL as measured by the SF-36 role-physical scale.	Cross-sectional: Lowest levels of HRQoL reported by depressed participants with normal memory regardless of disability level. Highest levels of HRQoL reported by participants with impaired memory and longer duration of illness regardless of disability level.
Koch et al., 2001 Participants recruited as part of larger study of employment and independent living concerns of people with MS. Mailed questionnaire to random sample of persons with MS who are members of the National MS Society (N=227).	EF: Age, sex, illness-related variables (number and range of MS symptoms, degree of persistence of the symptoms, age); employment-related variables (employment status, education level); familial support variables (social and financial resources). Outcome: HRQoL as measured by the Quality of Life Scale (rate levels of satisfaction with social life, family life,	Cross-sectional: Fatigue most common symptom. Total number of symptoms, education level, employment status, age explained 18% of variance in HRQoL. Total number of symptoms was negatively related, whereas employment, higher education levels, and aging were positively related to HRQoL.

	hobbies / recreation, education / intellectual development, ADL, romantic experiences, expectations and hopes for the future).	
Lankhorst et al., 1996 Patients with definite MS according to Poser criteria recruited (N=73). Made comparisons to rheumatoid arthritis patients (RA; N=25) and spinal cord injury patients (SCI; N=25) using available data.	Descriptive: Comparison of groups. Outcome: HRQoL as measured by the DIP – 3 symptoms questions and 36 disability questions in five domains: mobility, self-care, social activities, communication, and psychological status. Provides weighted score for all 39 items where 0=complete loss of QoL for this item, 1=no loss of QoL for this item.	Cross-sectional: Weighted scores smaller than 0.50 were found for items: walk (.49), work (.43), clean home (.43) and worry about deterioration (.46) for the MS group. Similar results were found for the RA group, except with the addition of pain (.49), and subtraction of walk (.57). The SCI group had scored smaller than 0.50 for stand (.49), walk (.42), and stairs (.43).
Merkelbach et al., 2002 Outpatient department in Germany. Clinically definite MS, not on medications that might affect mood or fatigue (N=87).	EF: Age, illness duration, fatigue (Revised clinical interview schedule, FSS, Chronic fatigue scale), disability (EDSS), depression (BDI). Outcomes: HRQoL as measured by the SF-36 summary scores (PCS & MCS).	Cross-sectional: PCS decreased with increasing EDSS, age, duration of disease. PCS & MCS decreased with increasing fatigue, depression. EDSS strongly associated with PCS but not MCS. Fatigue greater association than depression in PCS, but reverse in MCS. Fatigue and depression significantly related to each other.
Miller et al., 2003 Participants were enrolled in original	EF: Sex, disease duration, age, neurological function (MSFC), disability	Cohort: SIP PhysD and SIP total worsened over

Avonex® phase III study and had follow-up data (MRI scan, SIP, neurological exam) for at least 2 years during the trial (N=137). All had RRMS at time of enrolment.	(EDSS), whole brain atrophy (brain parenchymal fraction) – baseline, year 2, year 8, and score changes. Outcome: HRQoL as measured by the total SIP score, physical subscale (PhysD) SIP score, psychological subscale (PsycD) SIP score.	time, whereas SIP PsyD was stable. Change in MSFC from year 2 to follow-up, PhyD at baseline, change in EDSS for baseline to year 2, change in EDSS from year 2 to follow-up, disease duration explained 81% of the variance in the SIP PhyD. PsyD at baseline, change in MSFC from year 2 to follow-up, change in PsyD from baseline to year 2 explained 49% of the variance in the PsyD of the SIP. Change in MSFC from year 2 to follow-up, overall SIP score at baseline, change in overall SIP score form baseline to year 2, and change in EDSS from year 2 to follow-up explain 71% of the variance in the total SIP score. Authors conclude the psychosocial elements of HRQoL tend to be less variable over time and less responsive to change in objective measure of physical status.
Modrego et al., 2001 Hospital in Bajo Aragon, Spain. Clinically definite or probable MS, met Poser criteria, admitted to hospital. Excluded those who had been recently diagnosed (N=36).	EF: Number of MRI lesions, neurological impairment (EDSS – mild or nondisabled 0-3, moderately disabled 3.5-6, severely disabled (>6), disability (Incapacity Status Scale), handicap (Environmental Status Scale). Outcome: HRQoL as measured by the FAMS.	Cross-sectional: Moderately and severely disabled participants had significantly worse FAMS functioning scores than the mild group. Strong correlation between EDSS and ISS and ESS. Strong correlations between mobility, symptoms, emotional well-being of FAMS

		with ISS and ESS – clear relationship between these subscales and severity of MS. Weak correlations between general contentment, thinking and fatigue, family/social well-being, additional concerns of FAMS with ISS and ESS.
Murphy et al., 1998 Participants recruited by neurologists in 13 clinical centres. Random selection from database in one centre, all others on the basis of spontaneous consultations. Aged 18 years and older, met Poser criteria for at least 3 months prior to inclusion (N=267). Also recruited participants with no evidence of MS through family physicians in neighbouring local practices via spontaneous consultations. Age and sex matched to cases (N=90). Exclusion criteria included institutionalization, major comorbidities, any other neurological condition, participation in RCT.	EF: Age, sex, years since onset, disability (EDSS – 1.0-3.5, 4.0-6.0, 6.5-8.0). Outcomes: HRQoL as measured by the Functional Status Questionnaire (FSQ - physical function, social function, psychological function and general well-being subscales).	Cross-sectional: Physical, social function scores decreased with increasing EDSS. Psychological function did not vary across EDSS groups. General well-being decreased from low EDSS to moderate EDSS, but lesser extent to high EDSS. Scores of physical function and general well-being of cases were 40-50% lower than controls. Scores of psychological and social function of cases were 20% lower than controls.
Nicholl et al., 2001 All patients with definite MS in contact with rehabilitation ward or consultant in rehabilitation medicine in Chatsworth UK, thought by staff as able to participate (N=88).	EF: Age, sex, course, anxiety (Beck Anxiety Inventory), depression (BDI-II, Hospital Anxiety & Depression Scale), psychological disorders (General Health Questionnaire), symptoms (Brief Symptom Inventory), distress & psychological problems (Clinical Outcomes in Routine	Cross-sectional: Depression, duration, and psychological disorders account for 32% of the variance in the EuroQoL. Psychological disorders, symptoms, account for 50% of the variance in the MCS.

	Evaluation - CORE), activities of daily living (Extended Activities of Daily Living), disability (Guy's neuro disability scale), duration. Outcome: HRQoL as measured by the FAMS, MSQOL-54, EuroQoL.	Anxiety, psychological disorders, activities of daily living account for 52% of the variance in the PCS. Depression, psychological problems (as measured by CORE), and activities of daily living account for 68% of the variance in the FAMS. Authors conclude mood measures more important than disability measures in predicting QoL.
Nortvedt et al., 1999b Cohort of patients with onset of MS between 1976 and 1986 with definite or probable MS before 1995 in Hordaland County in Western Norway (N=194).	EF: Disability (EDSS - $\leq$ 2.5, 3.0-6.0, $\geq$ 6.5). Outcomes: HRQoL as measured by the SF-36.	Cross-sectional: Significantly lower mean scores for all dimensions compared with age and sex adjusted scores for general population. Participants with low EDSS scores had lower mean scores than general population in all dimensions except for mental health, but scored significantly better in all dimensions than 2 groups with higher EDSS scores. EDSS correlated significantly and negatively with all dimensions except bodily pain. EDSS explained 73% of variance in physical function 23% in social function, 21% in general health, but little in other dimensions. Higher EDSS scores had markedly reduced scores for mental health.
Nortvedt et al., 2000a	EF: Disability (EDSS), mental health	Cross-sectional:

Cohort of patients with onset of MS between 1976 and 1986 with definite or probable MS before 1995 in Hordaland County in Western Norway (N=194).	(Incapacity Status Scale). Outcomes: HRQoL as measured by the SF-36, SF-12 PCS and MCS. Correlation of RAND SF-36 physical and mental health factors.	All PCS scales highly correlated with EDSS. All MCS scales highly correlated with ISS. No significant correlation between MCS scales and EDSS, whereas mental subscales of mental health, role-emotional, social function, vitality significantly correlated with EDSS. SF-36 PCS and MCS not correlated – participants with highest scores on MCS have lowest PCS scores. RAND-36 PCS and MCS highly correlated. RAND-36 MCS correlated with EDSS. Authors propose SF-36 and SF-12 MCS profoundly underestimates the mental health problems of MS participants.
Nortvedt et al., 2000b Subjects from a clinical trial of interferon alpha-2a. Clinically or lab supported RRMS, EDSS of 5.5 or less, at least 2 relapses during the 2 years before enrolment, aged 18-50, stable disease at inclusion (N=91).	EF: Disability (EDSS – change from baseline to month 12 after the 6month drug free period), baseline MRI, relapse rate for 2 years preceding enrolment. Outcomes: HRQoL as measured by the SF-36 at baseline.	Cross-sectional: RR of 1.9 (95% CI: 1.0-3.5) for experiencing a worsening EDSS score between those who evaluated their health as poor or fair vs. those who evaluated their health as good, very good or excellent. High score of self-rated health at baseline correlated with a low EDSS score. Tendency between lower score on all SF36 scales except bodily pain and worse EDSS. Low scores on the SF36 mental health scale were significantly correlated with

		worsened EDSS scores 1 year later.
Nortvedt et al., 2001 Cohort of patients with onset of MS between 1976 and 1986 with definite or probable MS before 1995 in Hordaland County in Western Norway (N=194).	EF: Bladder dysfunction and mental health scales (Incapacity Status Scale), sexual disturbance, disability (EDSS). Outcomes: HRQoL as measured by the SF-36.	Cross-sectional: Bladder and sexual dysfunction correlated with higher (worse) EDSS scores. Sexual disturbance correlated with bladder dysfunction. Patients with bladder / sexual dysfunction had lower HRQoL scores than those without. Sexual problems showed greatest association with HRQoL. Strong association between depression (mental health scale) and bladder and sexual problems, especially among the patients with low EDSS scores.
Nortvedt et al., 2003 Review of studies in English published before 1 Jan 2002 that have presented data on quality of life (N=83 studies).	Detect common trends that can strengthen the basis for future studies.	Review: Three categories of studies: 1) Evaluating development of QoL questionnaires (n=27) 2) Evaluating factors associated with QoL (n=37) 3) Using QoL measures as outcome measures (n=19) Lower QoL has been found to be associated with bladder and sexual problems, long duration, severe disease course, fatigue, unemployment, family history of MS, and mental health problems.

O'Connor et al., 2001 Clinically definite SPMS patients recruited who were enrolled in phase I clinical trial of monthly IV micellar paclitaxel (N=29).	EF: Disability (EDSS), MRI data, neurological function (MSFC), change in MSQOL-54 domain scores. Outcome: Overall HRQoL as measured by the MSQOL-54. All measures taken at baseline and monthly for 6 months.	Case series: Changes in emotional well-being, health distress, and physical summary scales of the MSQOL-54 explained 80% of the variance in overall HRQoL. Changes in MRI data, EDSS, MSFC explained 47% of the variance in overall HRQoL. Authors conclude that overall HRQoL is more a measure of mental health than physical or MRI-related disability.
Parkin et al., 2000 Neurology service in Newcastle area in England. Records reviewed to identify participants who had a relapse in past 6 months (N=40), and those who had not (N=62). Questionnaires given.	EF: Remission / relapse, age, sex, employment status, disease duration, disability (EDSS). Outcomes: HRQoL as measured by the MS Quality of Life Inventory (MSQLI).	Cross-sectional: Relapse group had significantly worse physical function, role-physical, social function, change in health, physical health composite scores. Worse physical function, social function, sexual function, role-physical, and health distress scores with increased disability.
Patti et al., 2003 Participants selected from 308 consecutive patients who entered MS Centre of Catania, Italy during first 3 months of 1998 (N=132), and from all patients who resulted prevalent on January 1, 1995 in municipality of Catania (N=48; total sample N=180). Exclusion criteria: concomitant disease, exacerbation, MMSE	EF: Disability (EDSS), depression (BDI), disease duration. Outcomes: HRQoL as measured by the SF-36. Comparison to general population.	Cross-sectional: EDSS group of < 3.0 had significantly lower mean scores than general population in all SF-36 domains except bodily pain, but fared better than EDSS groups of 3.0-6.0, and < 6.0. BDI group of <11 (low depression score) had lower mean scores than general population in all SF-36 domains except

< 24, unaware of diagnosis.		bodily pain, but fared better than BDI groups of 11-17, and < 17. Low time since diagnosis (< 6 years) had lower mean scores than general population in all SF-36 domains except bodily pain. Scores on all SF-36 domains decreased, and BDI scores increased with increasing duration. All SF-36 scales except mental health showed significant correlation with EDSS. All SF-36 scales correlated with BDI and duration. Only in those with low EDSS did duration significantly influence SF-36 scales. Authors speculate that patients cope better with illness with time.
Pfennings et al., 1999 Invitation letter and questionnaires sent to 100 randomly selected persons with MS registered with the Dutch MS Society (N=61). Questionnaires also given to patients enrolled in a clinical trial at the Amsterdam MS Clinic (N=29).	EF: Sex, disability (EDSS – fully ambulatory 3.5, not fully ambulatory, not wheelchair bound 4.0-6.5, wheelchair bound 7.0-10.0), duration since diagnosis, progression of MS in past 6 months (stable, slowly progressive, rapidly progressive). Outcome: HRQoL as measured by the SF-36 and DIP) with question on fatigue added.	Cross-sectional: Men had better role-emotional and mental health scores. HRQoL scores decreased as disability and duration of disease increased. Rapidly progressive participants scored worse.
Provinciali et al., 1999 Consecutive Italian patients recruited from June 1996 to June 1997. Diagnosis of	EF: Cognitive performance, ADL, mood, handicap, disability (EDSS). Outcome: HRQoL as measured by the	Cross-sectional: Significant decrease in FAMS found after the patients reached an EDSS of 3.5, but

definite MS, met Poser criteria, 18-80 years of age (N=83). Exclusion criteria: MMSE <24, loss of visual acuity, previous causes of motor or cognitive impairment.	FAMS.	did not decline any further. Independent predictors of HRQoL were depression and handicap (as measured by the London Handicap Scale). Clinical depression found in mild and severe patients.
Rice et al., 1999 Exposure group – Patients involved in multi-centre trial re: interferon beta-1b. Clinically or lab supported definite RRMS, 18-50 years of age, EDSS less than 6.0, at least 2 attacks in last 2 years (N=117). Non-exposure group – Historical. RRMS and SPMS patients who took part in Burden of Illness Study in Canada who were never treated with Betaseron® (N=152).	EF: Age, sex, education level, current employment status, employment change due to MS, time since onset to Betaseron, time since onset to current year, type of MS, current EDSS (< 3.0, 3.0-6.0, >6.0), relapse at time of visit, EDSS at Betaseron initiation, duration of Betaseron treatment, current dose of Betaseron. Outcomes: HRQoL as measured by the SF-36.	Cohort study: HRQoL scores decreased as EDSS scores increased. Difference in HRQoL between the 3 disability levels was only significant in physical function, role-physical and general health. HRQoL of cases was higher than controls particularly for those with EDSS <3.0, especially role-physical, general health, physical function, social function. No difference in mental health related scales between cases and controls. Authors speculate that lower relapse rate in cases may explain better HRQoL despite similar EDSS values.
Roberts et al., 1998 Participants were part of larger study examining impact of MS on Q0L. Recruited from 2 Texas chapters of the National MS Society. 936 indicated interest in participating, questionnaires mailed (N=806).	EF: Age (young 18-45, middle-aged 46-60, old 61-78). Outcomes: Self-rated health as measured by the four-item self-rated health subindice of the multilevel Assessment Instrument.	Cross-sectional: Primary difference in age groups was in disability's direct effect for the younger group. Even though more disabled, older persons appear to protect their self-perceptions of health by relying less on their level of

		disability. Younger persons with MS may become less depressed as they age.
Rothwell et al., 1997 Patients admitted to the neurological ward for rehabilitation or attending the neurology outpatient clinics that had clinically definite or lab supported probable MS, no relapse during previous month, and were a resident in the region, invited to participate (N=42). Clinicians working in Dept. of Clinical Neurosciences also asked to participate (N=25).	HRQoL domains important to patients versus clinicians. Patients and clinicians rated the eight SF-36 domains.	Descriptive: Clinicians more concerned with physical manifestations of disease, patients more concerned with less tangible quantities such as mental health and vitality. The mental health, emotional role limitation, general health, and vitality domains of the SF-36 were more important to patients. The physical function, physical role limitation, social function, and bodily pain domains were more important to clinicians.
Rudick et al., 1992 Sample randomly selected from registries of patients attending the subspecialty clinics at The Cleveland Clinic Foundation. Definite diagnosis of MS (N=68), inflammatory bowel disease (IBD; N=162), or rheumatoid arthritis (RA; N=75) for $\geq$ 10 years.	EF: Disease type, age, sex, duration, disability (EDSS). Outcome: HRQoL as measured by the Farmer QoL Index – four clusters: functional and economic subscale; social and recreational subscale; affect and life in general subscale; medical problems subscale.	Cross-sectional: Far fewer participants with MS employed at time of survey. MS group had worst QoL scores, IBD group had best. No significant effect of age or duration on QoL scales. For each disease QoL scores were worse for women. EDSS correlated with QoL total score, functional and economic subscale, medical problems subscale. Cite Stewart et al. (1989) who found patients with multiple conditions have poorer functioning and well-being than

		those who suffer only one condition. Authors speculate that since MS has multiple problems, may be more disruptive to well-being than having two or more comorbid conditions.
Schwartz et al., 1999 Sample consisted of patients with definite MS who were patients of the MS Clinical Center at the University of Washington (N=44). Had to be married or cohabitation with a partner for at least 6 months.	EF: Spouse response inventory – 4 subscales – solicitous / punitive responses to patient pain or illness behaviours; encouraging / punitive responses to patient well behaviours, family environment scale, social support (Social Provisions Scale), marital quality (Dyadic Adjustment Scale item 31). Outcomes: HRQoL as measured by the SIP and SF-36. Depression as measured by the CES-D.	Cross-sectional: Patients who rated their spouses as more solicitous to pain or illness behaviours had higher physical disability as rated by the SIP. Patients who rated their spouses as more punitive to well behaviours had higher physical disability as rated by the SIP and SF-36. Patients who rated their spouses as more punitive to pain or illness behaviours had poorer general mental health and more depressive symptoms. Patients who rated their spouses as more encouraging to well behaviours were significantly less depressed.
Shawaryn et al., 2002 Major metro MS clinic in United States. Clinically definite MS, age 18 to 65, community dwelling, no psychiatric disorder or advanced form of dementia (N=90).	EF: Age, course, years since diagnosis, sex, years since onset; physical factors – global neuro impairment (EDSS), upper extremity function and motor speed (9-Hole Peg Test); cognitive factors – cognitive function (Paced Auditory Serial Addition Test), learning & memory (California Verbal Learning Test); illness	Cross-sectional: Age, course, years since diagnosis, EDSS, 9-HPT, CVLT, PASAT significantly predict all measures of HRQoL and depression, except for PDQ. These 7 factors account for 42% of the variance in the PCS, 26% in the MCS, 18% in fatigue, 25% in bladder control,

	intrusiveness (Illness Intrusiveness Scale) as a mediator Outcomes: HRQoL as measured by parts of the MSQLI – PCS & MCS of SF36, Modified Fatigue Impact Scale (MFIS), Bladder Control Scale (BWCS), Mental Health Inventory (MHI), and Perceived Deficits Questionnaire (PDQ). Depression as measured by the BDI.	30% in MHI, and 31% in BDI. Evidence that illness intrusiveness mediates relationship between factors. If illness intrusiveness is high, mobility limitations and learning and memory impairments affect HRQoL and fatigue.
Singer et al., 1999 MS clinic in Kingston, ON. Consecutive patients with clinically or lab supported MS between 1 March and 31 August 1994 (N=97). Also recruited: persons with end-stage renal disease receiving dialysis, kidney transplantation, or severe osteoarthritis of the hip prior to total hip replacement, to compare groups.	EF: Age, sex, disease groups. Outcome: HRQoL as measured by the SF-36. Scores compared between chronic condition samples and US general population.	Cross-sectional: For the physical function domain, scores declined with increasing age. For the mental health domain, little change with increasing age. Older patients with chronic medical conditions have similar mental scores but much poorer physical functioning scores than younger patients with same condition. Authors conclude this supports the notion of a psychological adjustment process.
Solari et al., 1999 MS patients presenting to three Institutes involved in study between April and Sept 1997. Clinically definite or lab supported MS, age 18+, knowledge of their diagnosis. Excluded those with relapse in month prior, one or more overt additional illnesses (N=204).	EF: Age, sex, severity of symptoms over the preceding year, disease duration, education, marital status, current employment status, disability (EDSS), cognitive functions (MMSE), depression (BDI). Outcomes: HRQoL as measured by the MSQOL-54.	Cross-sectional: Lower PCS scores associated with increasing EDSS, increasing age, marital status (married or cohabitating patients scoring worse), clinical worsening in previous year, disease duration. Full employment had positive impact on PCS.

		Depression, age, clinical worsening explained 50% of variance in PCS. Lower MCS scores associated with depression, increasing age, clinical worsening, disease duration, marital status (married or cohabitating scoring worse). Depression and age explained 40% of variance in MCS. Sex, MMSE, education did not influence PCS or MCS. Authors conclude age and depression have major influence on HRQoL, EDSS less so.
Solari et al., 2001 Mail survey of persons diagnosed with MS residing in Milan from March – June 1999 (N=251) and their proxies. Proxy available for 97% (N=243).	EF: Sex, age, education, employment status, disability (EDSS). Outcomes: HRQoL as measured by the MSQOL-54 and SF-36 proxy version (given to MS patient's significant other).	Cross-sectional: PCS & MCS scores lower in unemployed – especially physical role limitation, physical function, and emotional role limitation. EDSS groups - <4.0, 4.0-6.5, >6.5 – most differences in physical function and physical role limitation – differ significantly in all HRQoL domains except cognitive and sexual function. Good correlation between subjects and proxies in all domains except for general health and emotional role limitation.
Somerset et al., 2002 Purposeful sample of MS patients meeting eight sociodemographic characteristics considered to be relevant to MS. Selected	EF: Sociodemographic characteristics: Ethnicity (white or Afro-Caribbean), disability (ok – no obvious mobility problems, moderate – walks with aid,	Qualitative study: Core category – attain a QoL that included being reasonably happy and as socially active as desired regardless of any

via family doctor, neurology clinic, MS Centre, MS voluntary agency (N=16).	severe – uses wheelchair), health professional input (no regular, home visits, lives in special accommodation), carer (no regular, regular), occupation (professional, semi-professional, skilled, unskilled), place of interview (home, MS Centre, residential home). Outcomes: Areas of QoL important to persons with MS.	impairment or consequences of having MS. Personal control – support, dependency, health professionals could either increase or decrease person's feelings of control leading to increase or decrease in QoL. Illness trajectory – exacerbations, uncertainty/stress, personal crises led to decrease QoL.
Somerset et al., 2003 General practitioner offices in Scotland and England. Patients registered as having MS given questionnaire (N=318).	EF: 13 illness related variables, 6 sociodemographic variables, 11 variables related to personal experience of health and social services. Outcome: 2 QOL outcomes prioritized by people with MS in previous qualitative study: not being depressed (BDI < 8) and experiencing good social function (social function scale of the SF36)	Cross-sectional: Variables significantly associated with depression: lower emotional role limitation score and feeling of diminished control/increased dependency. Variables significantly associated with worse social function: lower emotional role limitation score, lower health transition score, lower mental health score, lower role physical score, feelings of diminished control / increased dependency, any contact with health professionals.
Stuifbergen et al., 1997 Study part of multiphase study of health promotion and QoL in men and women with chronic disabling conditions. Participants recruited from two MS society chapters in south western US. Had to be physician diagnosed and community	EF: Functional disability (Incapacity Status Scale), health-promoting behaviours – behavioural, cognitive, emotional (Health Promoting Lifestyle Profile II). Outcome: HRQoL as measured by the Quality of Life Index – MS Version. 72-item measure composed of two parts –	Cross-sectional: Scored the highest on the interpersonal and spiritual growth subscales, lowest on the physical activity subscale. Scored significantly lower than general adult group on physical activity and spiritual growth subscales, but

residing. Mailed questionnaires (N=807). Women participants only considered for this study (N=629).	satisfaction with various domains, importance of same domains.	significantly higher on interpersonal and stress management subscales. Those with RRMS or benign MS had significantly higher scores on physical activity and spiritual growth subscales. Authors speculate that as illness progresses, QoL diminishes and health-promoting behaviour decreases, but health-promoting behaviour regardless of disability level can enhance QoL.
Stuifbergen et al., 2000 Participants recruited from mailing lists of National MS Society. Mailed questionnaires to those who indicated interest, aged 18-70 (N=786).	EF: Severity of illness, health-promoting behaviours. Outcome: HRQoL as measured by the Quality of Life Index – MS version.	Cross-sectional: Positive relationship between health-promoting behaviours (resources, self-efficacy, acceptance) and HRQoL. Negative relationship between severity of illness and HRQoL.
The Canadian Burden of Illness Study Group, 1998 MS Clinics in Canada (14). Clinically or lab supported MS, met Poser criteria, at least 18 years of age, consecutively recruited from July to December 1995. Excluded those pregnant or delivered in last 3 months, any major acute or chronic disorder in last 3 months, any other neurological illnesses, or recent participation in drug trial (N=197).	EF: Disability (EDSS – mild $\leq$ 2.5, moderate 3-6, severe $\geq$ 6.5), employment status. Outcome: HRQoL as measured by the SF-36.	Cross-sectional: HRQoL impact is dramatic in participants with mild disease – compared to normal population, mild group scores were on average 30% lower for all subscales. As EDSS increased, physical function, role-physical, social function decreased significantly. Mental health scales did not significantly increase as EDSS increased. Unemployment increased as EDSS increased. Those having fewer depressive symptoms

		had significantly higher SF-36 scores for all scales except role-physical and physical function – for mild patients, emotional well-being plays role in determining HRQoL. Authors speculate psychological impact of disease rather than initial disease related disability may have large impact on HRQoL in early stage of disease, particularly those with depressive symptoms. Relative stability of HRQoL score with disease progression for SF-36 scales unrelated to physical function may reflect adaptation of the patient to disease and adjustment to living with long-term consequences of MS.
Vermesch et al., 2002 Consecutive patients recruited between June 1998 and May 1999. RRMS of at least one year duration, two relapses in three years prior to enrolment, 18 years +, baseline EDSS 0-5.5 (N=106). Exclusion criteria: previous immunomodulatory or immunosuppressive therapy in past 12 months, pregnancy or breastfeeding, presence of any other major disease, depression, epilepsy.	EF: Disability (EDSS), disease progression. Outcome: HRQoL as measured by SF-36. Comparison to general French population.	Cross-sectional: MS group worse off for all SF-36 scales than general population, varying from min. decrease in mental health to max. decrease in general health. Significant correlations between EDSS and physical functioning, physical role limitations, general health, social functioning, and PCS. 30/106 had 2 relapses and/or at least a 0.5 point increase in EDSS – significant decrease between the scores before and after a one-year period of treatment for

		physical and social functioning.
Vickery et al., 1995 Consecutive series of all 231 adults with a definite MS confirmed by one of two experts in MS based on an evaluation at UCLA over the preceding two-year period (N=179).	EF: MS symptom severity in past year (none, mild, moderate, extreme), current ambulation status (EDSS - walk, walk with aid, wheelchair bound), days unable to work or attend school due to health, hospital admission, depressive symptoms, duration. Outcome: HRQoL as measured by the MSQoL-54.	Cross-sectional: Global ratings of MS symptom severity in the prior year and level of ambulation were more highly associated with functioning scales (physical, social, role limitations) than with well-being scales (emotional well-being, energy, pain). Physical function had strong relationship with EDSS. EDSS had non-linear relationship with to almost all other dimensions. Significant associations between HRQoL and degree of symptoms severity in prior year, level of ambulation, employment limitations due to heath, admission to hospital in previous year and depressive symptoms.
Wang et al., 2000 Random sample drawn from 1800 MS patients registered at the Univ. of Calgary MS Clinic for ongoing study of economic costs of MS. Stratified to disability level (EDSS – 0-2.5, 3-5, 6-8, 8.5-9.5) (N=136).	EF: Age, sex, disability (EDSS), depression (WHO's CIDI-Auto according to DSM-IV criteria). Outcomes: HRQoL as measured by the MSQOL-54.	Cross-sectional: Those with depression had significantly lower scores than those without in domains of energy, cognitive function, mental health, general QOL, sexual function, role-limitation emotional. No evidence indicating association between depression and QOL due to confounding by age, sex, or disability.

4. METHODS

4.1 Purpose

The purpose of this research study was to describe the health-related quality of life (HRQoL) of Saskatchewan adults with relapsing-remitting MS, and to determine the factors associated with their HRQoL. This involved the following research question: What are the factors associated with the physical health summary scale and the mental health summary scale of the SF-36 Health Status Survey in persons with relapsing-remitting MS? Possible explanatory factors included demographic and socioeconomic status factors, health factors, and MS specific factors.

4.2 Background

Saskatchewan is a Canadian province with approximately 1,000,000 residents. In November of 1997, the provincial government of Saskatchewan decided to cover the costs of four new medications for relapsing-remitting MS under the Exceptional Drug Status Plan, a Saskatchewan Health Department program. Saskatchewan provides universal health coverage, and subsidizes the costs of approved medications under this provincial drug plan.

These four new medications, referred to as disease-modifying therapies, were found in clinical trials to reduce the number of relapses, the severity of relapses, and the number of MS lesions found on MRI images, by about one-third, in persons with relapsing-remitting MS (Halper, 2001). Two of the medications involve interferon beta-1a (Avonex® and Rebif®), one involves interferon beta-1b (Betaseron®), and one involves a small protein fragment called glatiramer acetate (Copaxone®). All four medications are expensive, nearing $20,000 Canadian dollars annually.

4.3 Population

The target population was all Saskatchewan residents newly approved for drug coverage of Avonex®, Betaseron®, Copaxone® or Rebif® for treatment of relapsing-remitting MS. Physicians referred potential applicants for coverage to the Exceptional Drug Status Plan, and a panel of physicians appointed by Saskatchewan Health determined approval for cost coverage of these medications. Criteria for approval were as follows: Saskatchewan resident with a confirmed diagnosis of relapsing-remitting MS; two or more MS attacks in the last two years; and demonstrated ability to walk 100 meters without assistance. Approval for cost coverage of the medication was withheld by the panel if the patient had a concurrent illness likely to alter compliance or substantially reduce life expectancy; was pregnant, planning a pregnancy or breast-feeding; or had severe depression. These criteria are consistent with criteria used in randomized controlled trials demonstrating the efficacy of the above medications (Arnoldus, et al., 2000; Nortvedt et al., 2000a; Rice et al., 1999).

The inclusion criterion for this present study was being newly approved for cost coverage of one of the four new medications for relapsing-remitting MS; that is, patients meeting the previously listed medical criteria who had applied to begin drug treatment. The inception period for this study was from December 12, 1997 to February 25, 2000. Participants were excluded from this study if they had been taking one of the four medications for more than 14 days prior to receiving and completing the baseline questionnaire. This time frame was chosen because no change in symptoms or disease status was expected to occur until patients had been taking one of these medications for more than 14 days (Hader W, M.D., personal communication, April 2002).

4.4 Procedure

All participants fulfilling the medical criteria for drug treatment, and who decided to take the medication, were seen by one of two nurses who coordinated the health care of those being prescribed the medication. All eligible participants were approached by one of the nurses and were asked to participate in the study. Participation was voluntary and the University of Saskatchewan Advisory Committee on Ethics in Human Experimentation and the University of Alberta Health Research Ethics Board approved the study (Appendix B). Each consenting patient provided signed consent and completed a self-report baseline questionnaire (Appendix C), approximately one month after being approved to begin drug therapy. The baseline questionnaire included questions about demographic and socioeconomic status, fatigue, comorbid medical conditions, and valid and reliable inventories to measure illness intrusiveness (Illness Intrusiveness Ratings Scale), depression (Beck Depression Inventory), and HRQoL (SF-36 Health Status Survey). Participants were also followed by telephone interviews, but the present study concerns only data from the baseline questionnaire.

4.5 Measures

4.5.1 Health-related Quality of Life

The measurement tool chosen for assessing the HRQoL of the participants was the SF-36 Health Status Survey. The SF-36 is a 36-item generic health measure designed to measure aspects of HRQoL common to every person regardless of age, disease, treatments, or other factors (Ware, 1993). The survey measures eight health concepts: 1) physical functioning; 2) role limitations due to physical health problems; 3) bodily pain;

4) general health; 5) vitality (energy / fatigue); 6) social functioning; 7) role limitations due to emotional problems; and 8) mental health (psychological distress and psychological well-being). In addition, the survey provides an overall picture of HRQoL by providing a physical and mental health summary score. The physical and mental health summary scores of the SF-36 served as the dependent variables in this study.

Respondents to the SF-36 are asked to answer 36 questions regarding their physical and mental health. The 36 items, eight subscales, and two summary scales are scored so that a higher score indicates a better health state (Ware, 1993). The scale scores are calculated by summing across items in the same scale, and then transforming the raw scale score to a 0 – 100 scale. All the subscales and summary scales are thus continuous in nature.

The survey is commonly used to assess HRQoL in both disease-specific and general populations. It was designed to allow for self-administration in persons 14 years of age and older, and for administration by a trained interviewer in person or by telephone (Ware, 1992). The survey has very strong psychometric properties (McHorney et al., 1993; McHorney et al, 1994; Ware, 1993), and has been used to establish HRQoL norms amongst various general populations including American, Canadian, and United Kingdom populations (Hopman et al., 2000). Normative data for the Canadian population indicate that women have slightly lower mean physical and mental health summary scale scores then Canadian men: 50.5 and 51.7 respectively versus 51.4 and 52.6 (Hopman et al., 2000). Canadian norms are higher than American norms in every domain of the SF-36, and higher than the United Kingdom norms in four domains, but the differences are quite small (Hopman et al., 2000). The Canadian Burden of Illness

Group (1998) used the SF-36 to compare the quality of life of MS patients with mild disease (EDSS ≤ 2.5) to the normal Canadian population. The MS participants' mean scores in all the SF-36 domains were much lower than the normal population, with all differences being statistically significant. In addition, the SF-36 has been used to measure HRQoL in clinical trials examining the impact of the four new medications on MS patients (Arnoldus, et al; 2000; Nortvedt et al., 2000a; Rice et al., 1999). The SF-36 has been used to monitor population health, estimate the burden of different conditions, measure treatment effects on HRQoL, and monitor outcomes in clinical practice (Ware, 1993).

4.5.2 Demographic and Socioeconomic Factors

The following potential explanatory demographic and socioeconomic, health, and MS specific factors were measured on the basis of their clinical or theoretical plausibility, or if prior research had identified the factor as having an association with HRQoL in MS participants (Table 4.1).

Table 4.1 Potential Explanatory Factors

Demographic & Socioeconomic Factors	**Health Factors**	**MS Specific Factors**
Sex Age Marital status Education level Total household yearly income Employment status Location of residence	Body mass index Fatigue severity Fatigue interference Depressive symptoms Comorbid medical conditions	Illness intrusiveness Disability level Number of MS attacks in past 6 months

The demographic and socioeconomic variables explored in the questionnaire included: *sex, age, marital status, education level, total household yearly income, employment status, and location of residence.*

Participants were asked to indicate their sex and date of birth. Age was calculated by subtracting each participant's birth date from the date they completed the questionnaire. Four categories were provided to the participants for indicating their current marital status: married / common law; separated / divorced; widowed; and single. Participants were asked to indicate their highest education level, which was divided into five categories: grade 8 or less; higher than grade 8, but did not graduate from high school; high school graduate; post secondary or some university; and university graduate. Participants were also asked to indicate their household's total yearly income before taxes. The categories offered were as follows: $0 to 20,000; $20,001 to 40,000; $40,001 to 60,000; and above $60,000.

Several options were presented for indicating employment status. The categories were: employed full-time; employed part-time; full-time homemaker; student; maternity leave; unemployed because of my MS; unemployed for reasons other than MS; workers compensation; disability or sick leave due to my MS; disability or sick leave for reasons other than my MS; retired due to my MS; and, retired for reasons other than my MS. The categories for current size of location of residence were: urban, which included large or small cities (population 5,000 to 100,000); or rural, which included towns (population 500 to 4,999), villages (population 100 to 499), rural municipality, or reserve.

4.5.3 Health Factors

The health factors explored in the questionnaire included: *body mass index, severity and interference of fatigue, self-reported depressive symptoms (as measured by the Beck Depression Inventory), and self-reported comorbid medical conditions* (Table 4.1). The participants were asked to provide their height and weight in order to calculate their body mass index (BMI). BMI is a measure of body weight in relation to height. It is calculated by dividing a person's weight in kilograms, by their height in meters squared (kg/m^2). BMI is one of the most accurate ways to determine when extra pounds translate into health risks (Calorie Control Council, 2002). BMI takes into account a person's weight and height to gauge total body fat in adults. Someone with a BMI of 26 to 27 is about 20 percent overweight, which is generally believed to carry moderate health risks. A BMI of 30 and higher is considered obese.

Questions were asked about participants' fatigue, based on the work conducted by Krupp et al. (1988) regarding fatigue in MS. Similar to the Krupp study, the participants were asked, "Are you bothered by fatigue? (Fatigue is defined as a feeling of tiredness, or having low energy levels.)". If the participants indicated yes, they were instructed to indicate the severity of the fatigue and how much their fatigue had interfered with their usual activities. The participants were asked to rate the severity of their fatigue on a scale of 0 to 10 where 0 means "no fatigue at all" and 10 means "fatigue as bad as it could be". The participants were then asked, "In the past four weeks, how much has your fatigue interfered with your usual activities rated on a 0 to 10 scale where 0 is 'no interference' and 10 is 'unable to carry on any activities'?". These questions regarding fatigue were important given Krupp et al.'s (1988) reference to work, which has shown that the fatigue in MS is perceived as different from the fatigue experienced prior to the development of MS. The fatigue severity rating and fatigue interference rating were both considered potential explanatory factors.

The short form of the Beck Depression Inventory (BDI) was used in this study. The BDI assesses the presence and severity of affective, cognitive, motivational, vegetative and psychomotor components of depression (Beck, 1967). The short form contains 13 of the 21 questions contained in the inventory, and is suitable for self-administration. Each question (item) reflects a particular symptom of depression. Respondents are asked to indicate the presence and severity of each symptom, in the past week, on a scale of 0 to 3. To score the BDI, the item scores are summed, ranging from 0 to 39, with higher scores reflecting greater severity of depressive symptoms.

Beck et al. (1988) reviewed research studies focusing on the psychometric properties of the BDI with psychiatric and nonpsychiatric samples for the years 1961 to June 1986. A meta-analysis of the BDI's internal consistency estimates resulted in a mean coefficient alphas of 0.86 for psychiatric patients and 0.81 for nonpsychiatric patients. The authors also examined the concurrent validities of the BDI with respect to clinical ratings and the Hamilton Psychiatric Rating Scale for Depression and found the mean correlations to be 0.72 and 0.73 respectively for the psychiatric patients, and 0.60 and 0.74 respectively for the nonpsychiatric patients. The BDI is a commonly used measure for assessing the presence of depressive symptoms amongst both psychiatric and nonpsychiatric patients.

The participants were asked about the presence and severity of other medical conditions in their lives using a self-report comorbidity questionnaire. The scale is reliable, has been validated against physician ratings and self-reported health quality of life, and has been used in a number of studies (Carroll et al., 2000; Carroll et al., 2002; Carroll et al., 2004; Côté et al., 2000a; Côté et al., 2000b; Côté et al., 2001; Jaroszynski et al., 1996; Mercado et al., 2000). Respondents are asked to indicate if they currently have any of the following conditions: muscle, bone, or joint problems; allergies; breathing problems; high blood pressure; heart and circulation problems; digestive system problems; diabetes; kidney, bladder, or urinary problems; neurological problems, in addition to MS; headaches; mental or emotional problems; cancer; gynecological problems; or blood problems. Examples are provided for each condition. Opportunity to list other problems is also provided. If the participants indicated they did have any of these conditions, they were instructed to indicate the degree to which the condition affects their health: not at all, mild, moderate, or severe. The questionnaire was scored by recoding each problem into three categories: no = 0 (reflecting those without the health problem); not at all or mild = 1 (reflecting those who reported having the health condition with no effect or a mild effect on their health); and moderate or severe = 2 (reflecting those who reported the health condition having a moderate or severe effect on their health).

4.5.4 MS Specific Factors

The MS specific factors explored in the questionnaire included: *illness intrusiveness (as measured by the self-reported Illness Intrusiveness Ratings Scale - IIRS), disability level (the Expanded Disability Status Scale (EDSS) as rated by a health care professional), and number of MS attacks in the last 6 months* (Table 4.1). The IIRS

(Devins et al., 1983) is a self-report instrument designed to ascertain the degree to which a participant's illness interferes with each of 13 life domains that have been identified as important to quality of life (Flanagan, 1982). The 13 domains are: work; active recreation; passive recreation; financial situation; relationship with spouse; sex life; family relations; other social relations; self-expression / self-improvement; religious expression; community and civic involvement; health; and, diet. Participants rate the level of intrusiveness into each life domain on a 7-point scale ranging from 1 = "not very much " to 7 = "very much". To score the scale, the item scores are summed, ranging from 13 to 91, with higher scores reflecting greater illness intrusiveness. The scale has been found to have strong psychometric properties (Devins et al. 1983), and has been used with the MS population in four studies conducted by Devins et al. (1987, 1993a, 1993b, 1993c).

Disability level was measured via the Kurtzke Expanded Disability Status Scale (EDSS). The EDSS (Kurtzke, 1983) was developed to follow the progression of MS disability and evaluate treatment results. The EDSS is a subjective measure based on the neurological exam. A health care provider, ideally experienced in caring for persons with MS, assigns a disability level score along a 0.5 increment scale ranging from 0.0 to 10.0, mainly based upon the functional ability of the MS patient (i.e. ambulation ability, ability to carry out daily activities). A score of 0.0 indicates a normal neurological exam, while a score of 10.0 indicates death. A score of 5.0 indicates the patient is ambulatory without aid for about 200 meters; disability impairs full daily activities. Ambiguities exist in the calculation of the EDSS score, thus making the scale subjective, and prone to intra-rater and inter-rater variability. The emphasis of the scale on physical capabilities means it neglects to assess for any cognitive or mental health dysfunction. The scale is ordinal in nature, and thus the meaning of a 1.0 change in disability level is different throughout the scale. Despite these shortcomings, the EDSS remains a widely used measure for assessing the progression of MS on a clinical basis, and for assessing current disability level for research purposes.

The final MS specific factor considered, as a possible explanatory variable was the number of MS attacks in the last six months. The participants were asked to indicate the number of attacks they had had based on the following definition of an attack: "… the appearance of new symptoms or worsening of old symptoms, lasting at least 24 hours, but with no fever. To be counted as an attack, your symptoms should have been stable for at least one month prior to the attack." This definition of an attack is that used currently by health care providers caring for persons with MS (O'Connor, 2002).

4.6 Statistical Analysis

Data analysis consisted of descriptive analyses and multivariate modeling. Means, standard deviations, and frequencies, were used for describing the characteristics of the MS sample, and also for describing how the sample scored on each of the measurements administered. Multivariable modeling was used for determining factors that were associated with the HRQoL of persons with relapsing-remitting MS.

The data were examined for small cell sizes. For those cell sizes that were less than five count, the category was examined to determine if it could be logically combined with another category to increase the size of the cell to greater than five. For those small cell sizes that could not be logically collapsed into other categories, the variable was eliminated from consideration. For example, if only one or two participants indicated they had a particular comorbid condition, then the condition would need to be eliminated from consideration since the variable would have an extremely skewed distribution.

Crude relationships between variables were examined with Pearson correlation coefficients for continuous measures; chi-square tests for associations between categorical measures; and t-tests and analysis of variance for associations between continuous and categorical measures. The variables were assessed for colinearity by examining the tolerance and variance inflation factors of the variables being considered for inclusion in the final models. When two or more variables were highly associated and appeared to be measuring the same construct, a decision was made about which variable to use in the multivariable models based on prior research and clinical experience.

The strategy for model building was as follows. Given the continuous nature of the SF-36 summary scale scores, multiple linear regression was employed for building two models. One model was built with the physical health summary score as the dependent variable, and the other model with the mental health summary score as the dependent variable. Possible explanatory variables included the demographic and socioeconomic factors, health factors, and MS specific factors.

Crude (single main effects) models were built as an initial step to guide the selection of variables that would be included in the multiple linear regression analyses. Variables that were categorical in nature (e.g. marital status, employment status, comorbid conditions) were dichotomized in order to enter them into the multiple linear regression models. Those possible explanatory factors that proved to have a crude relationship with the dependent variables at $p \leq 0.10$ were considered in the final models.

The possible explanatory factors were then systematically placed into multiple linear regression models for determining which variables continued to have a strong relationship with the dependent variables. Variables were retained in the final model if they had a p value ≤ 0.05 in that model. Explanatory variables not found to be statistically significant at the $p \leq 0.05$ level of significance were dropped from the final model one by one to assess whether excluding them in the final model affected the relationship between the remaining explanatory variables and the outcome. Furthermore, the variables were evaluated in light of the other variables included in the model. Decisions regarding whether to exclude any of the variables from the final model were made on the basis of its judged importance and also with consideration of goodness of fit of the model.

All first-order interactions between the explanatory variables composing the final models were also examined for possible inclusion. Those interactions having a relationship with the dependent variable of interest at the $p \leq 0.10$ level of significance were added to the final model to determine if the interaction remained significant in the final model at the $p \leq 0.05$ level of significance. Any interaction meeting this criterion was retained in the final model.

The variables considered for the physical HRQoL model are listed in Table 4.2. The decision was made to exclude the fatigue interference rating and the IIRS total score from the physical health model due to the conceptual relation between these independent variables and the dependent variable.

The variables considered for the mental HRQoL model are listed in Table 4.3. The decision was made to exclude depressive symptomology, as measured by the BDI, and the comorbid condition of mental / emotional health problems due to the conceptual relation between these independent variables and the dependent variable.

Table 4.2 Factors Considered for the Physical HRQoL Model

Demographic Factors	**Socioeconomic Factors**	**Health Factors**	**MS Specific Factors**
Age Sex Marital status	Education level Employment status Total household income Location of residence	Body mass index Fatigue severity Depressive symptoms (BDI Total Score) Comorbid conditions	Disability (EDSS score) Number of attacks in the past six months

Table 4.3 Factors Considered for the Mental HRQoL Model

Demographic Factors	**Socioeconomic Factors**	**Health Factors**	**MS Specific Factors**
Age Sex Marital status	Education level Employment status Total household income Location of residence	Body mass index Fatigue interference Fatigue severity Comorbid conditions	Disability (EDSS score) Number of attacks in the past six months Illness intrusiveness (IIRS total score)

5. RESULTS

5.1 Sample

During the study's inception period of December 12, 1997 to February 25, 2000, 292 Saskatchewan residents with relapsing-remitting MS were approved for drug coverage under the Exceptional Drug Status Plan. The majority of the eligible participants consented to complete the baseline questionnaire (90% of 292), resulting in a sample of 262 participants. Of these 262 participants, six participants indicated they had been on the medication for more than 14 days, and thus were excluded from the analysis. The sample for this study thus consists of 256 participants.

5.2 Sample Characteristics

Descriptive statistics for the demographic and socioeconomic variables are presented in Table 5.1. The average age of the study participants was 38.9 years with most participants being between 30 and 49 years. Most of the participants were female (70.7%), married or living common law (69.5%), and had post secondary or some university education (37.9%). Only one person indicated they were widowed, so the categories of separated / divorced and widowed were combined into one category, resulting in three categories of marital status for descriptive analysis purposes. Since only seven participants had grade eight or less, this category was combined with the category: "higher than grade eight, but did not graduate from high school", resulting in four categories for education level for descriptive analysis purposes.

A total household income of $20,001 to $40,000 was the most common income range reported amongst the participants (31.9%), and nearly two-thirds of the sample lived in an urban setting (60.5%). The greatest proportion of the participants were

Table 5.1 Demographic and Socioeconomic Characteristics of Study Sample (N=256)

Demographic and Socioeconomic Factors		**Study Sample n* (%)**
Age: mean (SD†)		38.9 (8.8)
	18-29	40 (15.6)
	30-39	99 (38.7)
	40-49	88 (34.4)
	50-67	29 (11.3)
Sex		
	Male	75 (29.3)
	Female	181 (70.7)
Marital Status		
	Married / Common Law	178 (69.5)
	Separated / Divorced / Widowed	27 (10.5)
	Single	51 (19.9)
Education Level		
	Grade 8 or less / Did not graduate	31 (12.1)
	High school graduate	75 (29.3)
	Post secondary / Some university	97 (37.9)
	University graduate	53 (20.7)
Total Household Income		
	\$0 – 20,000	53 (21.4)
	\$20,001 – 40,000	79 (31.9)
	\$40,001 – 60,000	61 (24.6)
	Above \$60,000	55 (22.2)
Employment Status		
	Employed full-time	97 (37.9)
	Employed part-time	39 (15.2)
	Full-time homemaker	28 (10.9)
	Not working due to MS‡	73 (28.5)
	Other§	19 (7.4)
Employment Affected by MS		
	No	118 (46.8)
	Yes	134 (53.2)
Location of Residence		
	Urban	155 (60.5)
	Rural	101 (39.5)

*Some missing data: 8 cases are missing from total household income; 4 cases are missing from employment affected by MS

†SD refers to standard deviation

‡Unemployed, on disability, on sick leave, or retired due to MS

§Student / maternity leave / WCB claimant / unemployed, on disability, on sick leave, retired not due to MS employed full-time (37.9%), followed by not working due to MS (28.5%). Due to small cell sizes in nine of the possible employment status categories, these categories were collapsed into two categories: not working due to MS and other. The category of not working due to MS included: unemployed, on disability or sick leave, or retired due to MS. The other category included: student; maternity leave; workers compensation; unemployed, on disability or on sick leave, or retired, for reasons other than the participant's MS. Thus, five categories remained regarding present employment status: employed full-time, employed part-time, full-time homemaker, not working due to MS, and other. Greater than half the sample indicated their employment was affected by their condition (53.2%).

Descriptive statistics for the health factors are found in Table 5.2a and 5.2b. Nearly all participants indicated that they were bothered by fatigue (88.9%). The mean score on the 11-point fatigue severity rating scale (0 to 10) was 4.6, with a modal score of 7. The mean score on the 11-point fatigue interference rating scale (0 to 10) was 4.1, with a score of 0 being the modal score.

The most common comorbid conditions reported were headaches; muscle, bone, or joint problems; mental or emotional problems; and not surprisingly, given the symptomology of MS, also kidney, bladder, or urinary problems. The least common comorbid conditions reported were cancer, blood problems, diabetes, and high blood pressure. A few participants indicated they had endocrine problems, and so these problems were included with the category of neurological problems, forming a new category of neurological and endocrine problems. Whenever possible, the "other problems" listed by the participants were placed into one of the appropriate listed

Table 5.2a Health Characteristics of Study Sample (N=256)

Health Characteristic		**Study Sample***
BMI, mean (SD†); range‡		25.1 (4.7); 15.8-44.6
Bothered by fatigue, n (%)	No	28 (11.1)
	Yes	224 (88.9)
Fatigue severity rating, mean (SD); range		4.6 (2.6); 0-10
Fatigue interference rating, mean (SD); range		4.1 (2.9); 0-10
BDI, mean (SD); range:		6.1 (4.8); 0-30

*Some missing data: 5 cases missing from BMI; 4 cases missing from bothered by fatigue; 54 cases missing from fatigue severity rating and fatigue interference rating

†SD refers to standard deviation

‡Range refers to the range in the sample

Table 5.2b Comorbid Conditions of Study Sample (N=256)

Comorbid Condition	**Category***	**n† (%)**
Muscle, bone, or joint problems		
	None	116 (45.5)
	Not at all or Mild	77 (30.2)
	Moderate or Severe	62 (24.3)
Allergies		
	None	162 (63.5)
	Not at all or Mild	71 (27.8)
	Moderate or Severe	22 (8.6)
Breathing problems		
	None	199 (78.0)
	Not at all or Mild	46 (18.0)
	Moderate or Severe	10 (3.9)
High blood pressure		
	None	239 (93.7)
	Not at all or Mild	14 (5.5)
	Moderate or Severe	2 (0.8)
Heart and circulation problems		
	None	228 (89.4)
	Not at all or Mild	23 (9.0)
	Moderate or Severe	4 (1.6)

Digestive system problems		
	None	185 (73.1)
	Not at all or Mild	43 (17.0)
	Moderate or Severe	25 (9.9)
Diabetes		
	None	251 (98.4)
	Not at all or Mild	2 (0.8)
	Moderate or Severe	2 (0.8)
Kidney, bladder or urinary problems		
	None	140 (54.9)
	Not at all or Mild	70 (27.5)
	Moderate or Severe	45 (17.6)
Endocrine and Neurological problems (except MS)		
	None	216 (84.7)
	Not at all or Mild	25 (9.8)
	Moderate or Severe	14 (5.5)
Headaches		
	None	97 (38.0)
	Not at all or Mild	99 (38.8)
	Moderate or Severe	59 (23.1)
Mental or emotional problems		
	None	151 (59.4)
	Not at all or Mild	74 (29.1)
	Moderate or Severe	29 (11.4)
Cancer		
	None	251 (98.8)
	Not at all or Mild	1 (0.4)
	Moderate or Severe	2 (0.8)
Gynecological problems		
	None	208 (81.9)
	Not at all or Mild	36 (14.2)
	Moderate or Severe	10 (3.9)
Blood problems		
	None	251 (98.8)
	Not at all or Mild	2 (0.8)
	Moderate or Severe	1 (0.4)

*Not at all or mild refers to comorbid health problems with no effect or mild effect on health. Moderate or severe effect refers to comorbid health problems with moderate or severe effect on health.

†Some missing data: 1 case missing from muscle, bone, or joint problems; allergies; breathing problems; high blood pressure; heart and circulation problems; diabetes; kidney, bladder or urinary problems; neurological and endocrine problems; and headaches; 2 cases missing from mental or emotional problems, cancer, gynecological problems, and blood problems; 3 cases missing from digestive system problems.

conditions. Several of the other problems listed related to MS, such as blurred vision and loss of balance, so these were not recoded.

Five of the comorbid conditions had at least one cell size less than five (high blood pressure, heart and circulation problems, diabetes, cancer, and blood problems), but only the high blood pressure and heart and circulation problems variables could be recoded to make the cell sizes greater than five. For these comorbid conditions, the categories of "not at all or mild" and "moderate or severe" were combined to form a "yes" category. The comorbid conditions of cancer, blood problems, and diabetes were excluded from the list of possible explanatory factors of the dependent variables because fewer than five individuals endorsed these conditions.

Descriptive statistics for the MS specific factors are found in Table 5.3. The average score on the Illness Intrusiveness Ratings Scale (IIRS) was 38.1, of a possible range of 13 to 91, with a score of 19 being the most common. The average disability level score (EDSS) was 2.4, with a score of 2.0 being the most common (19.5%). An EDSS score of 2.0 is defined by Kurtzke (1983) as minimal disability in one functional system (i.e., pyramidal, cerebellar, brain stem, sensory, visual, bladder/bowel, cerebral, and other), while a score of 2.5 is defined as minimal disability in two functional systems. The mean number of MS attacks in the past 6 months was 1.6, with most participants having had only one attack (42.2%), which is typical of a relapsing-remitting disease course (Halper, 2001).

Table 5.3 MS Specific Characteristics of Study Sample (N=256)

MS Specific Characteristic*	Mean (SD†)	Range‡
Illness Intrusiveness Scale Total Score	38.1 (16.0)	13-79
Disability Level (EDSS)	2.4 (1.3)	0-6.5
MS Attacks in Past 6 Months	1.6 (1.2)	0-8

*Some missing data: 60 cases missing from IIRS, 4 cases missing from EDSS, 2 cases missing from number of attacks; †SD refers to standard deviation; ‡Range refers to the range in the sample

Descriptive statistics for the two dependent variables of interest are presented in Table 5.4. The average score on the physical health summary scale of the SF-36 Health Status Survey was 39.4, out of a possible range of 0 to 100. The scores ranged from 15.7 to 59.5. The average score on the mental health summary scale of the SF-36 Health Status Survey was 47.2. The scores ranged from 16.1 to 68.0. Women had slightly lower mean physical and mental health summary scale scores then the men: 39.2 and 47.0 versus 39.7 and 47.8 respectively. Histograms and scatter plots of the dependent variables are presented in Figures 5.1 to 5.4.

Table 5.4 Physical and Mental Health Summary Scale Scores in Study Sample (N=256)

Summary Scale*	Mean (SD†)	Median	Range	25, 50, 75th Percentiles		
Physical Health	39.4 (10.1)	39.1	15.7-59.5	31.7	39.1	47.4
Mental Health	47.2 (10.3)	49.4	16.1-68.0	40.1	49.4	55.6

*Some missing data: 1 case missing from both summary scales.
†SD refers to standard deviation.

5.3 Statistical Assumptions

Descriptive statistics, including frequencies, means, standard deviations, and ranges, were used along with histograms and normal probability plots whenever appropriate, to assess for outliers and test the normality assumption. Review of the statistics and graphs indicated that the physical health summary scale dependent variable followed an adequately normal distribution, and that no responses to any of the variables fell outside of the expected range (Figure 5.1). Review of the statistics and graphs indicated that the mental health summary scale dependent variable was slightly skewed to the right (Figure 5.2). However, since the normality approximation works well in large samples, and the skewing was slight, the decision was made to analyze the variable without performing any transformations in order to avoid distortions of the clinical data. The normal probability plots confirmed the linear nature of the two dependent variables, namely the physical and mental health summary scales.

Regression diagnostics were performed for validating the assumptions of normality, linearity, and equality of variances of both the physical and mental health final models. Studentized deleted residuals were plotted against unstandardized predicted values for both models (Figures 5.3 and 5.4). The resulting graphs indicated the models met the assumptions of a multiple linear regression. Specifically, the normal Q-Q plots show that both models met the normality assumption since the points cluster around the straight lines.

Colinearity statistics for both models reported the tolerance and variance inflation factors to be around the 1.0 mark indicating relative independence of the factors in the model. No significant outliers were revealed in any of the graphs assessing for the presence of outliers in the dependent and independent variables.

Figure 5.1 Physical Health Summary Scale Histogram

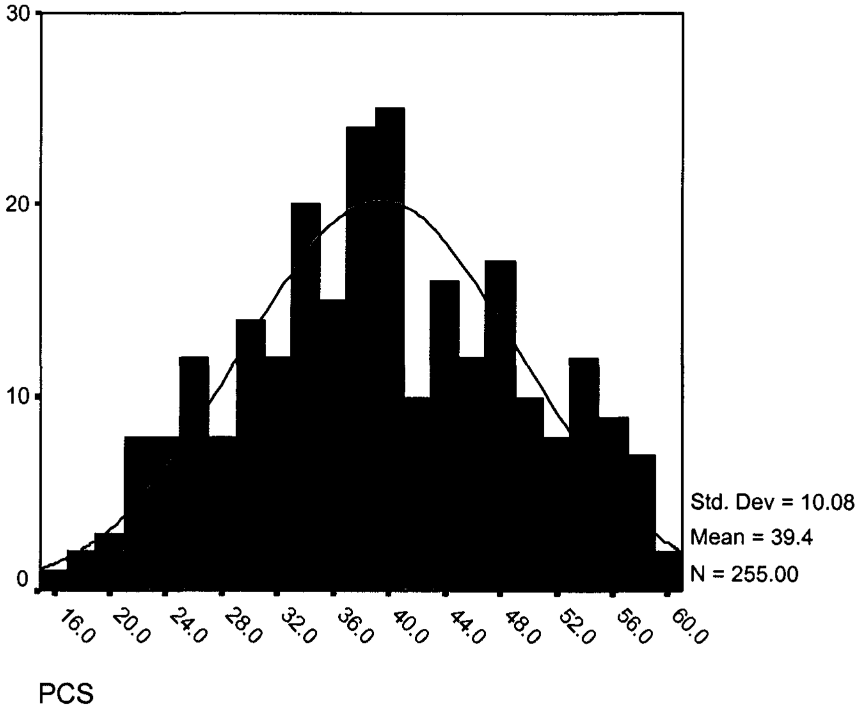


Figure 5.2 Mental Health Summary Scale Histogram

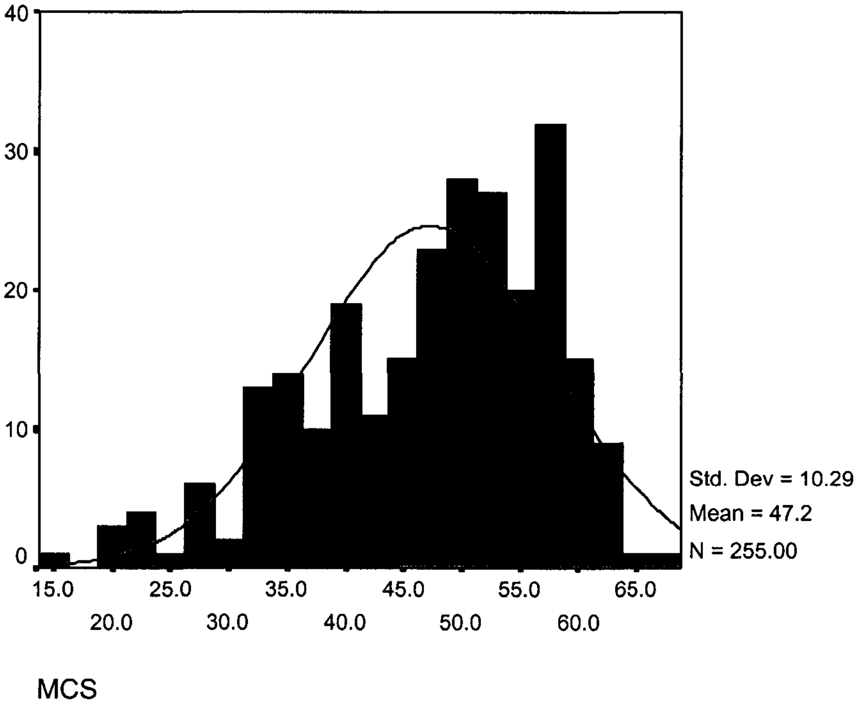


Figure 5.3 Physical Health Summary Scale Normal Q-Q Plot

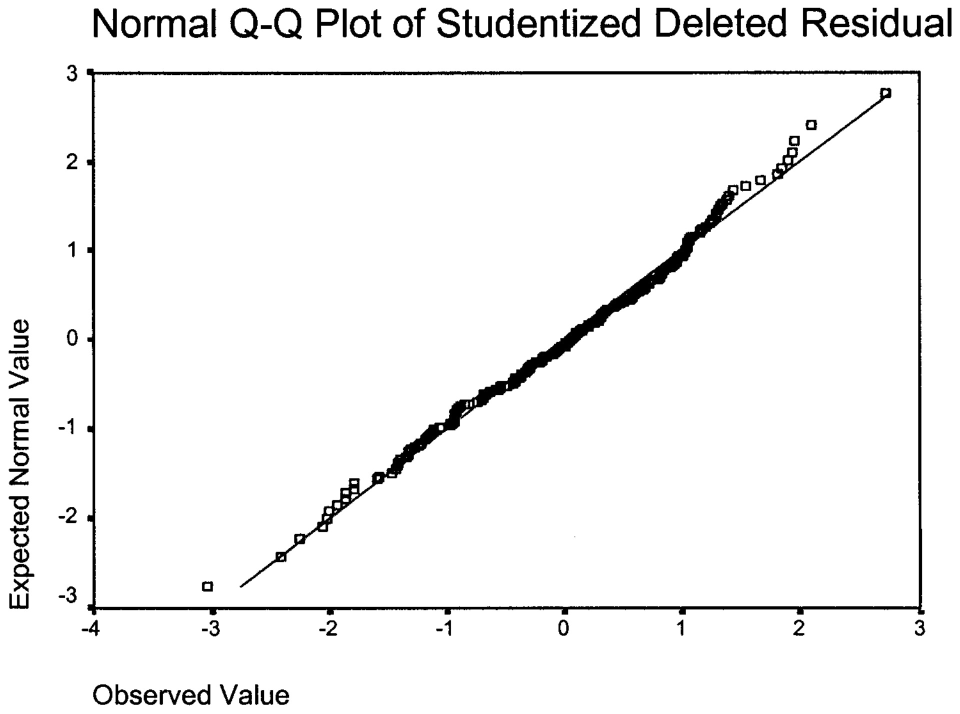
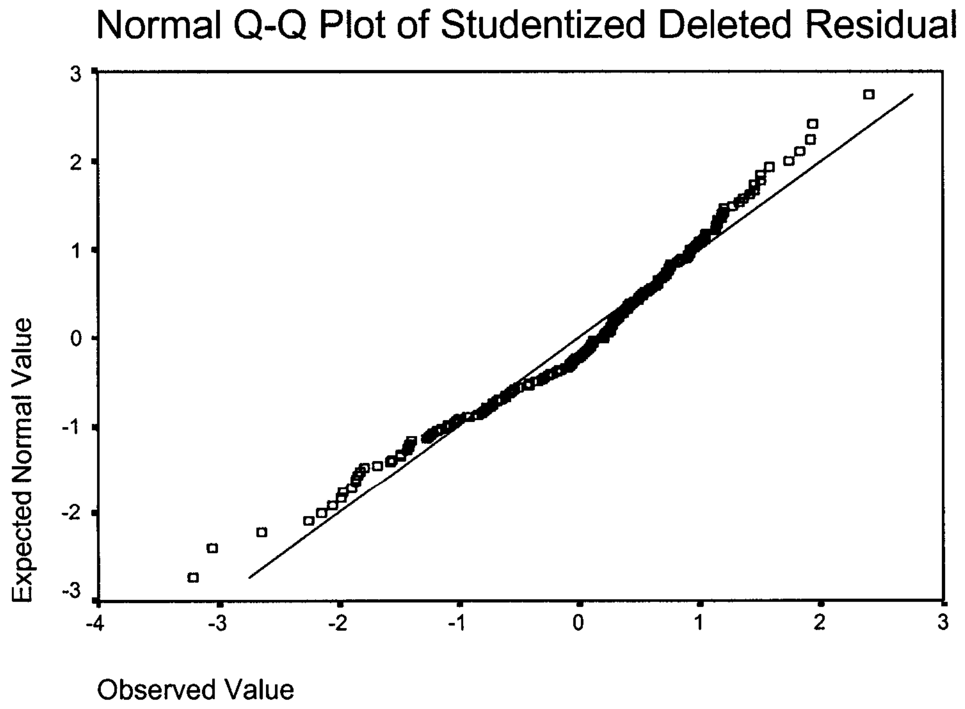


Figure 5.4. Mental Health Summary Scale Normal Q-Q Plot



5.4 Physical Health-related Quality of Life Model

Crude models were built for identifying those factors that are associated with the physical health component summary scale (PCS) of the SF-36 Health Status Survey. For the multiple linear regression analysis purposes, for both the physical and mental HRQoL models, marital status was dichotomized into married / common law and separated / divorced / widowed / single. Education status was dichotomized into grade 8 or less / did not graduate / high school graduate and post-secondary / some university / university graduate. Total household income was dichotomized into $0 to 40,000 and $40,001 and above. Employment status was dichotomized into either not working due to MS or employed / other (employed full-time, employed part-time, full-time homemaker, or other employment situation such as student). The comorbid conditions were recoded into either do not have the condition, or have the condition.

Fourteen variables were found to have an important independent relationship with the PCS at $p \leq 0.10$. Sex did not have a statistically significant association with the PCS ($p = 0.703$), but because of its biological and clinical importance, it was retained for inclusion in the final model. Including sex, 15 variables remained as possible explanatory variables of the PCS (Table 5.5).

Because the number of explanatory variables was high in comparison with the sample size, the 15 variables were grouped into three domains, and domain-specific multivariable models were built as an intermediary step in developing the final model. Explanatory variables in each domain-specific model having an association with PCS at the $p \leq 0.10$ were then entered into the final model. The first domain included the demographic and socioeconomic variables; the second, all the comorbid conditions; and

Table 5.5 Crude Associations Between Explanatory Factors and Physical and Mental Health Summary Scale Scores

Independent Variable	Dependent Variable	R Square	Adjusted R Square	F	Sig
Demographic and Socioeconomic Variables:					
Age	PCS	.057	.053	15.319	.000
	MCS	.008	.004	1.991	.159
Sex	PCS	.001	-.003	.146	.703
	MCS	.001	-.003	.285	.594
Marital status	PCS	.003	-.001	.694	.406
	MCS	.013	.009	3.349	.068
Education	PCS	.023	.019	5.913	.016
	MCS	.000	-.004	.004	.951
Employment Status	PCS	.137	.133	40.048	.000
	MCS	.035	.032	9.277	.003
Income	PCS	.007	.003	1.785	.183
	MCS	.001	-.003	.293	.589
Residence	PCS	.000	-.004	.008	.929
	MCS	.004	.000	1.122	.291
Health Variables:					
BMI	PCS	.015	.011	3.873	.050
	MCS	.000	-.004	.000	.996
Fatigue severity rating	PCS	.304	.301	87.453	.000
	MCS	.069	.065	14.910	.000
Fatigue interference rating	PCS*	N/A	N/A	N/A	N/A
	MCS	.047	.043	9.952	.002
BDI	PCS	.091	.088	25.385	.000
	MCS*	N/A	N/A	N/A	N/A
Muscle, bone, or joint problems	PCS	.084	.080	23.092	.000
	MCS	.004	.000	.934	.335
Allergies score	PCS	.001	-.003	.217	.642
	MCS	.001	-.003	.139	.709
Breathing problems	PCS	.035	.031	9.085	.003
	MCS	.002	-.002	.528	.468

High blood pressure	PCS	.000	-.004	.000	.989
	MCS	.005	.001	1.187	.277
Heart and circulation problems	PCS	.011	.007	2.756	.098
	MCS	.002	-.002	.482	.488
Digestive system problems	PCS	.072	.069	19.537	.000
	MCS	.027	.023	7.017	.009
Kidney, bladder, or urinary problems	PCS	.088	..085	24.458	.000
	MCS	.021	.018	5.539	.019
Neurological or endocrine problems	PCS	.013	.009	3.253	.073
	MCS	.002	-.002	.600	.439
Headaches	PCS	.017	.013	4.383	.037
	MCS	.031	.027	8.040	.005
Mental or emotional problems	PCS	.004	.001	1.133	.288
	MCS*	N/A	N/A	N/A	N/A
Gynecological problems	PCS	.009	.005	2.376	.124
	MCS	.003	-.001	.780	.378
Illness Related Variables:					
IIRS	PCS*	N/A	N/A	N/A	N/A
	MCS	.089	.084	18.907	.000
Disability level (EDSS)	PCS	.119	.115	33.556	.000
	MCS	.002	-.002	.576	.449
MS attacks	PCS	.056	.052	14.954	.000
	MCS	.006	.002	1.520	.219

*Crude analysis not conducted because independent variable measures same general construct as dependent variable the third, all the health and MS specific variables, found to have important crude relationships with the PCS.

The three domain multivariate models resulted in 12 possible explanatory variables to include in the final model: sex, age, education level, employment status, muscle / bone / joint problems, breathing problems, digestive system problems, kidney / urinary / bladder problems, BMI, fatigue severity rating, disability level (EDSS score), and number of attacks in the past six months (Tables 5.6-5.8). A model was created by entering all the above 12 variables into a linear regression analysis. Sex, education level, digestive system problems, kidney / urinary / bladder problems, and BMI were not found to be statistically significant. Sex however was retained in the model due to its clinical and biological importance.

Table 5.6 Demographic and Socioeconomic Factors Associated with Physical HRQoL

Variable	**ß***	**SE† (ß)**	**Sig**
Constant	39.573	3.117	.000
Males	-1.464	1.280	.254
Age	-.199	.067	.003
Post-secondary / Some University / University Graduate	2.872	1.184	.016
Employed / Other (FT, PT, Homemaker, or Other such as Student)	7.596	1.284	.000

*Model specifications: R Square = 0.190, Adjusted R Square = 0.177, F-statistic = 14.689, p=0.000.
ß-coefficients adjusted for all other factors in the model.
†SE refers to standard error

Table 5.7 Comorbid Conditions Associated with Physical HRQoL

Variable	**ß***	**SE†(ß)**	**Sig**
Constant	45.270	1.136	.000
Muscle, bone, joint problems	-4.009	1.263	.002
Breathing problems	-3.075	1.438	.033
Digestive system problems	-3.453	1.411	.015
Kidney, bladder, urinary problems	-4.238	1.233	.001
Neurological / endocrine problems	-1.186	1.648	.473
Headaches	-.059	1.285	.963

*Model specifications: R Square = 0.190, Adjusted R Square = 0.170, F-statistic = 9.591, p=0.000.
ß-coefficients adjusted for all other factors in the model. †SE refers to standard error.

Table 5.8 Health and MS Specific Factors Associated with Physical HRQoL

Variable	ß*	SE†(ß)	Sig
Constant	60.856	3.592	.000
BDI total score	-.129	.136	.344
BMI	-.255	.128	.047
Fatigue rating	-1.763	.254	.000
EDSS	-1.758	.487	.000
MS attacks	-1.225	.530	.022

*Model specifications: R Square = 0.383, Adjusted R Square = 0.367, F-statistic = 23.117, p=0.000. ß-coefficients adjusted for all other factors in the model.
†SE refers to standard error

The remaining eight significant variables were entered into a model: sex, age, employment status, muscle / joint / bone problems, breathing problems, fatigue severity rating, EDSS score, and number of MS attacks in the past six months. Except for sex, all of these variables had significance levels less than 0.05. The results are presented in Table 5.9. All of the first-order interactions between these eight variables were tested to determine if any of them might be of significance. However, none of the interactions proved to be significant at the $p \leq 0.10$ level of significance when entered into a crude (main effects) model with the PCS as the dependent variable.

The estimated beta coefficients for the factors in the final PCS model can be interpreted as follows (Table 5.9). Women may have slightly worse PCS scores than men. Older persons have worse PCS scores than younger persons. Those who are not working because their MS have worse PCS scores than those who are working part-time, full-time, as homemakers, or in another employment situation such as on maternity leave. Those participants who reported having muscle, joint, or bone problems, or breathing problems, have worse PCS scores than those participants who do not have these conditions. For those participants with higher (worse) fatigue severity, higher (worse) EDSS scores, and more MS attacks, the PCS score is worse.

In summary, the factors that were found to have a negative association with the PCS are: female sex, increasing age, not working due to MS, muscle / bone / joint problems, breathing problems, increasing severity of fatigue, increasing severity of disability, and increasing frequency of MS attacks in the past six months. Taken together, the eight variables in the PCS model explain 47.4% of the variance in the PCS (Table 5.9).

Table 5.9 Factors Associated with Physical HRQoL

Variable	ß*	SE†(ß)	Sig
Constant	56.807	3.300	.000
Males	.255	1.262	.840
Age	-.146	.067	.032
Employed / Other (FT, PT, Homemaker, or Other such as Student)	4.780	1.339	.000
Muscle, joint, or bone problems	-4.694	1.121	.000
Breathing problems	-3.410	1.409	.017
Fatigue severity rating	-1.335	.234	.000
EDSS	-1.507	.469	.002
MS attacks	-1.381	.495	.006

*Model specifications: R Square = 0.495, Adjusted R Square = 0.474, F-statistic = 22.927, p=0.000. ß-coefficients adjusted for all other factors in the model.
†SE refers to standard error

5.5 Mental Health-related Quality of Life Model

Crude (single main effects) models were built for identifying those factors that are associated with the mental health component summary scale (MCS) of the SF-36 Health Status Survey. Eight of the independent variables met our criteria for consideration in the final model (Table 5.5). Age and sex did not prove to have statistically significant associations with the MCS (p = 0.159 and 0.594 respectively), but were retained in the final model because of their biological importance. Thus, ten variables were considered as possible explanatory factors of the MCS.

Employment status, fatigue severity, fatigue interference, IIRS total score, and marital status were not significant at the $\alpha = .05$ level of significance. Each of these nonsignificant variables were dropped from the model separately to determine if the significance level of the other nine variables would change given the variable's exclusion from the model. The significance levels did not change when employment status and fatigue interference were dropped from the model. Thus, these two variables were dropped from inclusion in the final model. However, the significance levels of the variables did change when fatigue severity, IIRS total score, and current marital status were each dropped from the model. The IIRS total score variable appeared to have the greatest possible influence on the explanatory power of the model, and thus, the decision was made to retain the IIRS total score in the model while dropping the fatigue severity and current marital status variables.

A final model was constructed consisting of six variables: sex, age, digestive system problems, kidney / bladder / urinary problems, headaches, and IIRS total score. Except for sex, all these variables had significance levels less than 0.05. All of the individual first-order interactions between these six variables were tested, to determine if any of them was significant at the $p \leq 0.10$ level of significance, by entering them into crude (main effects) models with MCS as the dependent variable. The interaction between sex and age proved to be significant ($p=0.010$). Thus, this interaction term was included in the final MCS model. The results are presented in Table 5.10. The variable sex became significant with the addition of this interaction term.

The estimated beta coefficients for the factors in the final MCS model can be interpreted as follows (Table 5.10). Those participants who reported having digestive system problems, kidney/bladder/urinary problems, and or headaches, have worse MCS scores than those participants who do not have any of these conditions. In regards to illness intrusiveness, as the level of illness intrusiveness increases, there is a corresponding decrease (worsening) in MCS score. Finally, in regards to the sex and age of the participants, younger women have worse MCS scores than older women. The reverse is true for men however. Younger men have better MCS scores than older men.

In summary, the factors that were to found to have a negative association with the MCS are: getting older for males, but being younger for females, increasing severity of illness intrusiveness, digestive system problems, kidney/bladder/urinary problems, and headaches. Taken together however, the variables in this MCS model explain only 22.1% of the variance in the MCS (Table 5.10).

Table 5.10 Factors Associated with Mental HRQoL

Variable	**ß***	**SE†(ß)**	**Sig**
Constant	42.844	3.591	.000
Males	-20.815	7.229	.004
Age	-.751	.328	.023
Digestive system problems	-6.736	2.121	.002
Kidney, bladder, or urinary problems	-4.393	1.770	.014
Headaches	-3.142	1.496	.037
IIRS total score	-.119	.045	.009
Sex*Age interaction	.513	.180	.005

*Model specifications: R Square = 0.249, Adjusted R Square = 0.221; F-statistic = 8.851, p=0.000. ß-coefficients adjusted for all other factors in the model.
†SE refers to standard error

6. DISCUSSION

6.1 Purpose of the Present Study

The aim of this study was to explore the health-related quality of life (HRQoL) of Saskatchewan adults with relapsing-remitting MS. This was accomplished by describing their HRQoL, and by delineating the factors associated with the physical and mental health components of their HRQoL.

6.2 Sample of the Present Study

6.2.1 Demographic and Socioeconomic Characteristics

The sample consisted mainly of married women in their late thirties. Given that women are more likely to have a relapsing-remitting course of MS than men by a ratio of 3:1, the average age of diagnosis is 30 years of age, and the average length of having a relapsing-remitting course is 5 to 25 years (before becoming secondary progressive), this result is not surprising (Vollmer, 1999; Warren et al., 2001). There is some speculation that persons with MS have a higher rate of divorce than the general population, but there is conflicting evidence in the scientific literature. Only 11% of the participants were separated / divorced / widowed in this study.

Very few of the participants did not graduate from high school, which is not unexpected given the present day's minimum requirement for gainful employment. The finding that the most common reported total household income before taxes was $20,001 to 40,000 (32%) is consistent with the provincial income statistics for Saskatchewan. In 2002, the average income was $23, 405 (Saskatchewan Bureau of Statistics, 2003). The finding that 60.5% of the participants lived in an urban location is also consistent with provincial statistics. In 2001, 64.3% of the Saskatchewan population lived in an urban location (Saskatchewan Bureau of Statistics, 2003).

As of July 1, 2002, just over 1 million people lived in Saskatchewan, with about half of the population comprising the labor force. Of these half-a-million persons, only 5.7% were unemployed (Saskatchewan Bureau of Statistics, 2003). In this study, only 53.1% were employed full-time or part-time, with almost 30% not working because of their disease.

6.2.2 Health Characteristics

Fatigue is a concern for this sample, with almost 90% indicating they are bothered by fatigue. On both the fatigue severity and fatigue interference rating scales, the participants indicated their average level of fatigue severity and interference was approximately in the middle of the 11-point scales. The most common score on the fatigue severity scale was 7, while the most common score on the fatigue interference scale was 0. For most participants then, fatigue is a present and bothersome symptom, yet one that does not stop them from carrying out their day to day activities.

Unfortunately there were some missing responses from the fatigue severity and interference rating scales. Of the 224 participants who were to answer these questions because they indicated they were bothered by fatigue, 22 of them did not answer. Whether this introduces a possible response bias is difficult to assess. Perhaps it was due to a misinterpretation of the skipping pattern in this section of the questionnaire, perhaps they could not choose a value to circle on the 11-point visual analog scales, or perhaps they did not want to answer because of their fatigue. If their fatigue was quite bothersome, the final anchors of the scales would have provided them with an appropriate description of their fatigue, as would the initial anchors have provided an appropriate description if their fatigue did not bother them at all. When a person is fatigued however, it is often difficult to concentrate, and thus those who did not answer these questions may have done so because of their fatigue.

Mild depressive symptoms were found in the majority of participants, as the average score on the short-form of the BDI was 6.1. Beck et al. (1974) provide the following reference ranges for interpretation of the short-form of the BDI: 0-4, none or minimal; 4-7, mild; 8-15, moderate; 16+, severe depressive symptoms. Certainly some of participants had severe depressive symptoms, scoring as high as 30, while others had none, scoring as low as 0. All participants were screened for severe depression before being allowed to being drug treatment. Depression is not a static condition however, and thus participants could have developed depressive symptoms subsequently to being approved for the medication. It is perhaps worthy to note that depression is not uncommon in the MS population. It is estimated that 50% of persons with MS will have a diagnosis of major depression at some point during their disease course (Wang et al., 2000).

Given the symptomology of MS, it is not surprising that muscle, bone, or joint problems, and kidney, bladder, or urinary problems were among those comorbid conditions most commonly reported by the sample. Restrictions in mobility can certainly contribute to muscle, bone, or joint problems. The presence of a neurogenic bladder is very common in the MS population due to innervation of the autonomic nerve pathways. Headaches and mental and emotional problems were also commonly reported. Given the variability and unpredictability of MS, this is not an unexpected finding either. All of these comorbid conditions could certainly be caused from other illnesses other than MS as well, as having MS does not preclude a person from being diagnosed with another condition.

6.2.3 MS Specific Characteristics

Devins et al. (1993c) found that greater illness intrusiveness was associated with a chronic progressive course (as compared to relapsing-remitting), greater severity of MS as measured by the EDSS, greater physical disability as indicated by fatigue and the Sickness Impact Profile physical subscale, and higher numbers of stressful life events. Devins included chronic progressive participants in his study, and the average score on the IIRS was 43.5. MS was found to be more intrusive than rheumatoid arthritis and end-stage renal disease in another study conducted by Devins et al. (1993b), with IIRS scores of 42.6, 37.9, and 38.8 respectively. Chronic progressive MS participants were included in that study also. In a study conducted by Shawaryn et al. (2002), of which 51% of the sample had relapsing-remitting MS, the average score on the IIRS was 40.0.

In this study, the average score on the IIRS was 38.1. Given that no progressive participants were included in the study, it is not surprising that the average score is somewhat lower than the scores reported in Devins and Shawaryn studies. Each of the 13 questions of the IIRS have a scale from 1 to 7 where 1 = not very much and 7 = very much. The participants are thus averaging a score of a little less than 3 on each question to get an overall average of 38.1.

Unfortunately, a large number of cases were missing for the IIRS. Sixty persons did not complete the IIRS questionnaire. Given that this questionnaire addresses the impact of the illness on 13 different life domains found to be important to people, this large percentage of missing cases is indeed unfortunate (23%). Once again this raises the issue of response bias. If those who did not answer this questionnaire did so because they did not want to express how much their illness was interfering with their life, then the results have underestimated the degree to which MS is negatively impacting the participants' lives. The reverse is also possible, namely that those who did not answer did so because their MS is not a concern for them, and thus did not feel the need to complete the questionnaire. The results would then be overestimating the negative impact of the illness.

One hundred ninety-six participants completed the IIRS questionnaire however, which is a greater number than had been enrolled in the Devins (1993b, 1993c) and Shawaryn (2002) studies (N=94, 94, and 90 respectively). The results from this questionnaire should not be discounted despite the possible response bias.

The average EDSS score of 2.4 indicates the participants had minimal disability and were fully ambulatory (Kurtzke, 1983). The mean number of attacks is consistent with the natural history data of the relapsing-remitting course of MS, with the majority of the participants having only attack in the past six months (Halper, 2001).

6.2.4 Health-related Quality of Life (SF-36 Summary Scales) Characteristics

As mentioned in the methods section, normative data for the Canadian population indicate that women have slightly lower mean SF-36 physical and mental health summary scale scores then Canadian men: 50.5 and 51.7 respectively versus 51.4 and 52.6 (Hopman et al., 2000). In this study, the women also had slightly lower mean physical and mental health summary scale scores than the men: 39.2 and 47.0 versus 39.7 and 47.8 respectively. The physical health summary scores for both the women and men are much lower than the general population, whereas the mental health summary scores are only somewhat lower than the general population. The average physical health summary score for this study was 39.4, while the average mental health summary score was 47.2. The Canadian Burden of Illness Study Group (1998) report a similar average physical health summary score for the EDSS ≤ 2.5 study group as this study (39.6), but a slightly worse mental health summary score than this study (44.1).

A worsening in the physical health summary score compared to the general population is certainly expected in the MS population given the physical manifestations of the illness (e.g. weakness, ataxia, balance / gait disturbance, visual difficulties). The small difference in the mental health summary score compared to the general population is perhaps not surprising given the myriad of factors which contribute to a person's mental health, of which illness may or may not be one (e.g. stress, family discord, depression, grief). Nortvedt et al. (1999b), The Canadian Burden of Illness Study Group (1998), and Vermersch et al. (2002) similarly found their MS participants to have significantly worse physical HRQoL scores than the general population, but found little difference between the MS and general populations in regards to mental HRQoL. Perhaps the reason for the small difference in the mental health summary scores of this MS sample and the general population is that the mental health component of patients' HRQoL is being treated effectively through the use of support, counseling, and medication interventions by clinicians. Perhaps further investigation into this hypothesis would be of value.

Hope is also a factor that contributes to a person's mental health. The participants in this study were about to begin a new medication for their illness. Until the onset of these medications, steroids for exacerbations were basically the only form of treatment available. The hope that these medications might decrease the number and severity of future attacks might account for the better MCS scores in this sample than the Canadian Burden of Illness (1998) study sample.

6.3 Factors Associated with the Physical Health Component of Health-related Quality of Life

Several demographic, socioeconomic, health, and MS specific factors were considered in this study as possibly having significant associations with the HRQoL of Saskatchewan adults with relapsing-remitting MS. Eight factors were found to have a significant association with the physical health component (PCS) of the HRQoL of the study participants. Participants who were male, young, employed, had no muscle, joint, or bone problems, no breathing problems, low fatigue severity ratings, low (better) disability (EDSS) scores, and no or very few MS attacks in the last six months, had better PCS scores than their counterparts.

6.3.1 Demographic and Socioeconomic Factors

Similar to several of the studies reviewed in the best evidence synthesis (Benito-León et al., 2002; Brunet et al., 1996; Chang et al., 2002; Fruehwald et al., 2001;

Janardhan et al., 2002; Janardhan et al., 2000; Jønsson et al., 1996; Koch et al., 2001; Miller et al., 2003; Murphy et al., 1998; Nicholl et al., 2001; Nortvedt et al., 1999b; Parkin et al., 2000; Rice et al., 1999; Roberts et al., 1998; Shawaryn et al., 2002; Singer et al., 1999; Solari et al., 1999, Solari et al., 2001; Wang et al., 2000), sex did not have a statistically significant association with the PCS in this study. However, because of the biological and clinical importance of this variable, it was kept in the final model.

In studies conducted by Chang et al. (2002), Merkelbach et al., (2002), Shawaryn et al. (2002), and Solari et al. (1999), age was found to be a significant factor in regards to the physical HRQoL of MS participants, with older persons faring worse than younger persons. Chang et al. (2002) and Solari et al. (1999) both concluded that age has a major influence on HRQoL. This conclusion is further supported by this study. Since several studies found no significant relationship between age and HRQoL (Amato et al., 2001; Brunet et al., 1996; Cutajar et al., 2000; Fruehwald et al., 2001; Gulick, 1997; Hakim et al., 2000; Janardhan et al., 2000; Janardhan et al., 2002; Jønsson et al., 1996; Miller et al., 2003; Murphy et al., 1998; Nicholl et al., 2001; Nortvedt et al., 1999b; Parkin et al., 2000; Rice et al., 1999; Rudick et al., 1992; Solari et al., 2001; Wang et al., 2000), a longitudinal prospective study of MS patients to investigate the influence of age on HRQoL would certainly help to clarify this relationship.

Employment status was also found to have a significant relationship with the physical component of this study sample's HRQoL, with employed persons faring better than those who were not employed because of their MS. This finding is in line with the findings of other studies that looked at employment status and HRQoL (Aronson, 1997;

Koch et al., 2001; Lankhorst et al., 1996; Rudick et al., 1992; Solari et al., 1999; Solari et al., 2001; Vickery et al., 1995).

Marital status, education level, total household yearly income, and location of residence were not found to have significant associations with the PCS in this study. Some studies have found associations however, such as Aronson (1997) who found a household income of under $35,00 to be associated with HRQoL as a whole. Gulick (1997) found a significant positive correlation between living with a spouse and the Life Situation Survey, and also between employment status and the survey, even though employment status was not retained in her final model. Solari et al. (1999) found that those participants who were married or cohabitating had worse PCS scores than their counterparts. The variable of marital status is perhaps worthy of further investigation. Again, a prospective longitudinal study might help to clarify the relationship between marital status and HRQoL.

6.3.2 Health Factors

In the studies reviewed for the best-evidence synthesis, none appeared to investigate the relationship between comorbid medical conditions and HRQoL. The finding that muscle, bone, or joint problems, and breathing problems, are related to the physical components of this study sample's HRQoL is unique and worthy of further investigation. Intuitively it seems obvious that if a person has MS and some other major condition such as rheumatoid arthritis or asthma they are going to be worse physically. Health care providers who specialize in caring for persons with MS may tend to solely focus on the MS aspects of their patients' lives. Often matters unrelated to MS are referred back to the patient's family physician for further assessment and follow-up. Perhaps however, clinicians specializing in MS should make note if their patients have other serious medical conditions, such as muscle, bone, joint, or breathing problems. Patients having another comorbid condition might place them at risk for a declining HRQoL.

Fatigue has been implicated as having a negative association with the physical component of HRQoL in a number of studies (Amato et al., 2001; Aronson, 1997; Janardhan et al., 2002; Jønsson et al., 1996; Merkelbach et al., 2002; Nortvedt et al., 2003). It is thus not surprising that fatigue severity was found to be associated with the PCS in this study. Fatigue was reported by Aronson (1997) and Koch et al. (2001) to be one of the most prevalent distressing symptoms for persons with MS. The literature regarding fatigue and MS has certainly grown over the last ten years, examining the importance, assessment, and management of MS related fatigue. Unfortunately, fatigue is a rather nondescript term and difficult to measure objectively. Conflicting literature exists regarding the best way to help MS patients with their fatigue. In terms of HRQoL, perhaps clinicians would be best to take note when a patient addresses the issue of fatigue on his or her own initiative. This might be a signal that their fatigue level is beginning to influence their HRQoL. Clinicians may want to ask the same questions regarding fatigue as were included in this study, as a quick fatigue-assessment tool.

Perhaps it is somewhat surprising that depressive symptoms were not found to be associated with the PCS. Several studies found the opposite to be true, in that depressive symptoms or depression did have a negative association with the physical component of MS participants' HRQoL (Amato et al., 2001; Benito-León et al., 2002; Cutajar et al., 2000; Fruehwald et al., 2001; Janardhan et al., 2002; Jønsson et al., 1996; Kenealy et al., 2000; Merkelbach et al., 2002; Nicholl et al, 2001; Patti et al., 2003; Provinciali et al., 1999; Solari et al., 1999; The Canadian Burden of Illness Study Group, 1998; Vickery et al., 1995; Wang et al., 2000). The fact that this study did not find a similar association as the other studies might be due in part to the fact that the participants were screened for depression before being allowed to begin taking one of the new medications. In addition, as has been mentioned previously, the participants may have felt a sense of hope knowing they were about to begin a new treatment for their disease, and therefore had less depressive symptoms.

6.3.3 MS Specific Factors

Both disability level (as measured by the EDSS) and recent MS attacks (relapses / exacerbations) were found to be negatively associated with the PCS in this study, as per other studies examining the relationship between these factors and HRQoL. Almost every study which looked at disability level and the physical health component of HRQoL found a significant relationship (Amato et al., 2001; Benito-León et al., 2002; Brunet et al., 1996; Chang et al., 2002; Ford et al., 2001; Fruehwald et al., 2001; Henriksson et al., 2001; Janardhan et al., 2002; Janardhan et al., 2000; Merkelbach et al., 2002; Miller et al., 2003; Modrego et al., 2001; Murphy et al., 1998; Nortvedt et al., 1999b; Nortvedt et al., 2000a; Nortvedt et al., 2000b; O'Connor et al., 2001; Patti et al., 2003; Parkin et al., 2000; Pfennings et al., 1999; Rice et al., 1999; Rudick et al., 1992; Shawaryn et al., 2002; Solari et al., 2001; Solari et al., 1999; Stuifbergen et al., 2000; The Canadian Burden of Illness Study Group, 1998; Vermersch et al., 2002; Vickery et al., 1995). Jønsson et al. (1996) found that the EDSS did not correlate with the Laman and Lankhorst HRQoL questionnaire, but did report that the items of "worry about deterioration" and "walking" had negative HRQoL weightings.

As per other studies, which looked at number of relapses as a possible factor associated with HRQoL, the number of MS attacks in the past six months was found to have a significant negative association with the PCS (Chang et al., 2002; Cutajar et al., 2000; Grima et al., 2000; Henrikkson et al., 2001; Parkin et al., 2000; Rice et al., 1999; Solari et al., 1999; Somerset et al., 2003; Vickery et al., 1995). Using the Health Utilities Index to measure HRQoL, Grima et al. (2000) found that the utility values for those in relapse were lower then those in remission, with the utility values for participants recalling the worst week of their last relapse having the lowest values of all. The authors of the study concluded that a patient would have a utility decrease in HRQoL of 0.24 units if they progress from 1.0 to 6.0 EDSS score in 15 years. Meaning, 50% of recently diagnosed patients would have a decrease in utility that is 25% greater than would normally be expected to occur in 60 years from age 25 years.

In addition to being statistically significant, both disability level and number of relapses are clinically significant. An increase in EDSS score by 1.0 would mean increased disability for a patient. For example, an EDSS score of 2.5 reflects mild disability, whereas an EDSS of 3.5 reflects moderate disability. Similarly, an increase in the number of attacks a patient might experience within a six month time frame is most likely indicative of disease progression. Thus, close monitoring of the disability level and number of attacks patients are experiencing needs to be a top priority for clinicians.

6.3.4 Summary

In summary, the factors that were found to have a negative association with the PCS are: female sex, increasing age, not working due to MS, muscle / bone / joint problems, breathing problems, increasing severity of fatigue, increasing severity of disability, and increasing frequency of MS attacks in the past six months. Taken together, the eight variables in the PCS model explain 47.4% of the variance in the PCS (Table 5.9). These results are in keeping with the current literature, as the best-evidence synthesis found fatigue, employment status, relapses, disability, and probably age, to be associated with the physical health component of the HRQoL of persons with MS in the same manner as this study's findings. Marital status was not found to have an association in this particular sample of relapsing-remitting participants. Perhaps this factor might become important in more disabled samples of patients, when caregiver related issues tend to increase, but further research would need to test this hypothesis.

The combination of the eight factors that are associated with the physical health summary scale of the SF-36 can be thought of as telling about half the story of what factors are important in regards to the physical HRQoL of MS relapsing-remitting patients. The best-evidence synthesis also highlighted psychological difficulties, anxiety, cognitive difficulties, disease course, and disease duration as possibly having associations with HRQoL. Perhaps these factors or some other yet to be studied factors would help to tell the other half of the story.

6.4 Factors Associated with the Mental Health Component of Health-related Quality of Life

Several demographic, socioeconomic, health, and MS specific factors were considered in this study as possibly having significant associations with the HRQoL of Saskatchewan adults with relapsing-remitting MS. Five factors were found to have a significant association the mental health component (MCS) of the HRQoL of the study participants. Participants who were older and female, or younger and male, had a low illness intrusiveness score, had no digestive system problems, no kidney/bladder/urinary problems, and no headaches, had better MCS scores than their counterparts.

6.4.1 Demographic and Socioeconomic Factors

Perhaps the most unique and intriguing finding in this study, was finding that the interaction of sex and age is significantly associated with the MCS. The study found that younger women have worse MCS scores than older women, but that younger men have better MCS scores than older men.

None of the studies reviewed in the best-evidence synthesis appeared to investigate the possibility of first order interactions. The best-evidence synthesis did indicate however, that age possibly had a positive association with the mental health component of HRQoL, with older persons faring better. In addition, the synthesis gave some indication that sex might be an important factor in regards to mental HRQoL. The descriptive results indicated that the women in this sample fared worse on the mental health summary scale than their male counterparts.

This statistically significant interaction is also clinically significant. The possibility that the mental HRQoL of women may improve as they age, but worsen for men as they age, has implications for patient care and education in regards to HRQoL. Certainly further testing of this interaction between sex and age in terms of its associative strength and direction with the mental HRQoL of persons with MS is warranted. Once again, a longitudinal study employing and following newly diagnosed patients would help to clarify the influence of sex and age on mental HRQoL. The finding of this interaction lends support to the idea that sex is an important factor to consider when assessing the HRQoL of persons with MS whether for clinical or research purposes.

None of the other demographic and socioeconomic factors (marital status, education level, total household yearly income, employment status and location of residence) were found to have a significant association with the MCS. This is in contrast to the findings in the best-evidence synthesis to some degree, with marital and employment status having been sighted as possibly having associations. Aronson (1997) did find that being unemployed and having a household income under $35,000 was associated with decreased satisfaction with HRQoL as a whole. Gulick (1997) found living with a spouse and employment to have a positive association with HRQoL. Similarly, Jønsson et al. (1996) found family, friends, and good financial situation to have a positive association with HRQoL. Solari et al., (2001) found MCS scores were lower in the unemployed. Solari et al. (1999) also found MCS scores were lower in those who were married or cohabitating. This study's sample consisted of relapsing-remitting patients however, and thus perhaps marital and employment statuses are less of a concern for this particular disease course group in terms of their mental HRQoL compared to the progressive groups. Further research testing this hypothesis would need to be done.

6.4.2 *Health Factors*

Several studies have found negative associations between fatigue and MS participants' mental HRQoL (Amato et al., 2001; Janardhan et al., 2002; Jønsson et al., 1996; Merkelbach et al., 2002; Nortvedt et al., 2003). Fatigue had a significant crude relationship with the MCS in this study, but did not remain significant in the final model, although it did in the PCS model. The other studies listed above included progressive participants as well as relapsing-remitting participants, and thus this could explain the difference in findings. Merkelbach et al. (2002) found that fatigue had a greater association than depression in the PCS model, but the reverse was true in the MCS model.

Depression has been commonly reported as being negatively associated with the mental HRQoL of persons with MS (Amato et al., 2001; Benito-León et al., 2002; Cutajar et al., 2000; Fruehwald et al., 2001; Janardhan et al., 2002; Kenealy et al., 2000; Merkelbach et al., 2002; Nicholl et al., 2001; Patti et al., 2003; Provinciali et al., 1999; Solari et al., 1999; The Canadian Burden of Illness Study Group, 1998; Vickery et al., 1995; Wang et al., 2000). This finding is certainly not unexpected given the conceptual relation of depression to mental health. It was for this reason that depressive symptomology was not used as an independent variable in the MCS model building, for if a person is depressed, and then without question their mental HRQoL is negatively affected.

Interestingly, three comorbid conditions were found to have a significant association with the MCS: digestive system problems; kidney, bladder, or urinary problems; and headaches. Bladder problems and headaches are very common amongst the MS population. The potential for loss of bladder control in public is often a large mental strain for MS patients. Given that stress often manifests itself in physical symptoms, it is perhaps not surprising that digestive system problems and headaches were also associated with the MCS. The finding that comorbid conditions are associated with the physical and mental HRQoL of MS patients is worth further investigation, for the current literature is lacking in this area.

6.4.3 MS Specific Factors

In direct opposition to the PCS model, illness intrusiveness was the only MS specific factor found to be significantly associated with the MCS, with disability level (EDSS) and number of MS attacks in the past six months not being associated. This finding is supported by other studies investigating these factors. Disability is generally always associated with the physical component of HRQoL, but not the mental component (Amato et al., 2001; Benito-León et al., 2002; Brunet et al., 1996; Chang et al., 2002; Ford et al., 2001; Fruehwald et al., 2001; Henriksson et al., 2001; Janardhan et al., 2000; Janardhan et al., 2002; Merkelbach et al., 2002; Miller et al., 2003; Modrego et al., 2001; Murphy et al., 1998; Nortvedt et al., 1999b; Nortvedt et al., 2000a; Nortvedt et al., 2000b; O'Connor et al., 2001; Patti et al., 2003; Parkin et al., 2000; Pfennings et al., 1999; Rice et al., 1999; Rudick et al., 1992; Shawaryn et al., 2002; Solari et al., 1999; Solari et al., 2001; Stuifbergen et al., 2000; The Canadian Burden of Illness Study Group, 1998;

Vermersch et al., 2002; Vickery et al., 1995). It is interesting to note however that Nortvedt et al. (2000a) found the subscales of mental health, role-emotional, social function and vitality were significantly correlated with the EDSS even though the MCS was not. In another study conducted by Nortvedt et al. (1999b), persons with higher EDSS had markedly reduced mental health scores. Shawaryn et al. (2002) included EDSS in the MCS model as one of seven factors that explained 26% of the variance in the MCS. Although most authors conclude that the EDSS is not a valuable factor when assessing the mental HRQoL of MS patients, perhaps further study is warranted via a longitudinal study. Nortvedt et al. (2000b) did find that low scores on the SF-36 mental health scale were significantly correlated with worsened EDSS scores one year later.

Relapses were sighted as being associated with HRQoL in the best-evidence synthesis. Unfortunately, the studies exploring the relationship between relapses and HRQoL generally used questionnaires that evaluated HRQoL as a whole, and did not separate it into its physical and mental health components. Thus, it is possible that perhaps relapses are only associated with the physical aspects, but further research is required to explore this possibility.

Illness intrusiveness was included in the mental health model because of what it measures. The IIRS questionnaire evaluates the degree to which the disease is impacting important psychosocial domains of life. The findings of the best-evidence synthesis suggest that the psychosocial aspects of HRQoL are more important to patients than the physical aspects. This variable was statistically significant in the final model, and it is also clinically significant due its psychosocial nature. However, evaluating the impact an increase in IIRS total score may have on a patient clinically is difficult, since the IIRS questionnaire has not been used routinely in practice, and has not been assigned cut-off scores to tell when a patient has moved from mild to moderate to severe illness intrusiveness.

No studies were found in which illness intrusiveness was explored as a possible factor associated with HRQoL, yet it is an obviously important factor to patients, and thus worthy of further investigation. The value of this factor is also supported by Devins et al. (1993b) who found that the MS participants overall illness intrusiveness score was lower than that of the rheumatoid arthritis and end-stage renal disease participants.

6.4.4 Summary

In summary, the factors that were to found to have a negative association with the MCS are: getting older for males, but being younger for females, increasing severity of illness intrusiveness, digestive system problems, kidney/bladder/urinary problems, and headaches. Taken together, these variables in this MCS model explain only 22.1% of the variance in the MCS (Table 5.10). The combination of the five factors that are associated with the mental health summary scale of the SF-36 can be thought of as telling less than one-fifth of the story of what factors are important in regards to the mental HRQoL of MS relapsing-remitting patients. Thus, some other important explanatory variables must exist which would explain the rest of the variance in the mental HRQoL of persons with MS. The best-evidence synthesis also highlighted employment status, fatigue, depression, anxiety, psychological difficulties, cognitive difficulties, relapses, disease course, and disease duration as possibly having associations with HRQoL. Somerset et al. (2002, 2003) reports lack of personal control / increased dependency as being one of the most important factors relating to the mental and social aspects of MS patients' lives. Perhaps these factors or some other yet to be studied factors would help to tell the other two-fifths of the story.

These results add to the current body of knowledge regarding the mental health component of the HRQoL of persons with MS. The best-evidence synthesis found employment status, fatigue, depression, relapses, and probably age, to be associated with the mental health component of HRQoL. Employment status, fatigue, and relapses were not found to have an association in this particular sample of relapsing-remitting participants. Perhaps these factors might become important in more disabled samples of patients, but further research would need to test this hypothesis.

In keeping with the current literature, disability was not found to have a statistically significant association with the mental health component of HRQoL. The associations between sex and marital status and mental HRQoL are unclear in the current literature. This study sheds a unique light on the possible influence of sex on mental HRQoL. Marital status did not have an association with the MCS in this study.

6.5 Relevance to Clinical Practice

The findings from this study have important implications for health care providers caring for persons with relapsing-remitting MS. The factors that were found to be associated with the HRQoL of relapsing-remitting patients could be thought of as possible warning signs to clinicians that a patient might be at risk for deterioration in his/her HRQoL.

When a clinician meets with a patient, paying attention to the sex and age of the patient is important. Aging, and perhaps being female, are probable enemies to physical HRQoL. Aging and being female however are probably beneficial to mental HRQoL, whereas the opposite is true for aging males. Obviously clinicians cannot change the age and sex of their patients, but they can be sensitive to the fact that these factors might be playing a role in the HRQoL of their patients at certain times in their lives, and therefore be attentive to the verbal and nonverbal cues patients may give when they are struggling.

The presence of comorbid conditions needs definite attention, given muscle/joint/bone problems and breathing problems were associated with worse physical HRQoL, and digestive systems problems, kidney/urinary/bladder problems, and headaches were associated with worse mental HRQoL. Clinicians need to find out if their patients suffer from any other major condition, and if so, how it is being managed and how the patients' feel it impacts their MS and HRQoL. Perhaps some intervention work will be required to ensure the other major condition is indeed being managed appropriately, such as making referrals to other specialists or ordering medical tests. Rudick et al. (1992) offered an interesting observation in that since MS has so many different problems in and of itself, perhaps it is more disruptive to well-being than having two or more conditions. These authors cite another study conducted by Stewart et al. (1989) who found that persons with multiple conditions have poorer functioning and well-being than those who suffer from only one condition.

Patients complaining of fatigue should also raise a red flag for clinicians given the negative association between it and physical HRQoL. Fatigue can result from a multitude of reasons such as nocturia, insomnia, nighttime muscle spasms, stress, children, work, and so forth. Clinicians need to dig deep into the problem of fatigue to find out what the possible sources are and then begin to work on solutions.

Patients who are inquiring about employment options such as taking sick time, short-term or long-term disability because of their MS, might also be at risk for a decline in their HRQoL. Often the reason for the need to change employment status is due increasing disability, which is also associated with physical HRQoL. Noticing a change in EDSS score for the worse should also be warning sign. A large number of relapses in the last year, or an increasing number of relapses compared to previous years, should also raise concern.

Clinicians need to take time with patients who are experiencing one or all of these signs to discuss all the possible implications that a change in employment status, disability level, and or number of relapses will have on their physical HRQoL. Quitting work can be a positive step for some, while being a negative one for others. Those who define a large part of themselves through their work may have a very difficult time adjusting to being at home. Working with the patient to think of ways to keep that part of their identity intact, while acknowledging the restrictions increasing disability will have is important, such as volunteering, retraining, taking a course, or starting a new a hobby. Helping patients to redefine their definition of "normal", to set realistic goals, and to focus on what they can do despite increasing disability are very important measures for clinicians to take.

Patients whose chiefs concerns appear to be psychosocial in nature deserve attention. Since these concerns are very important to patients, and since greater illness intrusiveness was found to be negatively associated with the mental HRQoL of the study participants, clinicians cannot ignore the possible negative effect psychosocial concerns will have on patients' HRQoL. Often just a listening ear or a voice of encouragement is needed. Clinicians need to educate, support and advocate for their patients when needed. Ensuring patients get the assistance they need to cope with their struggles whether they be physical, psychosocial, or both, is imperative.

6.6 Strengths and Limitations of the Present Study

6.6.1 The Study Sample

During the study's inception period, 292 persons with relapsing-remitting MS in Saskatchewan were given the opportunity to begin one of the four new medications for relapsing-remitting MS and to participate in this study. Ninety percent of these persons agreed to participate, which is a very high response rate. The final size of the sample, 256 persons, is a good size clinically and statistically, and in terms of ensuring the reliability and validity of the results.

While this study's response rate is very high, the issue of selection bias needs to be addressed given that 30 persons refused to participate. It is possible the reason for the refusals is related to the outcome of interest in this study. If the potential participants who refused did so because they had poor HRQoL, and therefore did not feel up to participating in the study, then the results of this study underestimate the negative impact of MS on HRQoL.

Since all the potential participants would have met the exact same medical criteria in order to receive one of the new medications, they would have all been at approximately the same physical disability level (mild to moderate), and would have been screened for depression. HRQoL is a subjective concept however, and thus even though all the potential participants would have been at a similar level of functioning clinically, it is possible that those who refused did so because they felt poorly.

Those who refused may have also done so due to reasons associated with their MS. Perhaps if they were experiencing attacks, worsening of symptoms, or worsening of disability, this would have caused some to refuse participation. If those who refused did so because of a worsening of their illness, then the results of this study underestimate the negative impact of the illness.

It is difficult to ascertain whether the potential participants who refused did or did not do so for reasons related to their illness or the study's outcome, and thus the possibility of selection bias remains. The high response rate however decreases the concern of selection bias and increases the confidence in the representativeness of this sample.

6.6.2 The Study Design

The current study employed a cross-sectional design to explore the associations between a wide range of factors and HRQoL in persons with relapsing-remitting MS. It provides us with a "snapshot" of what factors were associated with this sample's HRQoL before they began drug treatment. This "snapshot" is unique in that it explored the relationship between comorbid conditions and HRQoL, and explored the significance of all the possible first-order interactions between those factors found to be associated with HRQoL.

As discussed previously in the best-evidence synthesis, cross-sectional studies have limitations, as they do not allow for testing of directions of associations. However, cross-sectional studies can be thought of as springboards for future research studies, providing specific ideas to explore and suggesting possible hypotheses to test.

The results from this study are valid in that they can be applied to other similar groups of relapsing-remitting MS patients. Primary progressive, secondary progressive, and benign groups are different from this study's sample, and therefore the findings should not be generalized to the entire MS population. Looking at the groups of MS separately however, might allow for more targeted interventions regarding patients' HRQoL.

The study did not include illness duration as a possible factor, nor a cognitive scale. Depression was explored, though other psychosocial factors such as anxiety, social support, and loss of personal control were not. The study used the baseline data gathered from a study designed to test the HRQoL of patients taking medication to reduce the attack rate, and thus, this study was limited by the design of that study. However, all of the most commonly sighted factors as having associations with HRQoL in the best-evidence synthesis were included (age, employment status, fatigue, depression, disability, and relapses).

6.6.3 Summary

This study will add to the current body of knowledge regarding what factors are associated with the HRQoL of persons with MS. By employing only relapsing-remitting participants, the study will provide health care providers and researchers with new knowledge regarding what factors are important to consider in the relapsing-remitting form of the disease. Perhaps by being attentive to the early warning signs of a deteriorating HRQoL, patients and their clinicians can begin to have the upper hand against a possible lifetime of declining HRQoL.

The unique findings of associations between comorbid conditions and HRQoL, and the interaction of sex and age and mental HRQoL will certainly bring new knowledge to the MS patient and professional community, and will also hopefully lead to further research to test these unique associations.

6.7 Future Research

A longitudinal study would be of great value for determining the direction of the associations between the various factors identified as being related to HRQoL. Ideally, the study would employ and follow newly diagnosed patients for several years, exploring a variety of physical and psychosocial factors.

Research questions that arise from this study include: 1) Do marital status and employment status become associated with mental HRQoL when looking at more disabled / progressive groups of patients? 2) Do relapses only have an association with the physical aspect of HRQoL? and 3) Does disability have an affect on the mental aspect of HRQoL? In addition, further exploration and testing is required to examine the influence of comorbid conditions on HRQoL, and the interaction of sex and age on mental HRQoL.

Perhaps replicating this study to examine the differences between primary progressive, secondary progressive, and benign MS patient groups would also be of value, to assist clinicians in knowing what factors associated with HRQoL are important for each type.

This study supports much of the information that is already known about the HRQoL of MS persons, but also adds unique information, and fuels the idea board for future research exploring this topic.

7. CONCLUSION

The purpose of this research was to explore the health-related quality of life (HRQoL) of Saskatchewan adults with relapsing-remitting multiple sclerosis (MS). This was accomplished through the production of a best-evidence synthesis of the literature on the HRQoL of persons with MS, and through the conduction of a research study designed to describe the HRQoL of Saskatchewan adults with relapsing-remitting MS, and to delineate the factors associated with their HRQoL.

The best-evidence synthesis indicated that age is most likely associated with HRQoL, with those who are younger probably having better physical HRQoL scores, but poorer mental HRQoL scores, than those who are older. Employment status was found to be associated with HRQoL, with those who work faring better than those who do not. Other demographic and socioeconomic factors that may be associated with HRQoL include sex and marital status, although the existence, strength, and direction of their associations require further investigation. Health and MS specific factors that are strongly associated with the HRQoL of persons with MS include fatigue, depression, and number of relapses, with greater severity in any of these areas meaning worse HRQoL. Disability level had a very strong negative association with the physical component of HRQoL, but a less clear association with the mental component. Further research into the existence, strength and direction of the association between disability and mental HRQoL is needed.

The synthesis also highlighted the importance of psychosocial factors such as cognitive function, social function, anxiety, and feelings of loss of control as possible factors influencing the HRQoL of persons with MS. From the patients' perspectives, it appears the psychosocial components are more of a concern than the physical in terms of their HRQoL.

Although the synthesis was comprised of mainly cross-sectional studies, the synthesis provides a unique understanding of what is known about the factors that are associated with the HRQoL of persons with MS. The need for a longitudinal cohort study to investigate the ability of these factors to cause an improvement or worsening of HRQoL became evident.

The research study found several factors to be associated with the HRQoL of persons with relapsing-remitting MS. Sex, age, employment status, muscle / joint / bone problems, breathing problems, fatigue severity, disability level, and number of MS attacks in the past six months comprised the final model of factors that have an association with the physical HRQoL of persons with MS. Digestive system problems, kidney / bladder / urinary problems, headaches, illness intrusiveness, and an interaction between sex and age comprised the final model of factors that have an association with the mental HRQoL of persons with MS.

The implications of the study's findings for clinical practice and future research were discussed. The knowledge gained from this study will add to the existing body of knowledge regarding the demographic, socioeconomic, health and MS specific factors that are most apt to influence the HRQoL of those living with MS. While persons with MS, their families, and their health care providers, wait for better treatments or a cure for this chronic disabling condition, maintaining or improving patients' HRQoL needs to be a top priority. Researchers and clinicians must strive toward improving the HRQoL of persons with MS by continuing to explore the factors that are associated with their

HRQoL and then applying the knowledge gained. This study provides insight into the factors associated with the HRQoL of MS patients in the relapsing-remitting stage of the disease, so that health care providers might identify patients who may be at risk for decline in their perceived quality of life early in their care, and thereby intervene appropriately, timely, and effectively.

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APPENDIX A:
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APPENIDX B:
University of Alberta and University of Saskatchewan Ethics Approvals

Health Research Ethics Board

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University of Alberta, Edmonton, Alberta T6G 2R7
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p.780.492.0459
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UNIVERSITY OF ALBERTA HEALTH SCIENCES FACULTIES,
CAPITAL HEALTH AUTHORITY, AND CARITAS HEALTH GROUP

HEALTH RESEARCH ETHICS APPROVAL

Date: December 2003

Name of Applicant: Karen Turpin

Organization: University of Alberta

Department: Public Health Sciences, Epidemiology Program

Project Title: **Health-related Quality of Life of Persons with Early Stage Relapsing-remitting Multiple Sclerosis**

The Health Research Ethics Board (HREB) has reviewed the protocol for this project and found it to be acceptable within the limitations of human experimentation. The HREB has also reviewed and approved the subject information letter and consent form, if applicable.

The approval for the study as presented is valid for one year. It may be extended following completion of the yearly report form, which will be sent to you in your renewal month. Any proposed changes to the study must be submitted to the Health Research Ethics Board for approval. Written notification must be sent to the HREB when the project is complete or terminated.

Glenn G. Griener

Dr. Glenn Griener
Acting Chair of the Health Research Ethics Board
(B: Health Research)

UNIVERSITY OF ALBERTA

File number: B-291202-PHS

Capital Health

CARITAS HEALTH GROUP

Health Research Ethics Board

2J2.27 Walter Mackenzie Centre
University of Alberta, Edmonton, Alberta T6G 2R7
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UNIVERSITY OF ALBERTA HEALTH SCIENCES FACULTIES,
CAPITAL HEALTH AUTHORITY, AND CARITAS HEALTH GROUP

HEALTH RESEARCH ETHICS APPROVAL

Date:	December 2002
Name of Applicant:	Karen Turpin
Organization:	University of Alberta
Department:	Public Health Sciences
Project Title:	**Health-related Quality of Life of Persons with Early Stage Relapsing-remitting Multiple Sclerosis**

The Health Research Ethics Board (HREB) has reviewed the protocol for this project and found it to be acceptable within the limitations of human experimentation. The HREB has also reviewed and approved the subject information letter and consent form.

The deliberations of the HREB included all elements described in Section 50 of the *Health Information Act*, and found the study to be in compliance with all the applicable requirements of the Act. The HREB determined that consent not be obtained for the disclosure of the health information to be used in the research from the individuals who are the subjects of the information.

The approval for the study as presented is valid for one year. It may be extended following completion of the yearly report form. Any proposed changes to the study must be submitted to the Health Research Ethics Board for approval. Written notification must be sent to the HREB when the project is complete or terminated.

for Gillian Johnson
Dr. Sharon Warren
Chair of the Health Research Ethics Board
(B: Health Research)

File number: B-291202-PHS

University of Alberta

Capital Health

CARITAS HEALTH GROUP

University of Saskatchewan
Advisory Committee on Ethics in Human Experimentation

February 6, 1998

Certificate of Approval

PRINCIPAL INVESTIGATOR	DEPARTMENT	EC #
J.D. Cassidy	Physical Medicine and Rehabilitation	98-23

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT

Saskatchewan Health Drug Plan

CO-INVESTIGATORS

W. Hader

SPONSORING AGENCIES

Institute for Health and Outcomes Research
Department of Physical Medicine and Rehabilitation
University of Saskatchewan and the
Multiple Sclerosis Clinics
Saskatoon and Regina

TITLE:

Health-Related Quality of Life in Multiple Sclerosis Patients Undergoing Drug Treatment to Reduce the Exacerbation Rate

APPROVAL DATE	TERM (YEARS)	AMENDED:	MODIFICATION OF:
February 6, 1998	3		

CERTIFICATION:

The protocol and consent form for the above-named project have been reviewed by the Committee and the experimental procedures were found to be acceptable on ethical grounds for research involving human subjects.

APPROVED.

H.E. Emson MA MD FRCPC
Acting Chair
University Advisory Committee on
Ethics in Human Experimentation

This Certificate of Approval is valid for the above term provided there is no change in the experimental procedures, subject to annual reapproval.

APPENDIX C:
MS Drug Evaluation Study Program Index Questionnaire

MULTIPLE SCLEROSIS DRUG EVALUATION PROGRAM

INDEX QUESTIONNAIRE

Institute for Health and Outcomes Research
Department of Physical Medicine and Rehabilitation
University of Saskatchewan

and the

Multiple Sclerosis Drug Program
Saskatchewan

1. Today's Date: __________ (Day) __________ (Month) __________ (Year)

2. Last Name: ____________________ (Please Print) First Name: _______________ Initial: ___

3. Address: (Please include street address, town or city, and postal code)

____

____

____

4. Phone Number: _____________ (home) _____________ (work)

5. Saskatchewan Health Services Number: ___ ___ ___ ___ ___ ___ ___ ___ ___

Institute for Health and Outcomes Research
University of Saskatchewan
Box 108, Royal University Hospital
Saskatoon, SK S7N 0W8
Phone: 966-4731 (Saskatoon) or 1-800-667-8505 toll-free (outside Saskatoon)

Consent Form: MS Drug Evaluation Program

Saskatchewan Health has recently approved new medications for the treatment of Multiple Sclerosis, and they want to know how effective they are for you and people like you with MS. Therefore, Saskatchewan Health has asked the ***Institute for Health and Outcomes Research*** at the ***University of Saskatchewan*** to find out how well these medications are working. We are a group of university-based research doctors who are experts in evaluating the effect of treatment on patients like you. Our Institute is completely independent from Saskatchewan Health.

To investigate this, we are asking you to fill out a questionnaire now, and return it to us in the pre-paid envelope provided. We will then phone you every three months over the next two years to find out how you are feeling. Today's questionnaire will take about 20 minutes to complete, and the telephone interviews will take about the same amount of time. There will be eight telephone interviews in all, over the next two years. Apart from the time we are asking you to spend talking with us, there will be no cost to you.

We also want to compare our information to the results of the clinical assessment that your doctor does before you start the drugs. This information is necessary to evaluate how much these new medications are helping and will require no extra effort or time for you or your doctor.

In addition, at the end of the drug evaluation period, we would like to use your Health Services Number to obtain information from Saskatchewan Health. This information on physician visits, hospitalizations and prescription drug use will help us to calculate the cost-effectiveness of the new MS drugs. We will be asking Saskatchewan Health for information on the number and types of health services you used the year before you began the medication and during the first two years of taking the medication. By using your Health Services Number, we will also be able to combine the Saskatchewan Health information with information that you have given us through questionnaire and telephone interviews.

All information that we use will be kept locked and secure at the Institute for Health and Outcomes Research at the University of Saskatchewan. At the end of the drug evaluation period, all information will be combined and reported anonymously. You will not be identified in any report, and there will be no way of knowing which information came from which person. We will never identify you personally in any way, or release any personal information without your permission. You are free to refuse to participate in this drug program evaluation now or at any point in the future. Your decision to participate in this evaluation will not affect your ongoing care or your eligibility for coverage for this drug. We stress, however, that the only way to determine how much these medications benefit MS sufferers in Saskatchewan is to get this information from everyone taking them. That is why we need your help by participating.

At the end of the drug evaluation period, we will ask all participants if they want a summary of our results, and we will send this summary to anyone who is interested. If you have questions or concerns about the drug program evaluation, please feel free to call or write to:

Institute for Health and Outcomes Research
University of Saskatchewan
Box 108, Royal University Hospital
Saskatoon, SK, S7N 0W8

*Phone number **966-4731** (Saskatoon) or **1-800-667-8505** toll-free (outside Saskatoon)*

If you agree to participate in this drug program evaluation, please sign your name below with the signature of a witness. Keep one copy for your own records.

I have read this document (or it has been explained to me) and I understand what I am agreeing to.

______________________	______________________	______________________
(Signature)	(Date: day/month/year)	(Witness)

Revised June 5, 1998

SECTION A: About Your Multiple Sclerosis

1. Which medication are you being prescribed? (please check one)

   ☐..Betaseron ☐..Copaxone ☐..Other, specify ________________

2. Have you started this medication yet?

   ☐..No (go to next question)

   ☐..Yes → ________ (Day) ________ (Month) ________ (Year)

3. How many attacks of Multiple Sclerosis have you had in the past **six months**? *(An attack is defined as the appearance of new symptoms or worsening of old symptoms, lasting at least 24 hours, but with no fever. To be counted as an attack, your symptoms should have been stable for at least one month prior to the attack.)*

   I have had _____ MS Attacks in the **past six months.**

4. Apart from seeing your doctor and taking the medication prescribed, what **other** types of therapies or treatments have you tried for your MS? (check all that apply).

   ☐..Physiotherapy
   ☐..Massage Therapy
   ☐..Acupuncture
   ☐..Vitamin Therapy
   ☐..Naturopathy/Homeopathy
   ☐..Exercise
   ☐..Chiropractic
   ☐..Reflexology
   ☐..Herbal Therapy
   ☐..Chelation Therapy
   ☐..Tai Chi
   ☐..Prayer, Meditation
   ☐..Other (Please specify: ______________________________________)

5. Are you bothered by **fatigue**? (Fatigue is defined as a feeling of tiredness, or having low energy levels.)

   ☐..No (Skip to next page)
   ☐..Yes (continue below)

   Please rate your **average** level of **fatigue** on a scale of 0 to 10 where 0 means "no fatigue at all", and 10 means "fatigue as bad as it could be".(please circle one number)

No Fatigue										Fatigue as bad as could be
0	1	2	3	4	5	6	7	8	9	10

In the past **four weeks**, how much has your **fatigue** interfered with your usual activities rated on a 0-10 scale where 0 is "no interference" and 10 is "unable to carry on any activities"? (please circle one number)

No interference										Unable to carry on any activities
0	1	2	3	4	5	6	7	8	9	10

The following items ask about how much your Multiple Sclerosis 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 Multiple Sclerosis and/or its treatment interfere with your:

1. HEALTH
Not Very Much 1 2 3 4 5 6 7 *Very Much*

2. DIET (i.e., the things you eat and drink)
Not Very Much 1 2 3 4 5 6 7 *Very Much*

3. WORK
Not Very Much 1 2 3 4 5 6 7 *Very Much*

4. ACTIVE RECREATION (e.g., sports)
Not Very Much 1 2 3 4 5 6 7 *Very Much*

5. PASSIVE RECREATION (e.g., 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. RELATIONSHIP WITH YOUR SPOUSE (girlfriend or boyfriend if not married)
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 RELATIONS
Not Very Much 1 2 3 4 5 6 7 *Very Much*

10. OTHER SOCIAL RELATIONS
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. RELIGIOUS EXPRESSION
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*

SECTION B: About Your Health

Please check the circle "☑" if you currently have any of the following health problems. If you do, to what extent have these problems affected your health in the last six months?

Not at all: the problem does not affect my health.

Mild: the problem makes my health a little worse than it should be.

Moderate: the problem makes my health worse than it should be.

Severe: the problem makes my health much worse than it should be.

Health Problem	Have it?	Affects your health?
a. **Muscle, bone or joint problems** (such as rheumatoid arthritis, osteoarthritis, back or neck pain, fibromyalgia, thin bones or osteoporosis, fracture, infection, others)	Yes ○ → No ○ ↓	Not at all .... ○ Mild .... ○ Moderate .... ○ Severe .... ○
b. **Allergies** (such as hay fever, dermatitis, eczema, allergies to medication, food allergy, others)	Yes ○ → No ○ ↓	Not at all .... ○ Mild .... ○ Moderate .... ○ Severe .... ○
c. **Breathing problems** (such as asthma, emphysema, bronchitis, fibrosis, lung scarring, TB, pneumonia, infection, common cold, others)	Yes ○ → No ○ ↓	Not at all .... ○ Mild .... ○ Moderate .... ○ Severe .... ○
d. **High blood pressure** (hypertension)	Yes ○ → No ○ ↓	Not at all .... ○ Mild .... ○ Moderate .... ○ Severe .... ○
e. **Heart and circulation problems** (such as angina, heart attack, heart failure, heart valve problem, hardening of arteries, varicose veins, claudication, foot or leg ulcers, others)	Yes ○ → No ○ ↓	Not at all .... ○ Mild .... ○ Moderate .... ○ Severe .... ○

Health Problem	Have it?	Affects your health?
f. **Digestive system problems** (such as ulcer, gastritis, inflammatory or irritable bowel disease, colitis, Crohn's disease, hiatus hernia, gall stones, pancreatitis, others)	Yes ○ → No ○ ↓	Not at all .... ○ Mild .... ○ Moderate .... ○ Severe .... ○
g. **Diabetes**	Yes ○ → No ○ ↓	Not at all .... ○ Mild .... ○ Moderate .... ○ Severe .... ○
h. **Kidney, bladder or urinary problems** (such as kidney failure, nephritis, kidney stones, urinary tract infection, prostate problems, bladder control problems, others)	Yes ○ → No ○ ↓	Not at all .... ○ Mild .... ○ Moderate .... ○ Severe .... ○
i. **Neurological problems except multiple sclerosis** (such as stroke, seizures, Parkinson's, paraplegia, quadriplegia, paralysis, Alzheimer's, dizziness, others)	Yes ○ → No ○ ↓	Not at all .... ○ Mild .... ○ Moderate .... ○ Severe .... ○
j. **Headaches** (such as migraine, tension, stress, sinus, others)	Yes ○ → No ○ ↓	Not at all .... ○ Mild .... ○ Moderate .... ○ Severe .... ○
k. **Mental or emotional problems** (such as depression, anxiety, substance abuse: alcohol or drugs, others)	Yes ○ → No ○ ↓	Not at all .... ○ Mild .... ○ Moderate .... ○ Severe .... ○
l. **Cancer** (such as breast, lung, prostate, cervix, stomach, colon, kidney, bone, metastasis or spread, lymphoma, leukemia, others)	Yes ○ → No ○ ↓	Not at all .... ○ Mild .... ○ Moderate .... ○ Severe .... ○

Health Problem	Have it?	Affects your health?
m. **Gynecological problems** (such as endometriosis, dysmenorrhea or menstrual problems, fibroids, ovarian cysts, others)	**Yes** ○ → **No** ○ ↓	**Not at all** .... ○ **Mild** .... ○ **Moderate** .... ○ **Severe** .... ○
n. **Blood problems** (AIDS or HIV+, anemia or low blood count, hemophilia or other bleeding problems, others)	**Yes** ○ → **No** ○ ↓	**Not at all** .... ○ **Mild** .... ○ **Moderate** .... ○ **Severe** .... ○
o. **Other problems** Please list: ____________________	**Yes** ○ → **No** ○	**Not at all** .... ○ **Mild** .... ○ **Moderate** .... ○ **Severe** .... ○

SF-36 HEALTH STATUS SURVEY/CANADA

INSTRUCTIONS: This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

Answer every question by marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

1. In general, would you say your health is:

(circle one)

Excellent 1
Very good 2
Good 3
Fair 4
Poor 5

2. Compared to one year ago, how would you rate your health in general now?

(circle one)

Much better now than one year ago 1
Somewhat better now than one year ago 2
About the same as one year ago 3
Somewhat worse now than one year ago 4
Much worse now than one year ago 5

3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

(circle one number on each line)

ACTIVITIES	Yes, Limited A Lot	Yes, Limited A Little	No, Not Limited At All
a. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
b. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
c. Lifting or carrying groceries	1	2	3
d. Climbing **several** flights of stairs	1	2	3
e. Climbing **one** flight of stairs	1	2	3
f. Bending, kneeling, or stooping	1	2	3
g. Walking **more than a kilometer**	1	2	3
h. Walking **several blocks**	1	2	3
i. Walking **one block**	1	2	3
j. Bathing or dressing yourself	1	2	3

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

(circle one number on each line)

	YES	NO
a. Cut down on the amount of time you spent on work or other activities	1	2
b. **Accomplished less** than you would like	1	2
c. Were limited in the **kind** of work or other activities	1	2
d. Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

(circle one number on each line)

	YES	NO
a. Cut down the **amount of time** you spent on work or other activities	1	2
b. **Accomplished less** than you would like	1	2
c. Didn't do work or other activities as **carefully** as usual	1	2

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

(circle one)

Not at all	1
Slightly	2
Moderately	3
Quite a bit	4
Extremely	5

7. How much bodily pain have you had during the past 4 weeks?

(circle one)

None	1
Very mild	2
Mild	3
Moderate	4
Severe	5
Very severe	6

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

	(circle one)
Not at all	1
A little bit	2
Moderately	3
Quite a bit	4
Extremely	5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks -

(circle one number on each line)

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the time
a. Did you feel full of pep?	1	2	3	4	5	6
b. Have you been a very nervous person?	1	2	3	4	5	6
c. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
d. Have you felt calm and peaceful?	1	2	3	4	5	6
e. Did you have a lot of energy?	1	2	3	4	5	6
f. Have you felt downhearted and blue?	1	2	3	4	5	6
g. Did you feel worn out?	1	2	3	4	5	6
h. Have you been a happy person?	1	2	3	4	5	6
i. Did you feel tired?	1	2	3	4	5	6

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

	(circle one)
All of the time	1
Most of the time	2
Some of the time	3
A little of the time	4
None of the time	5

11. How TRUE or FALSE is <u>each</u> of the following statements to you?

(circle one number on each line)

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
a. I seem to get sick a little easier than other people.	1	2	3	4	5
b. I am as healthy as anybody I know.	1	2	3	4	5
c. I expect my health to get worse.	1	2	3	4	5
d. My health is excellent.	1	2	3	4	5

SECTION C: About Your Mood

On this questionnaire are groups of statements. Please read each group of statements carefully. Then pick out the one statement in each group which best describes the way you have been feeling in the PAST WEEK, INCLUDING TODAY!. Circle the number beside the statement you picked. If several statements in the group seen to apply equally well, circle each one. *Be sure to read all the statements in each group before making your choice.*

1. 0 I do not feel sad.
   1 I feel sad.
   2 I am sad all the time and I can't snap out of it.
   3 I am so sad or unhappy that I can't stand it.

2. 0 I am not particularly discouraged about the future.
   1 I feel discouraged about the future.
   2 I feel I have nothing to look forward to.
   3 I feel that the future is hopeless.

3. 0 I do not feel like a failure.
   1 I feel I have failed more than the average person.
   2 As I look back on my life, all I can see is a lot of failures.
   3 I feel I am a complete failure as a person.

4. 0 I get as much satisfaction out of things as I used to.
   1 I don't enjoy things the way I used to.
   2 I don't get real satisfaction out of anything anymore.
   3 I am dissatisfied or bored with everything.

5. 0 I don't feel particularly guilty.
   1 I feel guilty a good part of the time.
   2 I feel guilty most of the time.
   3 I feel guilty all of the time.

6. 0 I don't feel disappointed in myself.
   1 I am disappointed in myself.
   2 I am disgusted in myself.
   3 I hate myself.

7. 0 I don't have any thoughts about killing myself.
   1 I have thoughts of killing myself, but I would not carry them out.
   2 I would like to kill myself.
   3 I would kill myself if I had the chance.

8. 0 I have not lost interest in other people.
   1 I am less interested in other people than I used to be.
   2 I have lost most of my interest in other people.
   3 I have lost all of my interest in other people.

9. 0 I make decisions about as well as I ever could.
1 I put off making decisions more than I used to.
2 I have greater difficulty in making decisions than before.
3 I can't make decisions at all anymore.

10. 0 I don't feel I look any worse than I used to.
1 I am worried that I am looking old or unattractive.
2 I feel that there are permanent changes in my appearance that make me look unattractive.
3 I believe that I look ugly.

11. 0 I can work about as well as before.
1 It takes an extra effort to get started at doing something.
2 I have to push myself very hard to do anything.
3 I can't do any work at all.

12. 0 I don't get more tired than usual.
1 I get tired more easily than I used to.
2 I get tired from doing almost anything.
3 I am too tired to do anything.

13. 0 I haven't lost much weight, if any lately.
1 I have lost more than 5 pounds.
2 I have lost more than 10 pounds.
3 I have lost more than 15 pounds.

I am purposely trying to lose weight by eating less: Yes_____ No___

SECTION D: About You

1. ☐..Male ☐..Female
2. Date of Birth: Day_____ Month_____ Year_____
3. Height: Feet _____ Inches _____ Weight: Pounds _____
4. What is your current marital status? (please check one)

   ☐..Married/Common Law ☐..Widowed
   ☐..Separated/Divorced ☐..Single

5. What is your highest education level? (please check one)

   ☐..Grade 8 or less
   ☐..Higher than Grade 8, but did not graduate from high school
   ☐..High School Graduate
   ☐..Post secondary or some university
   ☐..University Graduate

6. What is your household's total yearly income before taxes? (please check one)

   ☐..$0 - $20,000
   ☐..$20,001 - $40,000
   ☐..$40,001 - $60,000
   ☐..Above $60,000

7. What is your present employment status? (please check main one)

   ☐..Employed Full-Time
   ☐..Employed Part-Time
   ☐..Full-Time Homemaker
   ☐..Student
   ☐..Maternity Leave
   ☐..Unemployed because of my MS
   ☐..Unemployed for reasons other than MS
   ☐..Workers Compensation
   ☐..Disability or Sick Leave due to my MS
   ☐..Disability or Sick Leave for reasons other than my MS
   ☐..Retired due to my MS
   ☐..Retired for reasons other than my MS

8. My employment status is affected by my MS
   ☐..No ☐..Yes
9. Where do you currently live? (please check one)

   ☐..Large city (population more than 100,000)
   ☐..Small city (population 5,000 - 100,000)
   ☐..Town (population 500 - 4,999)
   ☐..Village (population 100 - 499)
   ☐..Rural municipality but not in city, town or village
   ☐..Reserve

Thank you for your assistance in completing this questionnaire.

Please place the completed questionnaire in the attached envelope and give it to the nurse to mail to us. Please keep your copy of the signed Consent Form.

Comments

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CURRICULUM VITAE

KAREN V.L. TURPIN

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(780) 352-4290 • karen.turpin@ualberta.ca

EDUCATION

Master of Science, University of Alberta, in progress. Completion anticipated Spring 2004.

- Epidemiology Program, Department of Medical Sciences-Public Health Sciences
- Courses: Epidemiological methods, statistics, public health fundamentals, critical appraisal of the literature, assessing health-related quality of life, SPSS

Bachelor of Science in Nursing with Honours, University of Alberta, 1996.

- Basic Collaborative Program, Faculty of Nursing

RESEARCH EXPERIENCE

Master's Thesis: Factors Associated with the Health-related Quality of Life of Persons with Relapsing-remitting Multiple Sclerosis (MS), September 2000 – April 2004

- Composed a best-evidence synthesis of the current English literature regarding factors associated with the health-related quality of life of persons with MS. Performed a thorough search, critical review, and summary of the literature.
- Conducted a research study to delineate the factors associated with the health-related quality of life of persons with relapsing-remitting MS. Analyzed a large and comprehensive database using SPSS.
- Supervisory committee: Linda J. Carroll, Ph.D (supervisor); J. David Cassidy, Ph.D; Walter Hader, M.D.; Steven Newman, Ph.D., M.D.

Research Nurse, Multiple Sclerosis Patient Care and Research Clinic, University of Alberta, May 2003 – Present

- Coordinate the "Phase III Myelin Basic Protein Synthetic Peptide Study".
    - Purpose of the study is to examine the effectiveness of a new drug treatment for persons with progressive multiple sclerosis. Aim of the drug is to slow or halt the progression of the disease.
- Screen potential participants for inclusion into study.
- Arrange research schedules with study team members and participants.
- Administer intravenous synthetic peptide and collect blood work.
- Perform clinical assessments with study participants.
- Document research activities, schedules, test results, and adverse events.
- Provide supportive nursing care.

Research Nurse, Multiple Sclerosis Patient Care and Research Clinic, University of Alberta, May 1998 – August 2000

- Conducted telephone interviews with patients and their family members to collect familial, genetic, and epidemiological data for the "Canadian Collaborative Study on Genetic Susceptibility to Multiple Sclerosis" project.

Research Nurse/Study Coordinator, Alberta Primary Care Research Unit, University of Alberta, August 1997 - August 1998

- Managed the day-to-day functions of a family medicine prevention research study.
- Prepared study materials and questionnaires, coordinated the activities of the research team, and arranged and conducted practice visits in both urban and rural physicians' offices across Alberta for data collection purposes.

Research Assistant, for Dr. J. Ross Kerr, Faculty of Nursing, University of Alberta, May 1995 - August 1995

- Assisted with the development of a health promotion model for seniors.
- Designed a questionnaire for data collection purposes.
- Organized and conducted the pilot study, and completed the data entry and analysis of pilot study data using SPSS.
- Arranged and conducted interviews with seniors, which included conducting physical and psychological assessments.

Research Assistant, for Dr. J. Ross Kerr, Faculty of Nursing, University of Alberta, June 1994 - August 1994

- Assisted in the completion of an evaluation report of the Adult Day Program Demonstration Project of Alberta Health.
- Conducted literature searches and reviews.

PROFESSIONAL EXPERIENCE

Clinic Nurse, Multiple Sclerosis Patient Care and Research Clinic, University of Alberta, May 2003 – Present

- Educate newly diagnosed patients and their families.
- Teach patients and their families about MS drug therapies.
- Provide information and supportive nursing care regarding secondary health complications (e.g. bladder/bowel dysfunction, pressure sores, infections).
- Provide supportive counselling.
- Liase with pharmacies, home care agencies, health care programs, and other health care providers in regards to patient needs.
- Record and report patients' symptoms to physician and relay physician's orders back to patient.
- Assist physician with medical procedures (e.g. lumbar puncture).

Administrative Assistant, Health Research Ethics Board (HREB), Panel B - Health Research, University of Alberta, August 1997 – May 2002

- Managed the day-to-day functions of the HREB, and was closely involved in all aspects of the research ethics process.
- Maintained an excellent working knowledge of granting agencies' requirements for ethics review in health research, the University of Alberta Standards for the Protection of Human Research Participants, Tri-Council Code of Ethical Conduct for Research Involving Humans, Health Information Act, and other applicable policies and legislation.
- Provided information to applicants from the University of Alberta, Capital Health, Caritas Health Group, and other applicants, of the ethics review application process.
- Conducted preliminary review of all applications, and ensured distribution of the applications to the appropriate primary reviewers.
- Organized the monthly board meetings for reviewing the ethics applications, arranged for the investigators to be at the meeting when their proposal is to be discussed, prepared the agenda and was responsible for taking minutes of the meeting.
- Prepared and handled all correspondence with all applicants regarding their application for ethics review.
- Created the HREB website, and was responsible for updating and managing the same. (www.hreb.ualberta.ca)

Well Child Clinic Nurse, Community Care and Public Health, Capital Health, Edmonton, February 1997 - April 1998

- Provided immunizations upon obtaining informed consent. Provided information regarding the after care and expected reactions for the various immunizations.
- Addressed parental concerns, and provided counselling and teaching regarding nutrition, growth and development, injury prevention, and common childhood illnesses/conditions.
- Performed physical assessments, as well as assessments of vision, hearing, dental care, and speech and language.

Registered Nurse, The Canadian Red Cross Society, Blood Donation Centre, Edmonton, August 1996 - May 1997

- Screened donors for actual or potential medical problems that could affect their health or the recipient's health if they donated, and deferred the donors as necessary.
- Performed phlebotomies.

PRESENTATIONS

Turpin KVL, Carroll LJ, Cassidy, JD, Hader W. (2003, May). Health-related quality of life in relapsing-remitting multiple sclerosis. Abstract in Spectrum of Multiple Sclerosis Care, 2003 Annual Conference Proceedings. (Poster presented at the 17th Annual Meeting of the Consortium of Multiple Sclerosis Centers, May 28 – June 1, 2003, San Diego, California).

Warren SA, **Turpin KVL**. (2001, Sept.). Measuring quantity and quality of life in MS: A comparison of three approaches. Abstract in Multiple Sclerosis: Clinical and Laboratory Research, Vol. 7, Supp.1. (Poster presented at the 17th Congress of the European Committee for Treatment and Research in Multiple Sclerosis, Sept. 12-15, 2001, Dublin, Ireland).

RESEARCH GRANTS

Warren SA, **Turpin KVL**, Milke D. **The Capital Care Foundation Research Grant**. Chronic pain in persons with multiple sclerosis (MS) residing in continuing care centres (CCCs) of The Capital Care Group (TCCG); $20,000; 2004-2006.

SCHOLARSHIPS

- Graduate Student Scholarship, Alberta Learning, April 2002, $2,000.
- Faculty of Medicine and Dentistry 75th Anniversary Award, Jan 1 – Dec 31, 2002, $14,000.
- Province of Alberta Graduate Scholarship, May 1, 2001 – Apr 30, 2002, $9,300.
- Medical Sciences Graduate Award, Faculty of Medicine, Jan 1 – Dec 31, 2001, $5,000.
- Nursing Alumni Association Scholarship, 1996, $1,000.
- Alberta Heritage Foundation for Medical Research Summer Studentship, 1995, $6,000.
- Louise McKinney Post-Secondary Scholarship, 1995.
- Nursing Alumni Association Scholarship, 1995, $1,000.
- Alberta Heritage Foundation for Medical Research Summer Studentship, 1994, $6,000.
- Louise McKinney Post-Secondary Scholarship, 1994.
- Alexander Rutherford Heritage Scholarship, 1991.
- Edmonton Public School Board Scholarship, 1991.

AWARDS / HONOURS

- Best Student Oral Presentation, Department of Public Health Sciences Research Day, May 2, 2003, $100.
- Faculty of Nursing's Dean's List & First Class Standing; 1993, 1994, 1995, 1996
- Addison-Wesley Book Award, Faculty of Nursing, 1994.

PROFESSIONAL AFFILIATIONS AND MEMBERSHIPS

- Alberta Association of Registered Nurses; since 1996.
- Mu Sigma Theta Tau International Nursing Honour Society; inducted 1995.

COMMUNITY INVOLVMENT

- Treasurer, Brightview Church, 2003 – Present.
- Graduate student representative, Faculty of Graduate Studies & Research Academic Appeals Committee, University of Alberta, 2000 - Present.
- Assistant registrar and board member, Faith Camp Board, 2000 - Present.
- Finance chair, Mu Sigma Theta Tau Executive Committee, 1998-2001.

REFERNCES

- Available upon request.