MULTIPLE SCLEROSIS: RISK PERCEPTION, SYMPTOMS AND TREATMENT

A Thesis Submitted to the College of
Graduate and Postdoctoral Studies
In Partial Fulfillment of the Requirements
For the Degree of Doctor of Philosophy
In the School of Public Health
University of Saskatchewan
Saskatoon

By

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ABSTRACT

Multiple sclerosis (MS) is a neurological disease of the central nervous system which causes the nerves to deteriorate over time. MS affects individuals between the ages of 20 to 45 years of age and both biological and environmental factors are associated with the disease. Canada has one of the highest rates of MS in the world along with several European countries. The definitive cause and cure for MS had not been determined and because of this the quality of life of people living with MS is poor. This thesis investigates the following topics: population awareness about second hand smoke exposure and its association with MS; the importance of having social support and its effect on managing pain in MS; medication use; and the effectiveness of exercise in improving the physical, mental and social quality of life of people living with MS.

The analysis shows that there was a lack of knowledge in second hand smoke exposure and risk of MS development in the Canadian population. Individual responses in agreeing or disagreeing to whether second hand smoke exposure was a risk factor for MS varied based on the provinces in which respondents resided, demographic factors, having a member of the household smoke inside the home and whether the respondents were bothered by second hand smoking.

Analysis of national survey data of people living with MS found that having social support was beneficial for reducing pain. Having someone to take you to the doctor, confide/talk to, to do something enjoyable with and to take you to the emergency was found to be significantly associated with a lower reporting of pain. In a separate analysis, using complementary treatment for MS was associated with lower odds of medication use. The use of behavior modification models as a tool for medication adherence is important for individuals living with chronic conditions who have a hard time coping with change.

In an analysis of the effect of complementary therapies on MS, aerobic exercise such as treadmill training, cycling, aquatic exercise and high intensity interval training and physiotherapy was found to have greater effect on physical, mental and social health as opposed to other types of complementary treatments.

ACKNOWLEDGEMENTS

First, I would like to thank God for giving me the knowledge and strength to complete this research. I would like to express my sincere gratitude to my PhD supervisor, Dr. Carl D'Arcy for his unconditional support, guidance, advices and expertise throughout this research.

I want to thank my thesis advisory committee Dr. Rein Lepnurm, Dr.Wolfgang Walz, Dr. Xiangfei Meng and Dr. Cindy Feng (chair) for their support and guidance. I would like to express my gratitude to all of the faculty members who have taught me throughout the years at the University of Saskatchewan. I also want to thank Mrs. Marylin Rana, thesis-based program assistant for organizing committee meetings and for her support.

I also want to express my gratitude to Statistics Canada for their support in granting me permission to use the Survey on Living with Neurological Conditions in Canada (SLNCC) data set and the Saskatchewan Research Data Centre (RDC) for providing me accesses to carry out the data analysis.

I acknowledge the financial support received from the School of Public Health and University of Saskatchewan for Graduate Scholarships and Graduate Teaching Fellowship. I acknowledge the Canadian Research Data Centre Network for the Emerging Scholars Grant as well as travel awards received jointly from the College of Graduate and Postdoctoral Studies, the International Student and Study Abroad Centre, the Graduate Students Association and the University of Saskatchewan Students' Union as well as the Canadian Institute of Health Research (CIHR) and School of Public Health.

DEDICATION

To my Mom (Mary Expedita Sebastiampillai Alphonsus) and Dad (Alphonsus Santhiyapillai) for their love, support, guidance, prayers and for believing in me.

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LIST OF ABBERVIATIONS

CCHS	Canadian Community Health Survey
CAMS	Complementary and alternative medical treatments
d	Cohen's d
EDSS	Expanded Disability Status Scale
MS	Multiple Sclerosis
OR	Odds Ratio (Measure of association between exposure and outcome)
ROC	Receiver Operating Characteristics curve
SLNCC	Survey on Living With Neurological Conditions in Canada

CHAPTER 1: AN INTRODUCTION TO MULTIPLE SCLEROSIS

1.1 Demographic Factors Associated with Multiple Sclerosis

Multiple sclerosis (MS) is a neurological disease of the central nervous system that attacks the myelinated axons.[1–3] As of 2008, the countries with the highest estimated prevalence include Hungary (176 per 100 000), Slovenia (150), Germany (149), United States of America (135), Canada (132.5), Czech Republic (130), Norway (125), Denmark (122), Poland (120) and Cyprus (110).[4] The Canadian Institute for Health Information (CIHI) states that there are an estimated 93,500 Canadians who live with MS which makes Canada one of the countries with the highest rates of this disease.[5] In a recent study in Ontario, Canada found that the prevalence of MS increased by 69% from 1.57 per 1,000 in 1996 to 2.65 in 2013.[6] This increase in prevalence was due to decline in mortality rates, the incidence remained stable.[6] In another study based in Canada estimated the number of incidence MS cases per year to rise from 4051 cases in 2011 to 4794 cases per 100 000 in 2031.[7]

When looking at the demographic variables, women are affected in greater numbers in comparison to men and people of Northern European descent are at an increased risk.[1] MS affects individuals starting between the ages of 20 to 45 years of age and though sometimes the disease starts in childhood.[8–10] Both biological and environmental factors are associated with the disease.[8–10] Life expectancy of patients with MS is shortened 7 to 14 years compared to the general population.[11] However, disability as a result of the disease is progressive and therefore diminishes the quality of life over time.[12] About 20% of patients are bedridden after 15 years following the onset of MS. Another 20% of patients may require a wheelchair or use crutches because of walking diffculties.[12]

1.2 Types of Multiple Sclerosis

There are four categories of MS which include relapsing-remitting, secondary progressive, primary progressive and progressive relapsing MS.[1] Approximately 85% of patients with MS have the relapsing remitting form which consists of episodic relapses and remissions. The first attack is known as a clinically isolated syndrome (CIS) which is a single episode of neurological symptoms which suggest that MS is present (figure 1.1).[13] Magnetic resonance imaging (MRI) tests are usually done in order to find if there are any abnormalities in the brain or spinal cord.[13] If multiple attacks occur then the disease is seen as entering in the relapsing remitting stage (RRMS) (figure 1.2).[13] RRMS is characterized by unpredictable relapses which are defined as flare-ups in which new symptoms may occur.[13] After RRMS, the patients disease tend to evolve into secondary progressive MS (SPMS) (figure 1.3).[13] In this stage relapses and remission become less noticeable and disease progression is steady.[13] Only 15% of patients will have a primary progressive MS type and some will transition to progressive relapsing MS (figure 1.4).[13] Progressive relapsing MS is caused by a slow progression in disability without relapses.[13]

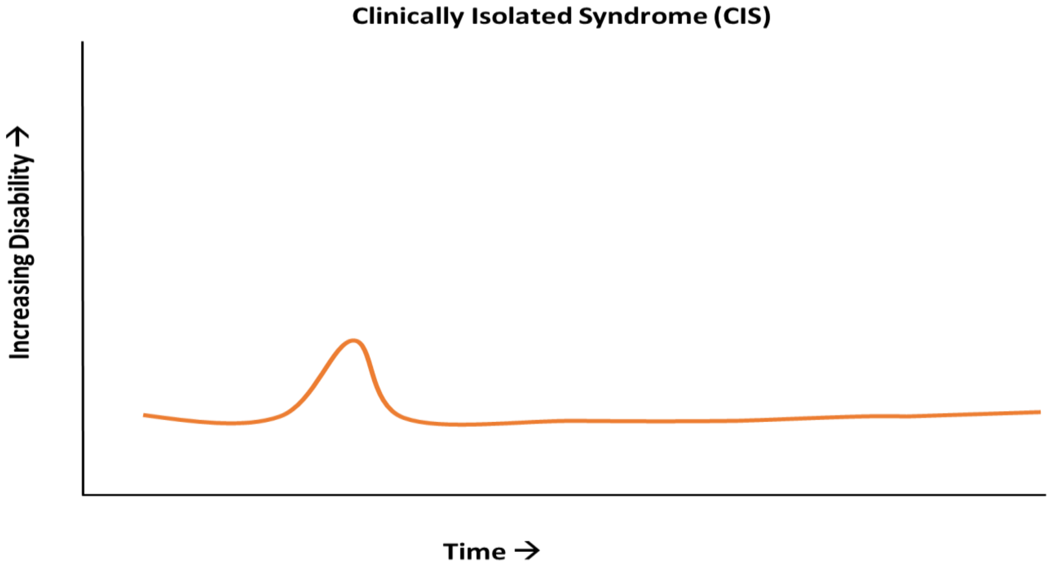

Figure 1.1: Clinically isolated syndrome is the first attack of MS on an individual and lasts for 24 hours which causes inflammation or demyelination. Figure adapted from (MS Society of Canada,2018).[13]

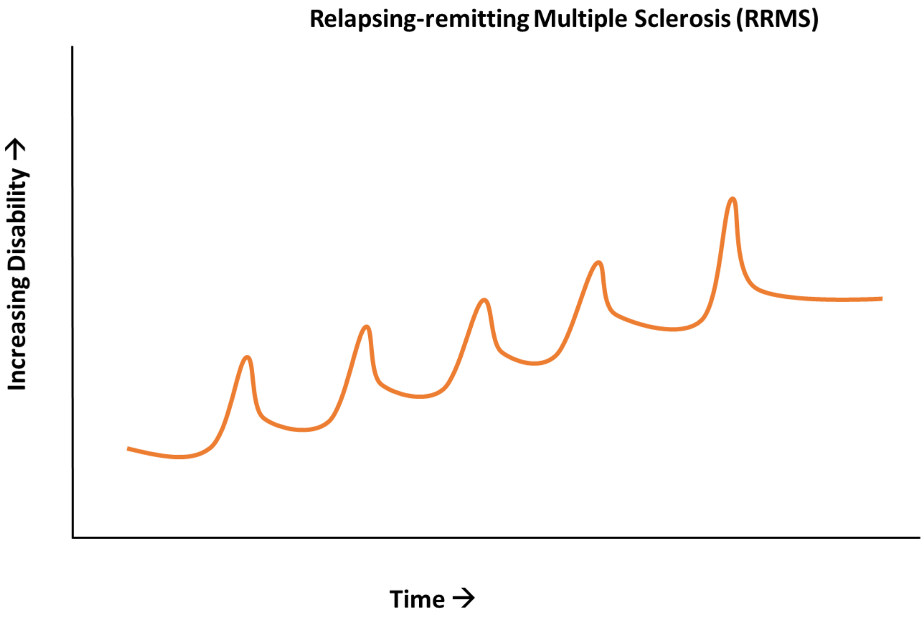

Figure 1.2: Relapsing-remitting MS is the most common type with new symptoms appearing during relapses. Figure adapted from (MS Society of Canada,2018).[13]

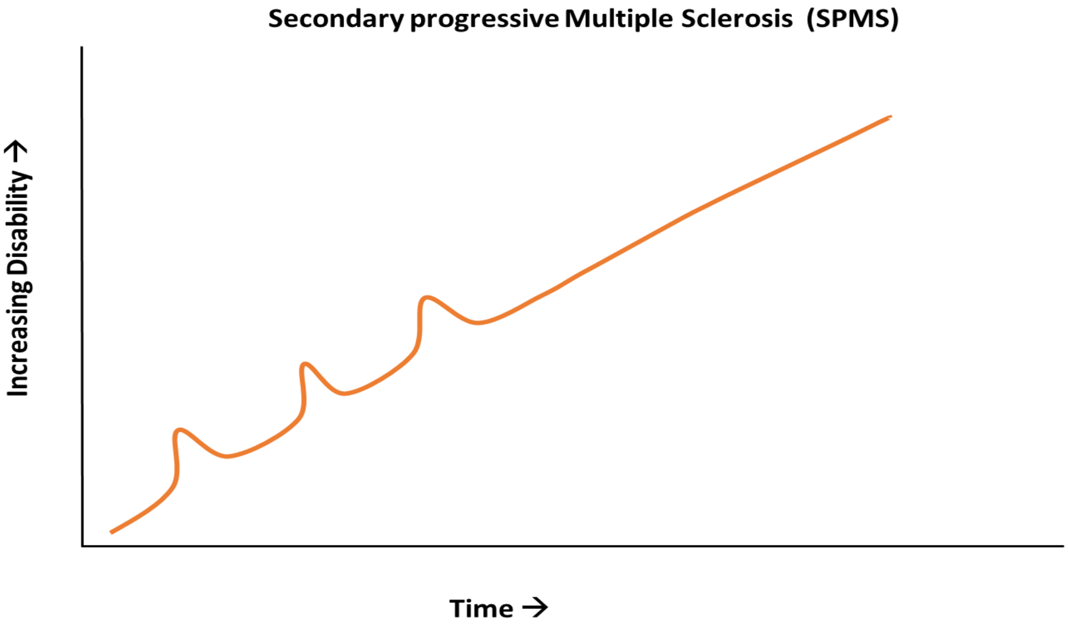

Figure 1.3: Secondary progressive MS starts off with relapses and disability gets worse over time. Figure adapted from (MS Society of Canada,2018).[13]

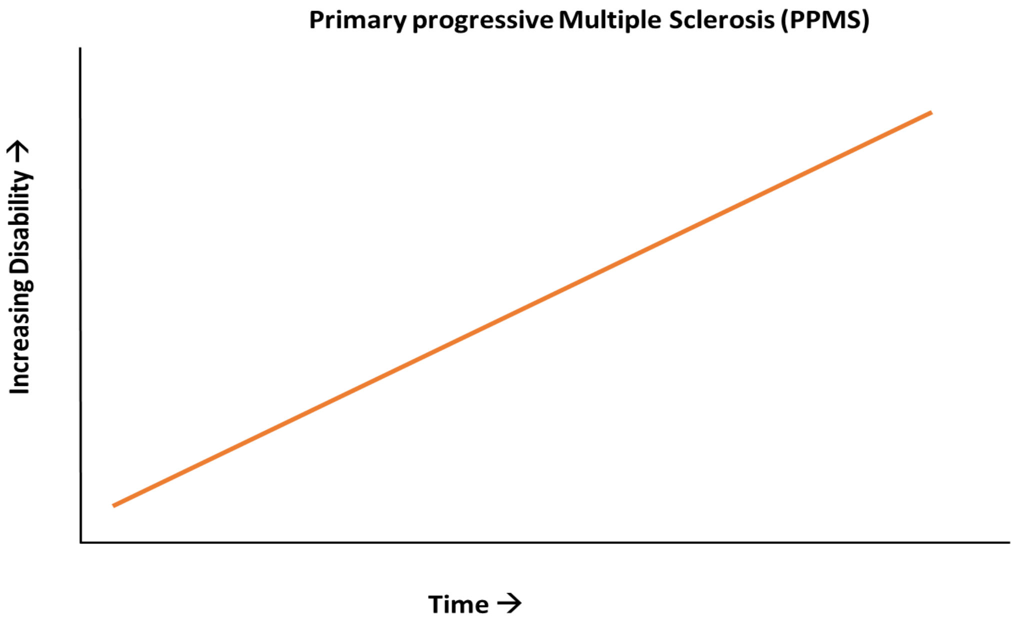

Figure 1.4: Primary progressive MS is defined by a gradual increase in disability without relapses. Figure adapted from (MS Society of Canada,2018). [13]

1.3 Diagnosis of Multiple Sclerosis

The diagnosis of MS is commonly based on the McDonald criteria which looks at the clinical presentation of symptoms.[14] Based on the criteria, the number of attacks and number of lesions that are present are used to indicated whether an individual has MS.[14] Magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) are used in order to make the diagnosis.[14]

1.4 Genetic and Environmental Factors Associated with Multiple Sclerosis

There are two prominent features of MS; 1) the disease occurs in clusters among families, and 2) the disease varies in frequency globally.[15] In several twin studies, it has been suggested that the clustering in families is determined mainly by genetic factors however the regional difference in the prevalence of MS occurs from both genetic and population level environmental factors.[16,17]

The risk of developing MS is based on the degree of relatedness. Studies have shown that first, second and third degree relatives of people who have MS were also more likely to have the disease in comparison to the general population.[18] Table 1-1 describes the risk factors for MS throughout the life course. The human leukocyte antigen (HLA) has been known to have the largest genetic contribution to MS susceptibility. In the early stages of life there are protective factors such as having protective human leukocyte antigen (HLA) haplotypes during in utero or childhood.[19] Human leukocyte antigens are a cluster of genes on the short arm of chromosome 6 and certain haplotypes such as HLA-DR1 and HLA-DR53 are considered to be protective against MS.[20,21] During adolescence, protective factors include being exposed to the sun, having enough vitamin D levels and having a diet rich in fish oils. Although individuals can act on some protective factors, risk factors such as genetic predisposition to MS and sex of birth cannot be individually controlled.

Table 1.1: Protective and risk factors associated with MS. Adapted from (Ramagopalan et al., 2010).[22]

Stages of life	**Protective factors**	**Risk Factors**
In utero	• Protective HLA haplotypes	• Family history or genetic factors • Female sex • Being born in May • Born in high latitude regions
Childhood		
Adolescence	• Amount of sun exposure • Vitamin D supplements • Diets high in fish oils	• Exposure to Epstein Barr virus • Smoking • Vitamin D deficiency • Living in high altitude regions
Adulthood	• None identified	• Exposure to Epstein Barr virus • Smoking

Along with genetics, environmental factors have been known to play a role in MS development.[9,23] Epstein-Barr virus (EBV) has been found to be a risk factor in many studies.[9] The risk for MS increases among individuals who have a history of infectious mononucleosis which occurs due to EBV infection as a teenager or in adulthood.[9] The increased risk of developing MS for individuals who had EBV is possibly due to the enhanced permeability of the blood brain barrier which is triggered by the acute primary EBV infection.[24] Once the B-cells cross the blood brain barrier and enter CNS, various mechanisms take part that result in the development of MS pathology.[24] Other environmental factors such as smoking and lack of vitamin D can result in an interaction with EBV which could also lead to MS.[24] However, some studies have found that there is a low risk for MS among individuals who are seronegative for EBV and more than 95% of the adult population are infected with EBV therefore it is not possible for all of them to develop MS.[9] This is known as the EBV paradox.

Other risk factors for MS include cigarette smoking. Studies have indicated that smoking increases the risk of conversion from clinical isolated syndrome to MS.[22,25] Several studies have found an increased risk of developing MS among individuals who smoke cigarettes.[26] One study found a hazard ratio of 3.6 (95% CI 1.3 to 9.9) for individuals who had ever smoked a cigarette compared with individuals who had never smoked.[26] Another study done in Sweden found that smoking affects the risk of developing MS regardless of the age at exposure and both duration and intensity of smoking increases the risk of MS.[27] Second hand smoke exposure is associated with many health effects such a cardiovascular disease and cancer and is also a risk factors for MS. In a study done on passive smoke exposure and its effect on MS, it was found that exposure to smoke is associated with higher risk of developing MS.[28]

Lack of vitamin D is also a risk factor for MS. Vitamin D is available from two sources, the first is through exposure to ultraviolet B radiation (UVB) through sunlight and the second is through diet.[29] Foods such as milk, cereal, orange juice, cheese, salmon, tuna and vitamin supplements contains vitamin D2.[29] Increased vitamin D which is associated with lower risk of MS could be due to apoptosis of the autoreactive B-cells.[24] There is an inverse relationship between amount of UVB received from sunlight and vitamin D concentration. One study found that individuals who were exposed to sunlight for at least 2 hours per day had lower odds of getting MS OR=0.47

(95%CI 0.26 to 0.84).[29] Another study found that higher sun exposure as a child and in early adolescence was associated with a decreased risk of MS development.[30]

However, other studies have found that vitamin d levels and sunlight are independent of each other.[31] Vitamin D supplementation compared to natural sunlight has still not been proven to be effective in altering disease activity.[31] Regardless of whether these hypothesis are valid, individuals who have low levels of vitamin D could still take these supplements at moderate doses as a protective mechanism.[31]

1.5 Treatment for Multiple Sclerosis

There is no cure for the disease, however, there are several treatment options for minimizing the symptoms of MS such as medication, venous angioplasty, stem cell therapy, urinary catheterization, rehabilitation and psychotherapy however, medication is the most widely used treatment for controlling symptoms of MS and preventing relapses from occurring.[32] Disease modifying therapies help shorten the duration of MS attacks and decrease their frequency. There are currently eight types of medications that are used to reduce disease progressions.[1] These include drugs such as Beta interferons (Avonex, Rebif, Betaseron, Extavia), Glatiramer acetate (Copaxone), Mitroxantrone (Novantrone), Natalizumab (Tysabri), Fingolimod (Gilenya).[1] Since medications don’t cure MS, many patients turn to other types of treatments and become less adherent to taking medication as prescribed. One of the most controversial treatments is an angioplasty procedure known as liberation therapy in which the “blocked” veins are opened up in order to improve blood flow and drainage from the brain.[33] Chronic cerebrospinal venous insufficiency (CCSVI) in which the veins are blocked was proposed by the Italian physician Dr. Zamboni as the cause of MS, however evidence now strongly suggests that CCSVI does not lead to MS.[34–36]

1.6 Complementary treatment for MS

Complementary treatment is treatment that is used along with medication.[37] Non-invasive MS treatments include a wide range of options such as exercise, food and diet, stress management and acupuncture.[37] At least a third of MS patients have used complementary and alternative treatments (CAM). Exercise is one type of complementary treatment that has been shown to improve movement and balance among patients with MS. In addition, exercise reduces stress and promotes recovery in patients with MS.[38,39] However there has been few studies that have examined the effect of various types of exercises and physical therapy on the different domains of quality of life such as physical, mental and social. Although exercise may benefit overall quality of life, the effects on specific domains such as the physical domain; the mental and social domains has been less studied.

Types of complementary treatment include cannabis, diet, exercise, vitamin and mineral supplements, relation techniques, acupuncture, massage and psychological approaches.[40] Many reviews have stated that exercise and yoga has improved many aspects of a person's life especially in those with MS.[41] Yoga is an Indian practice that incorporates mind and body awareness. There are many types of yoga such as Hatha which focuses on poses and breathing, Ashtanga and Vinyasa yoga which is more physically demanding, Iyengar yoga which is based on the precision of the poses, Bikram yoga which is taught in a heated room and Kundalini yoga based on breathing and physical poses.[42] In a randomized controlled trail of yoga and exercise in MS it was found that subjects with MS who participated in either a 6 month yoga or exercise class showed an improvement in fatigue as opposed to the control group.[43] In another study done on an Ananda yoga program found that significant improvements were found in strength, balance, mental health and overall quality of life.[44] Other types of complementary treatments such as massage therapy has also been found to reduce pain, improve balance and walking speed and those who used both massage therapy and exercise therapy were also found to reduce pain.[45]

1.7 The health care cost of MS

In Canada the total per capita health care cost for adults who were 20 and older in 2011 was $16,800 for individuals with MS.[7] The total annual heath sector costs for MS is expected to risk to $2 billion by 2013.[7] In a study done in Canada where MS patients completed a web based questionnaire, it was found that the mean cost per patient per year increased as disability increased.[46] Patients with mild disability define by an expanded disability status scale (EDSS) score from 0 to 3 spent a mean of $30,836 per year and for a patient with severe disability (EDSS 4 to 6.5) a patient spent a mean of $77,981 per year.[46] Another Canadian study stated that the largest cost associated with EDSS was the inability to work which increased as EDSS increased.[47] However if disease progression is delayed or slowed these costs can be reduced.

1.8 Overview of MS in Canada

Canada has one of the highest rates of MS in the world.[48] Based on the Survey of Living with Neurological Conditions in Canada (SLNCC) 2010 to 2011 there were 93,500 Canadians diagnosed with Multiple Sclerosis (MS) with a prevalence of 290 cases per 100,000 people.[49] The crude prevalence rate was steady from 2003 to 2012 for males and females. The crude prevalence was in the range of 2 to 3 per 1,000 for females and for males the prevalence was around 1 per 1,000 (Figure 1.5).

The age standardized incidence rates per 100,000 for individuals 20 years of age and older are shown below in Figure 1.6. Throughout the years the age standardized incidence rates were greater in females as opposed to males with a rate of approximately 20 to 30 per 100,000.[50] These rates were steady from 2003 to 2012. However for males the rates were approximately 10 per 100,000 from 2003 to 2012.[50] The crude incidence rates of MS varied between age groups and sex; see figure 1.7. Individuals between the ages of 35 to 49 had the highest crude incidence rate of MS per 100,000 people in 2015.[50] A study done on timing of birth and risk of multiple sclerosis found that in Canada fewer patients with MS were born in November compared with controls.[51] This was confirmed in a British dataset where there were more people with MS who were born in May.[51] One of the explanations for this association is that the seasons may affect with the development of the central nervous system and immune system. Maternal level of vitamin D could be correlated to increased births of MS in certain months of the years.[51]

Regional variation of MS prevalence in Canada was also identified (Table 1.2).[48] One study has pointed out that the areas of the major cities in the prairies being located further north than in the other regions could be a possible explanation for the increased prevalence.[48]

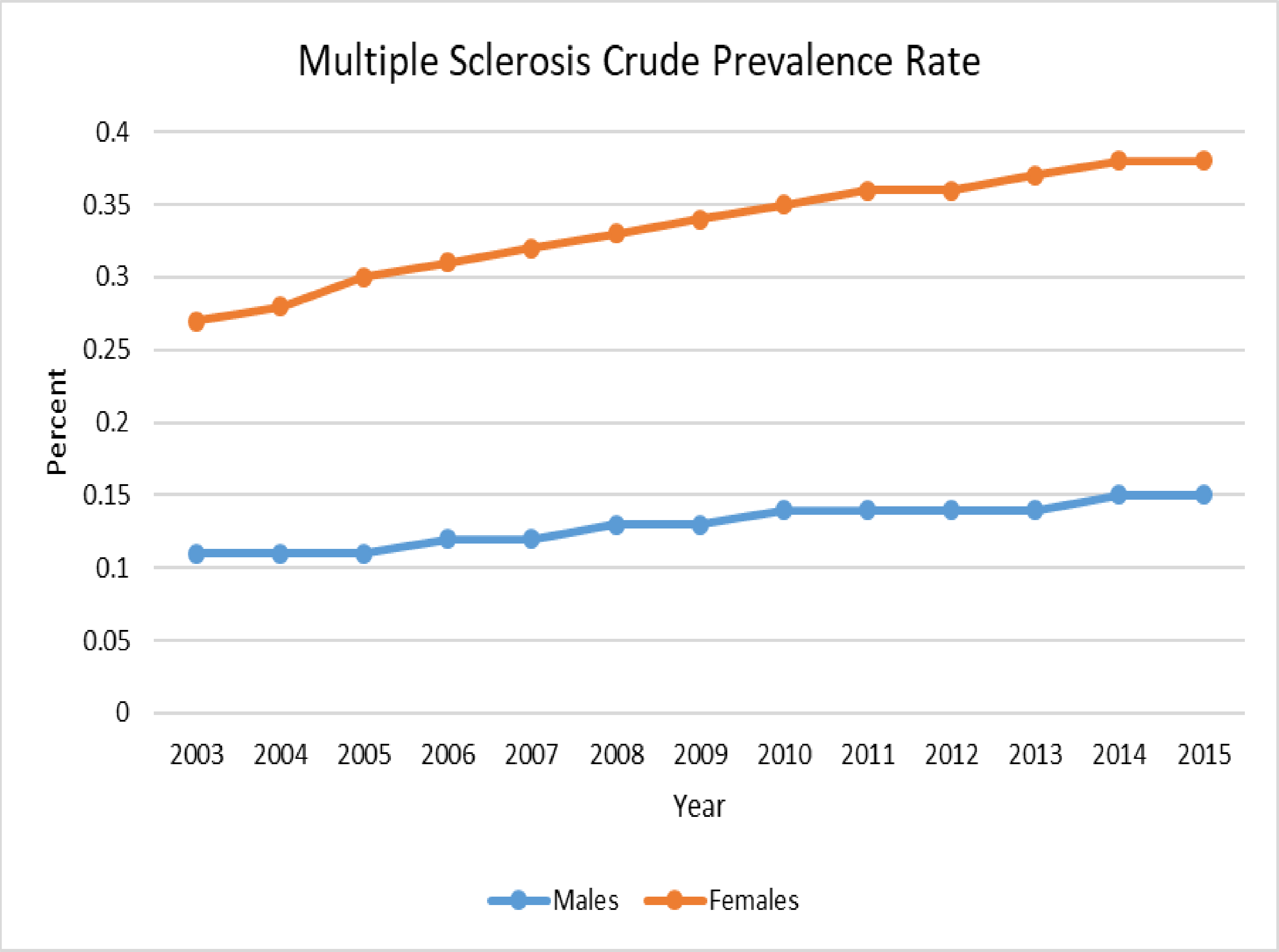

Figure 1.5: Multiple sclerosis crude prevalence rate for individuals aged 20 years and older in Canada from 2003 to 2015. Adapted from (Public Health Agency of Canada, Public Health Infobase, 2018).[50]

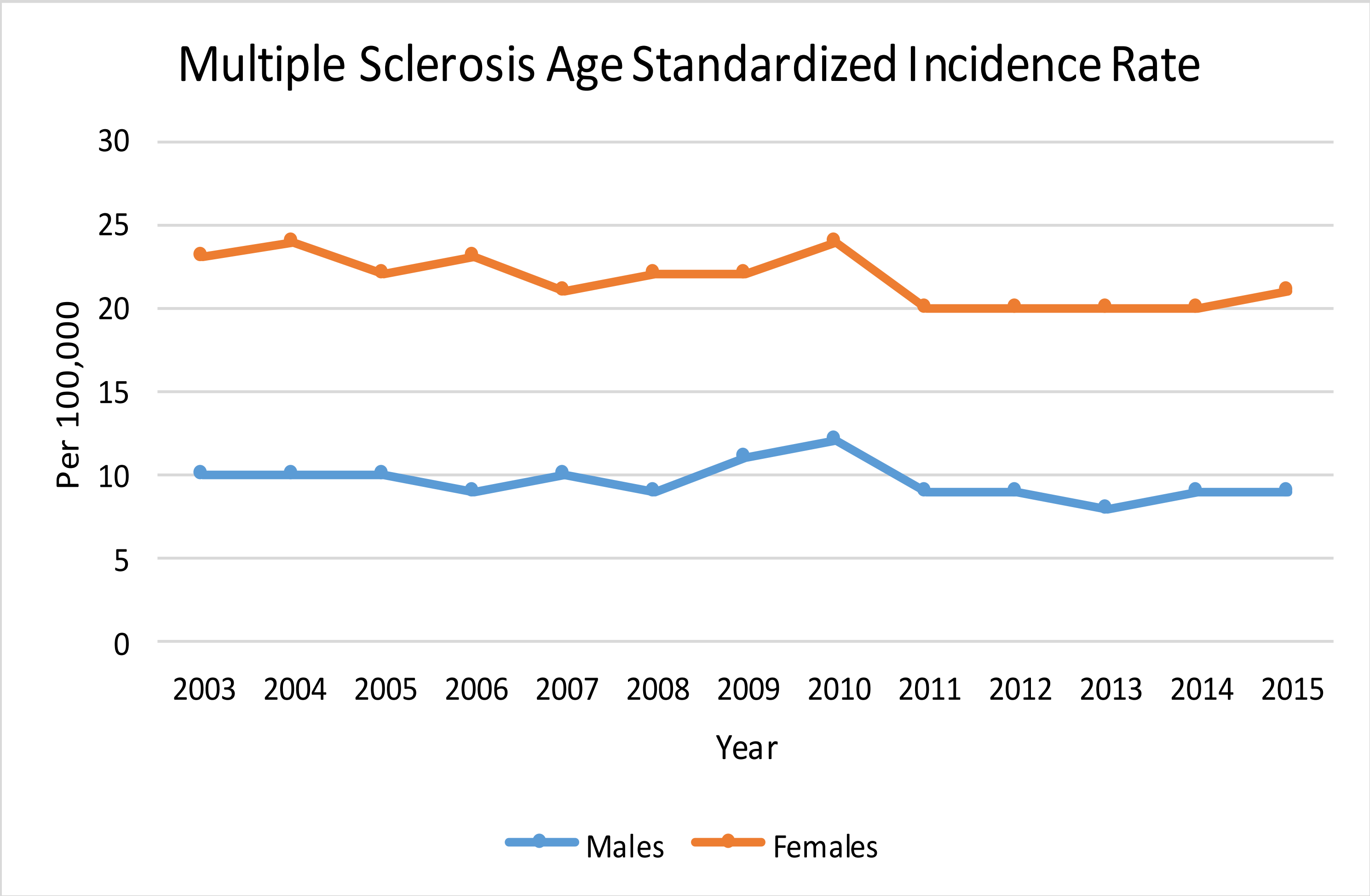

Figure 1.6: Multiple sclerosis age standardized incidence rate per 100,000 for individuals ages 20 years and older in Canada from 2003 to 2015. Adapted from (Public Health
Agency of Canada, Public Health Infobase, 2018). [50]

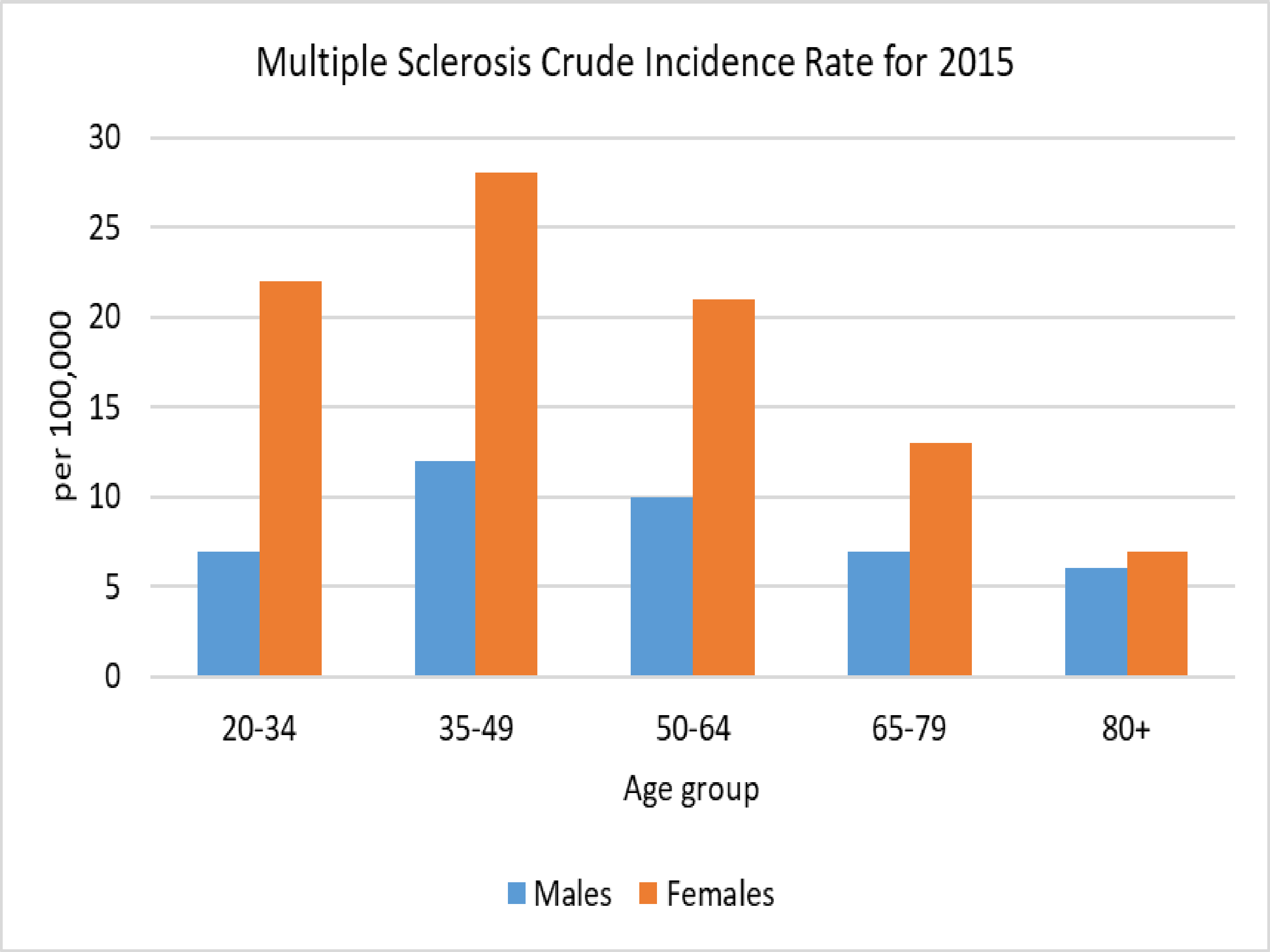

Figure 1.7: Multiple sclerosis crude incidence rate per 100,000 in Canada for 2015. Adapted from (Public Health Agency of Canada, Public Health Infobase, 2018). [5]

Table 1.2: Prevalence of MS in Canadian Provinces. Adapted from (Beck et al.,2005).[48]

Regions in Canada	Prevalence
British Columbia	240 per 100,000
Prairies (Alberta, Saskatchewan, Manitoba)	340 per 100,000
Ontario	230 per 100,000
Quebec	180 per 100,000
Atlantic Canada (New Brunswick, Newfoundland and Labrador, Nova Scotia, Prince Edward Island)	350 per 100,00

Based on the survey of living with neurological conditions in Canada (SLNCC), living with MS had a moderate, quite a bit or extreme effect on 63% of people's lives.[49] In addition to this, MS prevented sleep for the majority of MS patients (62%).[49] In terms of social impact, more than half of survey respondents stated that MS had limited their job opportunity moderately or extremely.[49] When looking at comorbidities associated with MS, bowel and or bladder problem seemed to be the major problem with 59% of people reporting they had this in comparison to the general population. The next major problem were mood disorders with 22% of people reporting this problem followed by high blood pressure at 17% , heart disease at 5% and diabetes at 6%.[49]

Psychiatric comorbidities such as depression and anxiety are common in MS and have been reported in many studies.[52–54] Some ways to treat depression are through medication, cognitive behavioral therapy, exercise and electrical therapies.[53] Studies have also investigated the impact of physical comorbidity on the health related quality of life (HRQoL) of people living with MS.[55]

It was found that increased disability, depression and anxiety symptoms, fatigue and physical comorbidity were associated with decreased HRQol.[55]

In terms of treatment for MS, 82.5% stated they received treatment while 17.5% didn't. The majority of patients (83.7%) received medications such as injections, infusions and pills. 48.5% of patients stated they used rehabilitation therapy, 27% used counselling or psychotherapy services, 25.3% used complementary or alternative medications, 15.6% used urinary catheterization and 10.3% used venous angioplasty/liberation therapy procedures.[49]

Managing MS involves many health care providers along with tests which are costly. In a cross sectional analysis of 669 adults with MS who were enrolled in a province wide observational study between 2011 and 2013 found that over the two years of follow-up, there were 150 hospitalizations which involved 99 patients and 11,213 outpatients visits which involved 637 patients.[56] In addition to this, individuals with MS are living a long period of time with the illness which reduces the quality of life. Based on the study done on MS mortality rates in Canada from 1975-2009, it was found that the highest mortality rates were after 2000 (Figure 1-6).[57] In 2013, the total number of deaths were 252,338 in Canada of which 521 deaths were due to MS.[49]

A study on the relative mortality and survival in MS based on British Columbia MS registry from 1980 to 2007 found that the median survival age was 78.6 years for women and 74.3 for men.[58] The survival was long for relapsing onset (R-MS) with an age of 49.7 years than for primary progressive MS (PPMS) which had a survival age of 32.5 years.[58] The reduced survival time for people with PPMS could be due to the delays that occur for diagnosis.[59] The MS survival times were considered long for this study, however in comparison to the general population the risk of death was still considered greater.[58]

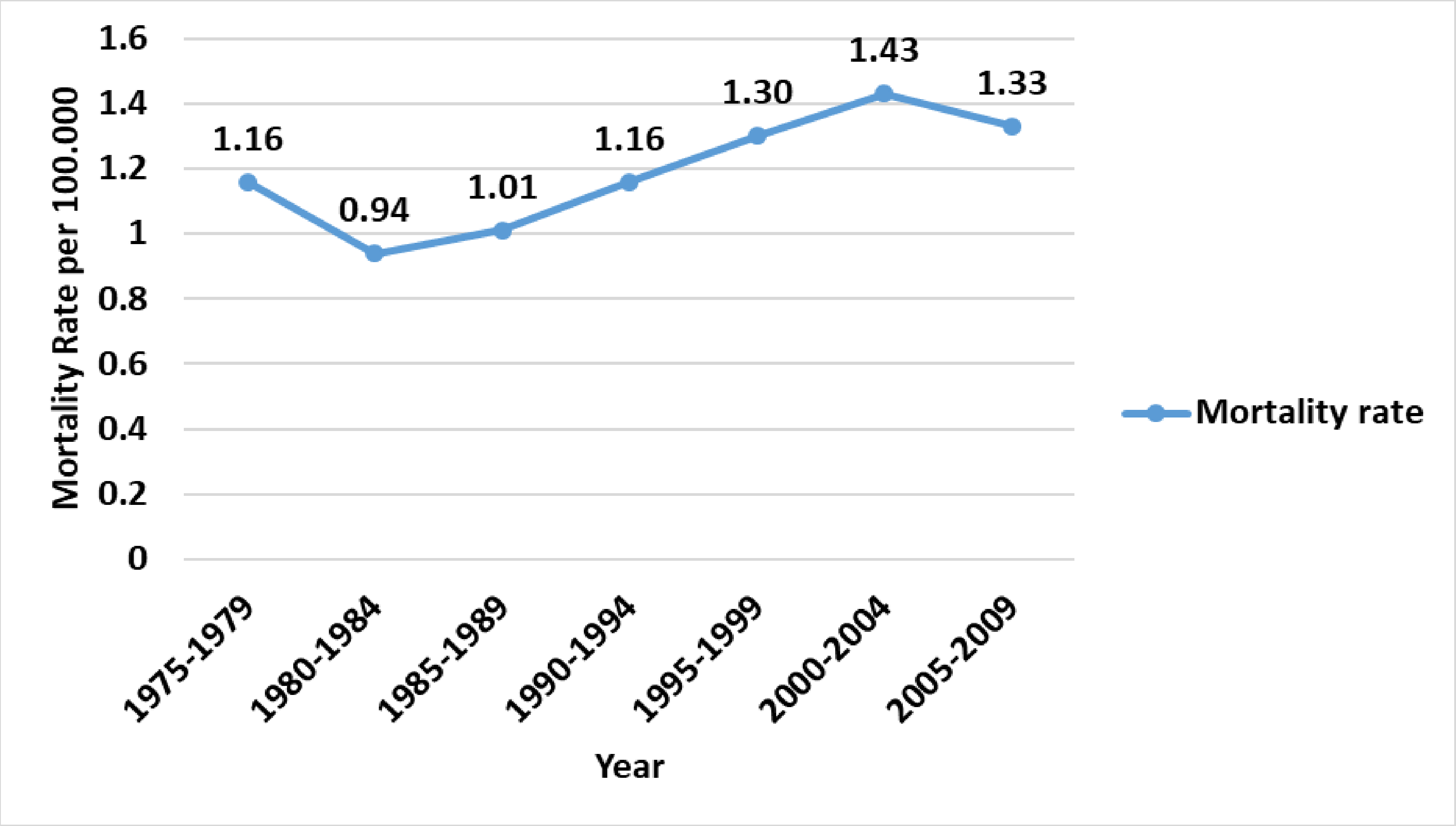

Figure 1.8: Mortality rates from MS in Canada from 1975 to 2009. Adapted from (Public Health Agency of Canada, Public Health Infobase, 2018).[57]

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CHAPTER 2: OBJECTIVES OF THIS RESEARCH

2.1 Rationale for this Research

The purpose of this research is to explore at a population level the gaps in MS research in terms of prevention of risk factors such as second hand smoking and to explore factors associated with medication use and exercise uptake. In addition, this research explores the psychosocial factors associated with MS and how these factors contribute to the pain experienced by MS patients. Although there has been extensive MS research exploring the risk factors of the disease, not much of the research has examined the issues at a population level.

2.2 Context of this Research

This research examines areas of MS from risk factors, through symptoms to treatment options and their impact on patients' well-being. The four areas of research concern: 1) the general population's knowledge about a specific risk factor for MS (second hand smoking), 2) predictors of pain in MS patients, 3) factors associated with medication adherence for MS, and 4) types of complementary treatment for MS and their effect on the health and well-being of MS patients. This research will help improve our knowledge of MS and its treatment. Hopefully the findings will inform policies and programs that are created to provide better patient care.

Chapter 2 gives an overview of multiple sclerosis in Canada in terms of rates of MS throughout the years, rates of MS based on provinces and common comorbidities associated with MS.

Chapter 3 investigates Canadian data on the predictors associated with people's level of agreement on whether second hand smoking is a risk factor for MS. The data on smoking was obtained from the Health Canada: Smoking Survey (2004-2005). The analysis also examined whether their perception of whether second hand smoke exposure could lead to MS development varies depending on the province in which they live, smoking levels in those provinces and other characteristics of their immediate social environment. A multilevel mixed effects logistic regression model will be created and odds ratios will be calculated to assess whether individual level and area level factors are associated with odds of people agreeing to second hand smoke exposure leading to development of MS.

Chapter 4 explores aspects of pain, a very common symptom of MS. The main question examined is, “does a lack of support from family or friends have an interaction effect on a lack of sleep and mental health problems and further whether this is associated with reported pain among individuals with MS?” The data examined is from the national Canadian Survey of Living with Neurological Conditions. Multivariate logistic regression is used.

The next two chapters explore aspects of the treatments for MS. Chapter 5 examines the predictors of medication use in people living with MS. Data from the national Survey of Living with Neurological Conditions in Canada (SLNCC) is again used and a multivariate logistic regression analysis was conducted.

Chapter 6 is a meta-analysis of a variety of complementary treatment modalities such as exercise types, yoga and physical therapy on their impact on the physical, mental and social health of people living with MS. The final chapter summarizes our findings and discusses potential avenues for further research and the policies and programs to provide better treatment for MS patients.

2.3 Study Design

This thesis uses two general types of study designs. Cross sectional survey designs are used in chapters 3, 4 and 5 and a systematic review with meta-analysis is used in chapter 6. Cross sectional studies are more advantageous over other study designs because it is relatively inexpensive, many outcomes and risk factors can be assessed and it takes less time to carry out.[1] The disadvantage is that measurement occurs only at one point in time therefore causality cannot be inferred.

Meta-analysis combines the results of multiple studies which allows results to be generalized to a larger population.[2] However the disadvantages of this is that several small studies cannot replicate the result of a single large study and a meta-analysis cannot correct for biases which may have occurred in the original studies.[2]

2.4 Data Sources

The data examined in Chapters 3, 4, 5 are from large scale national Canadian surveys. In Chapter 3 the analysis is from the 2005 Health Canada-Smoking survey. The survey conducted by Health Canada collected information about the Canadian general public which included smokers and non-smokers in the provinces of Quebec, Ontario, Saskatchewan, Newfoundland and British Columbia. The final sample consisted of 1,404 people in Quebec, 1,443 people in Ontario, 1,413 people in Saskatchewan, 1,442 people in Newfoundland and 1,468 people in British Columbia.[3,4] The surveys measured knowledge attitudes and behaviours of the population of both smokers and non-smokers in each of the provinces.

The Survey of Living with Neurological Conditions in Canada (2011) was used for the analysis in chapters 4 & 5.[5] This survey is a cross sectional survey that was linked to the Canadian Community Health Survey (CCHS).[6] The CCHS collects information which is related to the health status, health care utilization and health determinants for the Canadian population. For 2 years (2010 and 2011), the CCHS collected information on a set of 18 neurological conditions and participants who had one of these conditions were recruited to participate in the SLNCC. The SLNCC sampled the population of household residents who were 15 years of age and older in one of Canada’s 10 provinces. The final sample consisted of 8,200 people with neurological conditions with a response rate of 81.6%.[5]

For the meta-analysis in Chapter 6, articles from 1990 to 2017 (27 years) were collected from a database search from PubMed, Medline and Scopus using specific search strategies with detailed inclusion and exclusion criteria applied to screen the articles that are to be selected for inclusion in the systematic review and meta-analysis.

2.5 Statistical Analysis

This thesis uses a variety of statistical analyses depending on the nature of the question being examined. Descriptive analysis is used to explore the demographic characteristics of the population and samples surveyed. Multilevel mixed effects logistic regression analysis (Chapter 3) is used for binary outcomes as well as to explore the area level effect on the outcome. Multivariate logistic regression (Chapter 4 and 5) will be used for binary outcomes in order to determine odds ratios.

For chapters 4 and 5 where SLNCC data sets were used, replicated sampling weights and bootstrapped variance estimation were used as recommended by Statistics Canada in order to take into account the survey design [5] A set of (n=500) replicate weights were used in order to account for non-responses. The bootstrapping sampling weights used in the analysis were created for SLNCC by Statistics Canada. For the SLNCC linked data set, the bootstrap replicates are the sub samples that were drawn and used to estimate the variance of the CCHS estimates.[5] In order to take into account the SLNCC sample design, each of the CCHS bootstrap replicates were adjusted. [5]

For the meta-analysis (Chapter 6) Cohen’s *d* which is the mean difference is computed for physical health scores, mental health scores and social health scores.[7] The standard mean difference will be calculated based on the mean difference between the treatment and control group divided by the pooled standard deviation.[7]

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CHAPTER 3: PREDICTORS OF PEOPLE'S PERCEPTIONS OF SECOND HAND SMOKE EXPOSURE AS A RISK FACTOR FOR MULTIPLE SCLEROSIS

Abstract

Objective: There are many health problems associated with exposure to second hand smoke exposure. Being exposed to second hand smoking earlier in childhood may cause development of MS. The primary objective of this study was to examine the predictors associated with people's perception on second hand smoke exposure being a risk factor for MS.

Methods: The data set was drawn from the Health Canada: Smoking Survey conducted in 2004 and 2005 by Environics Research Group in partnership with Health Canada to survey the public in the province of British Columbia (N=1,468), Newfoundland (N=1,442), Quebec (N=1,404), Ontario (N=1,443) and Saskatchewan (N=1,413). A multilevel mixed effects logistic regression model analysis was carried out in order to determine whether people's perceptions of second hand smoking as a risk factor for MS varied based on the province of residence.

Results: Age, sex, having a household member who smoked inside their home, if respondents were bothered by second hand smoke exposure and smoking status were associated with increased odds of people agreeing to second hand smoke exposure being a risk factor for MS development. In addition to this the province of residence was associated with survey respondents agreeing or disagreeing to whether second hand smoke exposure is associated with MS development.

Conclusion: The study results could guide in the development of stop second hand smoking campaigns on social media, TV and bus stop shelters. This could help raise awareness about the risk of second hand smoking and its association on the risk of development of MS.

3.1 Introduction

Second hand smoke exposure is detrimental to health since it leads to ischaemic heart disease, lower respiratory infections, asthma and lung cancer.[1] There are many environmental factors that are associated with multiple sclerosis (MS) development and exposure to cigarette smoke is one of them.[2] However people's perceptions about second hand smoke exposure on MS development is an understudied area.

Recent studies have reported the harmful effects of second hand smoke exposure on development of MS among children as well as adults.[3–5] Children who had parents who smoked were a greater risk of having a first episode of MS RR=2.12 (95% CI 1.43 to 3.15).[5] Hedstrom et al. 2011 assessed the effect of passive smoking on the risk of MS and found that individuals who have never smoked were at a 1.3 times greater odds 95% CI (1.1-1.6) of developing MS if they were exposed to passive smoking.[3] Passive smoking as a risk factor for MS is a fairly new topic that hasn't received much attention. Therefore not many people are aware of the impact that second smoke exposure has on MS. Many smoking campaigns inform people about smoking and risk of lung cancer and cardiovascular disease but fail to talk about its impact on MS development.

In a meta-analysis study conducted by Zhang et al.2016 on risk of smoking on MS, they found that along with smoking being a risk factor for MS development, passive smoke exposure also increased the risk of developing MS as opposed to individuals who were unexposed.[6] Some studies have stated that that a person's genetic background also plays a role in whether passive smoke exposure will result in MS development later on in life. Individuals who have a special class II allele HLA-DRB1*15 were 3 times more likely to develop MS as opposed to individuals who don't have the allele.[7–9]

Hedström et al. (2014) explored the interaction of passive smoking and HLA genotype and found that compared to non-smokers who did not have the two genetic risk factors (HLA-DRB1*15 and HLA-A*02) individuals who had the two risk factors and who were not exposed to passive smoking were OR=4.5 (95% CI 3.3 to 6.1) times more likely to develop MS.[10] However individuals who had the two genetic risk factors and who were exposed to passive smoking were OR=7.7 (95% CI 5.5 to 10.8) times more likely to develop MS.[10] Thus indicating that development of MS is associated with genetic factors and could be influenced by exposure to passive smoking.[10] Apparent in these studies is that both environment and genetics plays a role in MS development.

MS is a rare condition, not many people will be aware of the condition or the risk factors associated with MS such as passive smoking. If people are not aware of the risk factor then prevention is difficult. Several studies have been conducted on demographic factors of people's perception of second hand smoke exposure in relation to lung cancer or chronic obstructive pulmonary disease. However studies on exploring people's perception of second hand smoke exposure on MS is rare. It is important to evaluate population knowledge on MS so as to gain a better understanding on ways to educate people. The objective of this research is to determine the demographic, socioeconomic and personal predictors associated with people's perception on whether they think that second hand smoking is a risk factor for MS. As a secondary objective, whether this perception varies based on the province of residence will also be examined in order to find out if there is a macro level effect. The model for this objective is shown in Figure 3.1.

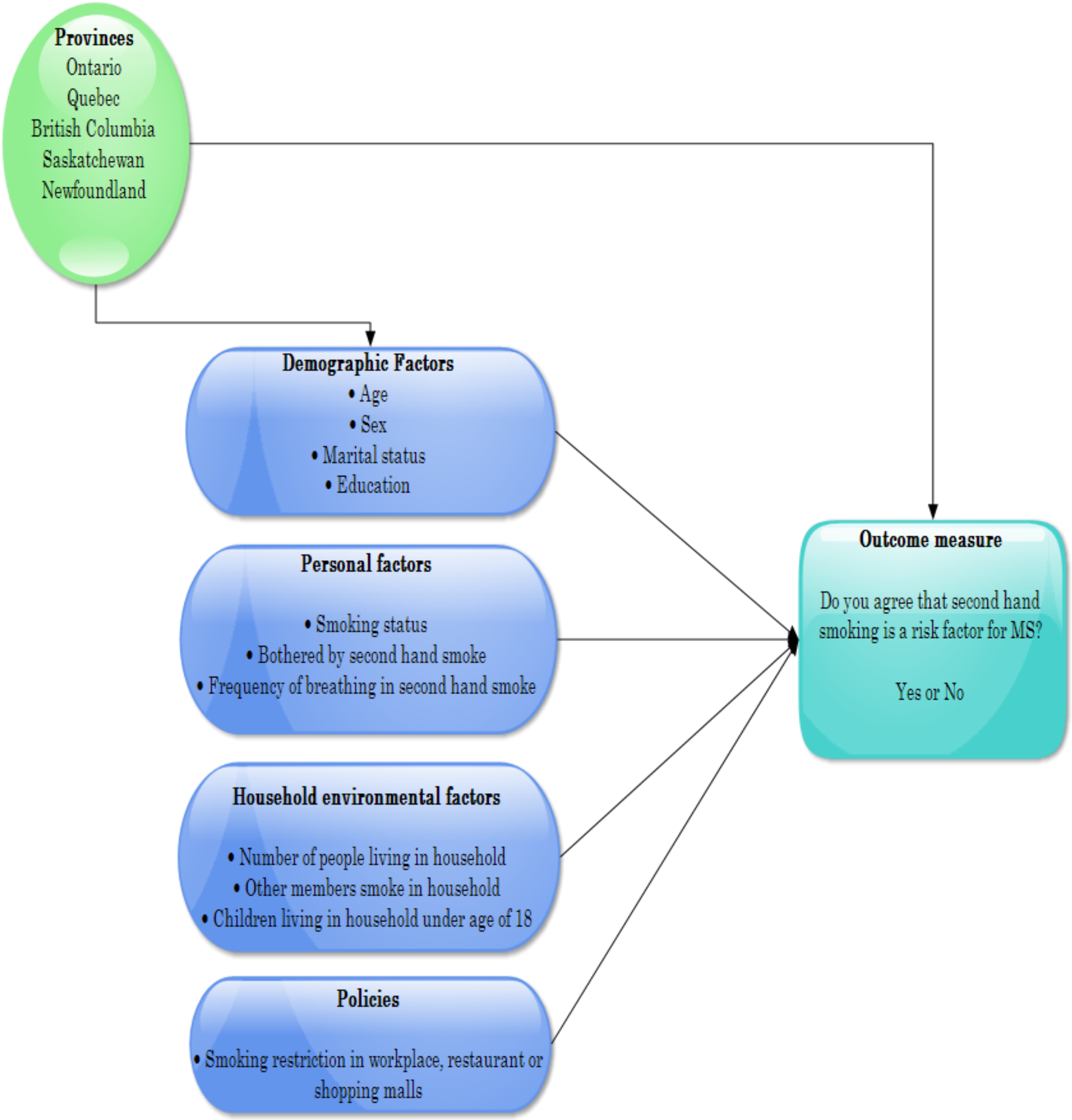


Figure 3. 1: Model for predictors associated with people's perceptions of whether second hand smoke exposure is associated with MS.

3.2 Methods

3.2.1 Data Source

The data set was drawn from the Health Canada: Smoking Survey conducted in 2004 and 2005 by Environics Research Group in partnership with Health Canada to survey the public in the province of British Columbia (N=1,468), Newfoundland (N=1,442), Quebec (N=1,404), Ontario (N=1,443) and Saskatchewan (N=1,413) on smoking.[11,12] This data file is a public use file. Random digit dial sampling process was used to select people in each province. The survey was conducted to measures the knowledge, attitudes and behaviors of the population towards smoking and second hand smoking in public places. Only individuals who were 18 years of age and older were included in the analysis.

3.2.2 Study Sample

There was a total of 7,170 respondents in the initial Health Canada Smoking survey. The study sample was restricted to individuals 18 years of age and older since this is the legal age of smoking. After age restriction was applied, there were 7,166 people respondents who remained. The sample was restricted to individuals who answered the question to whether second hand smoke can cause MS (N=4,815). After missing values were removed, 4,229 observations remained for the analysis. Figure 3.2 shows the flowchart of study sample.

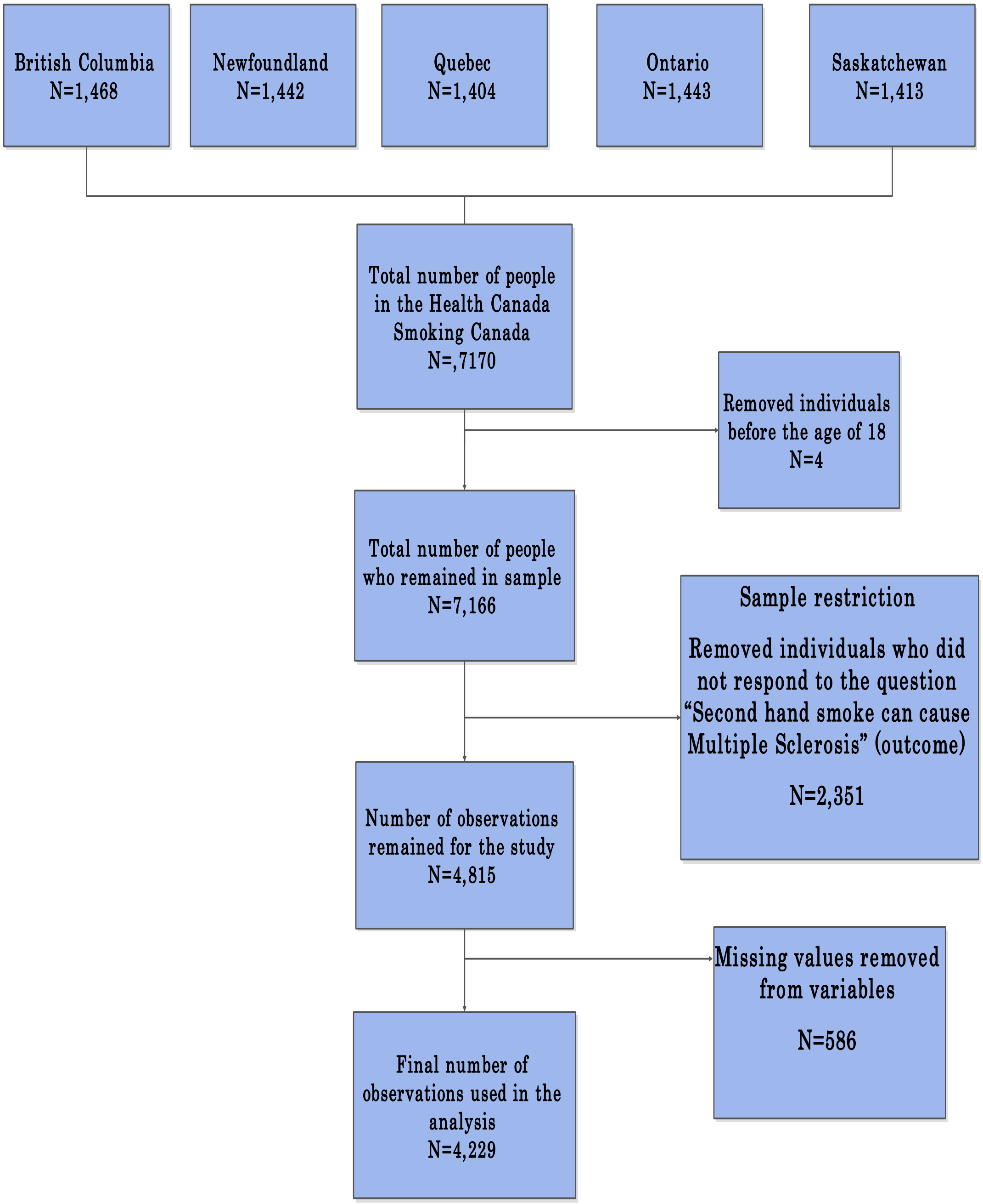


Figure 3. 2: Flow chart of study sample used for complete case analysis.

3.2.3 Variables assessed

Survey respondents were asked whether they agree that second hand smoking was a risk factor for MS. Individuals were asked to rate their agreement and had 4 categories to choose from (strongly agree, somewhat agree, somewhat disagree or strongly disagree). In this analysis individuals who replied strongly agree or somewhat agree were classified as “1=Yes” and those who replied as somewhat disagree or strongly disagree were categorized “0=No”. This was the dependent variable of interest.

The factors that were included in the analysis were sex, age, marital status, education, number of people living in the household, whether other members of the household smoked in the house, if they were bothered by second hand smoke, if they had children under the age of 18, the frequency of breathing in second hand smoke and smoking restrictions in either workplace, restaurant or shopping malls. The predictors used for the analysis are shown in Table 3.1.

3.3 Analysis

A two level multilevel mixed effects logistic regression model analysis was carried out in order to determine whether people’s perceptions of second hand smoking as a risk factor for MS varied based on the province of residence. Two approaches were used to build the final models and then compared to see which procedure gave better results. A complete case analysis was conducted in which only variables with complete values were used in the model and missing values were removed. Unadjusted and adjusted odds ratios with 95% CIs with p-values were computed. Univariate analysis was conducted using a ($p < 0.20$). Manual backward selection was used to build the multivariable model based on ($p<0.05$). Confounders were tested in the final model and were retained if the addition of that variable changed the coefficients of the other variables by more than 20%. Interactions were assessed and added to the model if they were significant at ($p<0.05$). Akaike’s information criterion (AIC) was used to compare fit of models. The effectiveness of the final model was assessed using receiver-operating characteristics (ROC) and plots of standardized residuals. The analysis was performed using STATA IC 15.[13]

As a secondary analysis, imputation was carried out in order to take into account bias, loss of power and precision that could be associated with missing values. The pattern of missingness was assessed. Based on the pattern of missingness for each variable, multiple imputation by chained equation was chosen. The method by Rubin et al. 1987 was used for the imputation procedure.[14] Univariate analysis was conducted using a ($p < 0.20$). Manual backward selection was used to build the multivariable model based on ($p<0.05$). Confounders and interaction terms were tested in the models and results were reported as ORs with 95% confidence intervals. Akaike's information criterion (AIC) was used to compare fit of models. The effectiveness of the final model was assessed using receiver-operating characteristics (ROC). Both models based on complete case analysis and imputation were compared to find the best model for the data.

3.4 Results

3.4.1 Results based on complete case analysis

The final sample consisted of 4,229 observations. Based on the descriptive statistics, there were 1,639 individuals who agreed that second hand smoking causes multiple sclerosis (MS) and 2,590 individuals who disagreed to second hand smoking causing MS. Figure 3-3 shows the number of respondents based on province of residence. Ontario and Saskatchewan had higher levels of responses. In terms of smoking status 60% were smokers and 40% were nonsmokers. When comparing across provinces, Newfoundland had the highest rate of people agreeing (49%) to second hand smoke exposure causing MS, while Quebec had the lowest percentage of people agreeing (33%) (Figure 3-4). Univariate analysis indicated that all predictors were significant with the dependent variable which are shown in Table 3-1. Based on the multivariate analysis sex, age, education, if members of household smoked inside home, if respondent was bothered by second hand smoke, their smoking status and the interaction between sex and smoking status was significant.

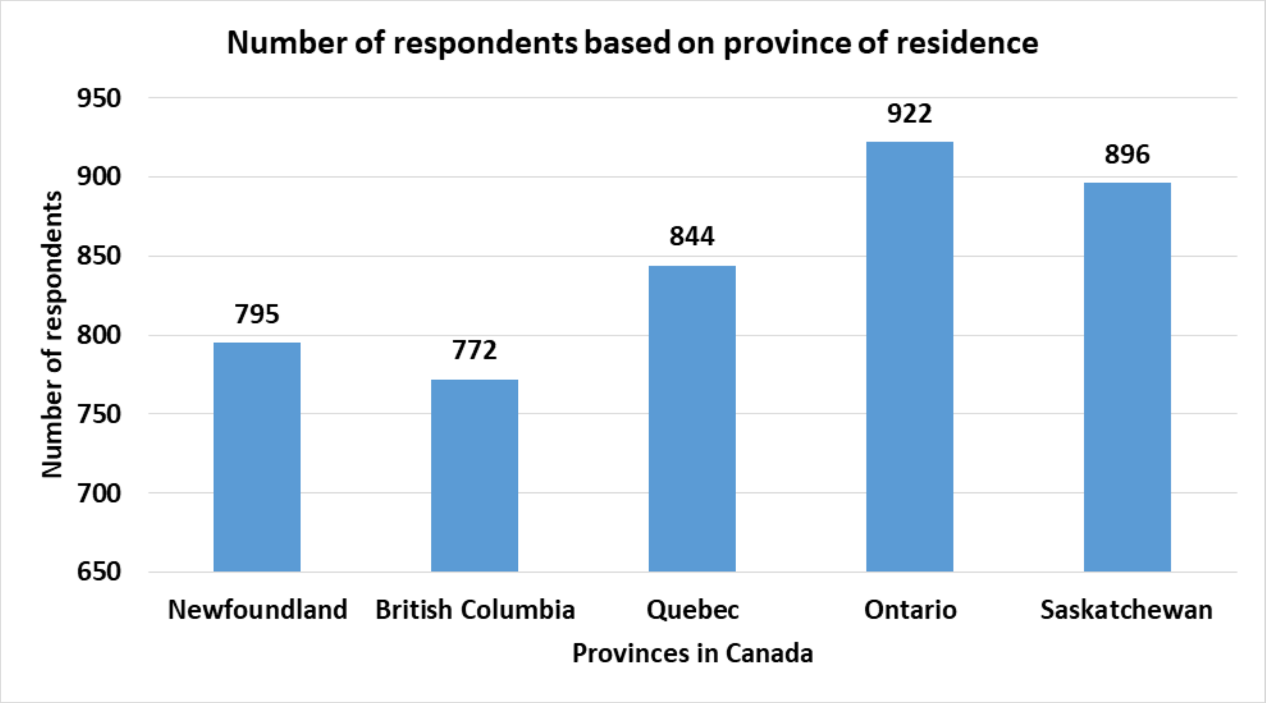
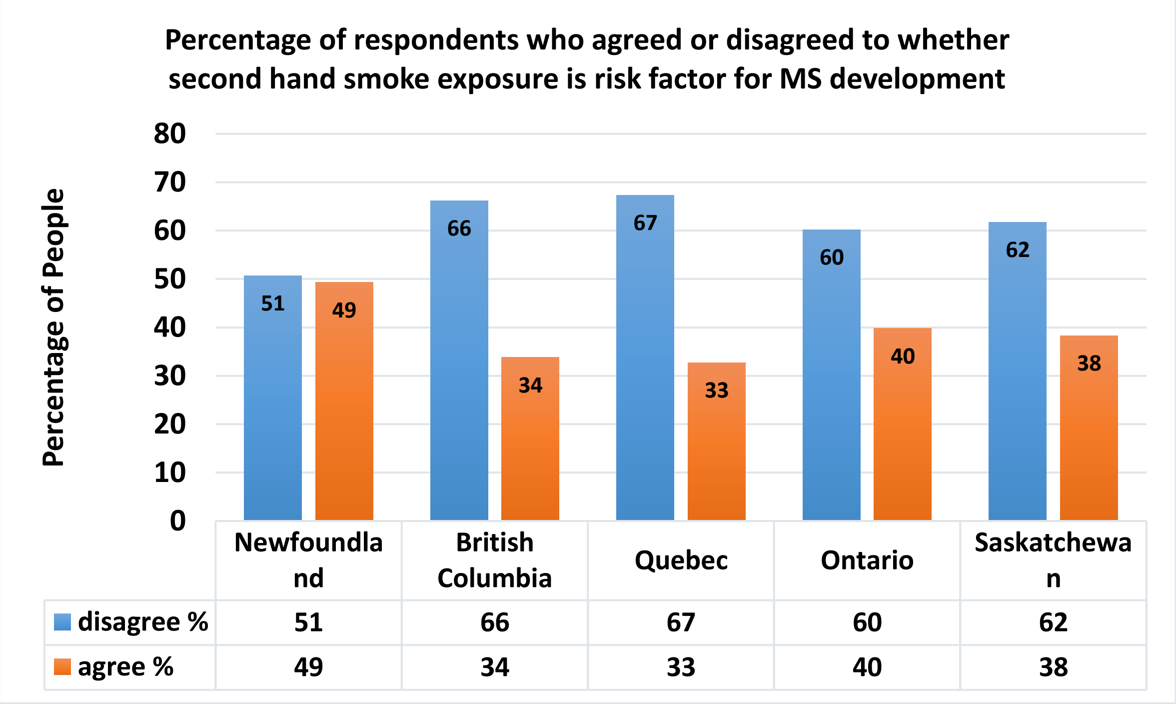


Figure 3. 3: Number of respondents by province.



	Newfoundland	British Columbia	Quebec	Ontario	Saskatchewan
🟦 disagree %	51	66	67	60	62
🟧 agree %	49	34	33	40	38

Figure 3.4:The percentage of respondents who agreed or disagreed to second hand smoke exposure being a risk factor for MS development out of 4,229 observations.

Table 3. 1:Descriptive statistics and univariate analysis for perception of second hand smoking as a risk factor for MS based on complete case analysis (N=4,229).

Variables	OR	95% CI	P-value	N
Sex			p<0.001*	
Male	Ref			2,074
Female	0.78	0.69-0.88	p<0.001	2,155
Age			p<0.001*	
≤24	Ref			496
25 to 30	0.73	0.56-0.95	0.021	444
31 to 36	0.84	0.65-1.07	0.164	519
37 to 42	0.68	0.54-0.87	0.003	571
43 to 48	0.58	0.45-0.74	p<0.001	576
49 to 54	0.56	0.43-0.72	p<0.001	544
55 to 60	0.55	0.42-0.72	p<0.001	469
≥61	0.95	0.75-1.21	0.696	610
Marital status			0.0083*	
Married or living as a couple	Ref			2,566
Single	1.03	0.88-1.20	0.69	1,028
Widowed	1.2	0.90-1.60	0.213	207
Separated	0.92	0.66-1.30	0.64	153
Divorced	0.63	0.48-0.83	0.001	275

Variables	**OR**	**95% CI**	**P-value**	**N**
Education			p<0.001*	
Less than high school degree	Ref			727
High school degree	0.63	0.51-0.77	p<0.001	915
More than high school but less than university	0.54	0.45-0.64	p<0.001	1,716
University degree or greater	0.45	0.37-0.56	p<0.001	871
Number of people living in household			0.0002*	
Less than 2 people	Ref			2,199
Greater than 3 people	1.27	1.12-1.43	p<0.001	2,030
Do other members of your household smoke inside your home?			p<0.001*	
Yes	0.67	0.58-0.78	p<0.001	1,076
No	Ref			3,153
Bothered by second hand smoke p<0.001*				
Very much	Ref			1,263
Somewhat	0.56	0.47-0.66	p<0.001	1,151
Not very much/not at all	0.31	0.27-0.36	p<0.001	1,815
Smoking status			p<0.001*	
Smoker	Ref			2,551
Non-smoker	1.95	1.72-2.21	p<0.001	1,678

Variables	**OR**	**95% CI**	**P-value**	**N**
Children in household under age of 18	0.0043*			
Yes	1.21	1.06-1.37	0.004	1,552
No	Ref			2,677
Frequency of breathing in second hand smoke			p<0.001*	
Everyday	Ref			1,849
Once to few times a week	1.43	1.23-1.66	p<0.001	1,225
Less than a month to 3 times a month	1.27	1.08-1.49	0.004	979
Never	1.42	1.03-1.95	0.028	176
Smoking restriction in workplace or restaurant or shopping malls			p<0.001*	
Yes	0.7	0.59-0.82	p<0.001	3,497
No	Ref			732

* Significance at p<0.20

Table 3. 2: Multivariate analysis for perceptions of second hand smoke as a risk factor for MS based on complete case analysis (N=4,229).

Variables	**OR**	**95% CI**	**P-value**	**N**
Sex			p<0.001*	
Male	1.67	1.40 -2.00	p<0.001	2,074
Female	ref			2,155
Age			p<0.001*	
≤24	ref			496
25 to 30	0.83	0.62-1.10	0.193	444
31 to 36	0.86	0.65-1.15	0.309	519
37 to 42	0.67	0.50-0.89	0.006	571
43 to 48	0.59	0.44-0.79	0.000	576
49 to 54	0.57	0.42-0.77	0.000	544
55 to 60	0.55	0.40-0.76	0.000	469
≥61	0.86	0.63-1.19	0.365	610
Marital status			0.54	
Married or living as a couple	ref			2,566
Single	0.97	0.80-1.17	0.744	1,028
Widowed	1.01	0.72-1.42	0.938	207
Separated	1.01	0.71-1.45	0.948	153
Divorced	0.77	0.57-1.04	0.085	275
Education			p<0.001*	
Less than high school degree	ref			727
High school degree	0.58	0.47-0.72	p<0.001	915
Greater than high school diploma but less than university degree	0.46	0.38-0.57	p<0.001	1,716
University degree or greater	0.31	0.25-0.40	p<0.001	871

Variables	**OR**	**95% CI**	**P-value**	**N**
Number of people living in household including themselves			0.10	
Less than 2 people	ref			2,199
Greater than 3 people	1.17	0.97-1.41	0.097	
Do other members of your household smoke inside your home?			0.03*	
Yes	ref			1,076
No	1.22	1.02-1.45	0.029	3,153
Bothered by second hand smoke			$p<0.001$	
Very much	3.27	2.69-3.97	$p<0.001$	1,263
Somewhat	1.80	1.52-2.14	$p<0.001$	1,151
Not very much/not at all	ref			1,815
Smoking status			$p<0.001$*	
Smoker	ref			2,551
Non smoker	1.50	1.20-1.87	0.000	1,678
Children in household under age of 18			0.45	
Yes	1.08	0.88-1.32	0.450	1,552
No				2,677

Variables	OR	95% CI	P-value	N
Frequency of breathing in second hand smoke			0.05	
Never	ref			176
Everyday	0.91	0.64-1.30	0.604	1,849
Once to few times a week	1.04	0.74-1.48	0.810	1,225
Less than a month to 3 times a month	0.88	0.57-1.15	0.228	979
Smoking restriction in workplace or restaurant or shopping malls			0.08	
Yes	0.85	0.71-1.02	0.077	3,497
No	ref			732
Interaction of Sex and Smoking status			0.01*	
Male×smoker	1.42	1.09-1.87	0.010	

* Significance at $p<0.05$

In the model building process marriage status, number of people in the household, the frequency of breathing in second hand smoke and smoking restriction in either workplace, restaurant or shopping malls were removed (p-values>0.05). When testing for confounders it was found that all the variables removed were confounders and were included back into the model. The interaction of sex and smoking status was found to be significant at (p=0.01). Table 3-2 shows the multivariate analysis. Males (OR=1.18 95%CI 1.40 to 2.00) were more likely to agree that second hand smoke could cause MS compared to females.

A gradient effect was seen in age whereby as age increased the less likely people were to agree to second hand smoking causing MS. Individuals between the ages of 37 to 42 years of age were less likely to agree to second hand smoking causing MS (OR= 0.67 95%CI 0.50 to 0.89) compared to individuals who were less than 24 years of age. Similar findings were found for individuals between the ages of 43 to 48 (OR=0.59 95%CI 0.44 to 0.79), 49 to 54 (OR=0.57 95% CI 0.42 to 0.77) and 55 to 60 years of age (OR=0.55 95%CI 0.44 to 0.76). Table 3-3 shows comparison between age categories.

When comparing between ages, individuals who were 61 and over were more likely to agree that second hand smoke causes MS in comparison to those who were 43 to 48 years of age (OR=1.46 95% CI 1.10 to 1.94), 49 to 54 years (OR=1.52 95%CI 1.16 to 2.00) and 55 to 60 years of age (OR=1.57 95% CI 1.19 to 2.08). Education was significant in the final model whereby individuals with a high school degree (OR= 0.58 95% CI 0.47 to 0.72) were less likely to agree that second hand smoking could cause MS. Individuals with greater than high school diplomas but less than university degree (OR=0.46 95%CI 0.3 to 0.57) were less likely to agree to second hand smoke causing MS compared to individuals with less than a high school degree. Similar results were found for individuals with a university degree (OR=0.31 95%CI 0.25 to 0.40) or greater. However, the odds ratios remained within the same range across different levels of education levels with only slight differences.

Having household members who smoke inside their home was also associated with whether or not people think that second hand smoke could cause MS. Individuals who had no household members who smoked in their home were more (OR=1.22 95%CI 1.02 to 1.45) likely to agree that second hand smoke could cause MS. The level that people felt bothered by second hand smoking was also associated with whether or not they felt that second hand smoking could cause MS.

Individuals who were very much bothered by second hand smoke were more (OR=3.27 95% CI 2.69 to 3.97) likely to agree that second hand smoke could cause MS compared to those who were not very much bothered or who were bothered not at all. Similar results were found for individuals who were somewhat bothered by second hand smoke (OR= 1.80 95%CI 1.52 to 2.14). Smoking status was also found to be significant in the model. Non-smokers were more (OR=1.50 95%CI 1.20 to 1.87) likely to agree that second hand smoke leads to MS compared to smokers.

The interaction of sex and smoking status was significant in the final model. Male smokers were more (OR=1.42 95%CI 1.09 to 1.87) likely to agree that second hand smoke causes MS. When comparing interaction terms, it was found that female non-smokers were more (OR=1.50 95%CI 1.20 to 1.87) likely to agree that that second hand smoke causes MS compared to female smokers. Significance was also found when comparing female smokers to male smokers (OR=0.60 95% CI 0.50 to 0.71) as well as between female smokers and male non-smokers but to a lesser extent (OR= 0.57 95% CI 0.45 to 0.71).

The interactions in the model are depicted in Figure 3-5. Non-smoking females had a higher probability of agreeing to second hand smoke exposure leading to MS development compared to female non-smokers. Male smokers had a higher probability of agreeing that second hand smoke exposure leads to MS development compared to female smokers. Figure 3-6 shows that as age increased the probability of agreement to second hand smoke exposure decreased. Figure 3-7 shows that those who were very much bothered by second hand smoking had a greater probability of agreement to the question as opposed to those who were not bothered by second hand smoke exposure. The ROC curve suggested that that the multilevel mixed effects logistic regression model correctly classified 70% of people on their perceptions of whether second hand smoke causes MS indicating a fair model (95% CI 0.69 to 0.72). The model without interaction term was compared to the model with an interaction term using Akaike's information criterion (AIC). The results indicated that the model with the interaction term with sex and smoking status had an (AIC= 5,201) compared to the model without the interaction term (AIC= 5,205). Therefore the model with the interaction term was considered better since it has a lower AIC. For the random effects of the model, 1.9% of the total variability in the dependent variable was explained by the province level.

Table 3. 3: Comparison of categorical variables that were significant from multivariate analysis based on $p<0.05$.

	OR	**95% CI**	
Age Comparison		Lower	Upper
61 and over vs 43 to 48	1.46	1.10	1.94
55 to 60 vs 49 to 54	0.97	0.73	1.28
61 and over vs 49 to 54	1.52	1.16	2.00
61 and over vs 55 to 60	1.57	1.19	2.08
Interaction of Sex and Smoking Status			
Male			
(Male#non-smoker) vs (Male#smoker)	1.05	0.85	1.31
(Female#smoker) vs (Male#smoker)	0.60	0.50	0.71
(Female#non-smoker) vs (Male#smoker)	0.90	0.72	1.12
(Female#smoker) vs (Male#non-smoker)	0.57	0.45	0.71
(Female#non-smoker) vs (Male#non-smoker)	0.85	0.69	1.05
(Female#non-smoker) vs (Female#smoker)	1.50	1.20	1.87

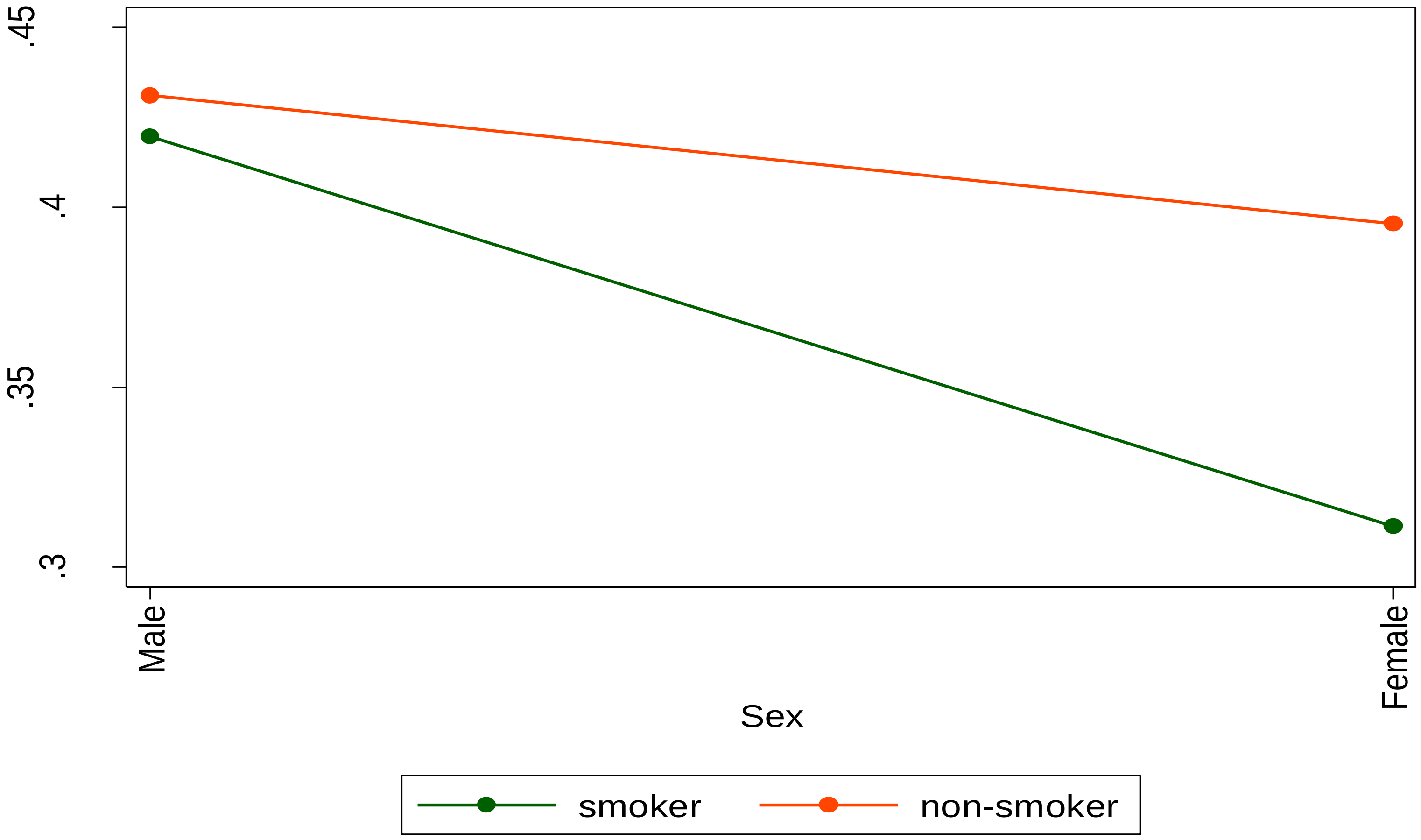


Figure 3. 5: Predicted probabilities and 95% CI of agreement for second hand smoking as a risk factor for MS by sex and smoking status.

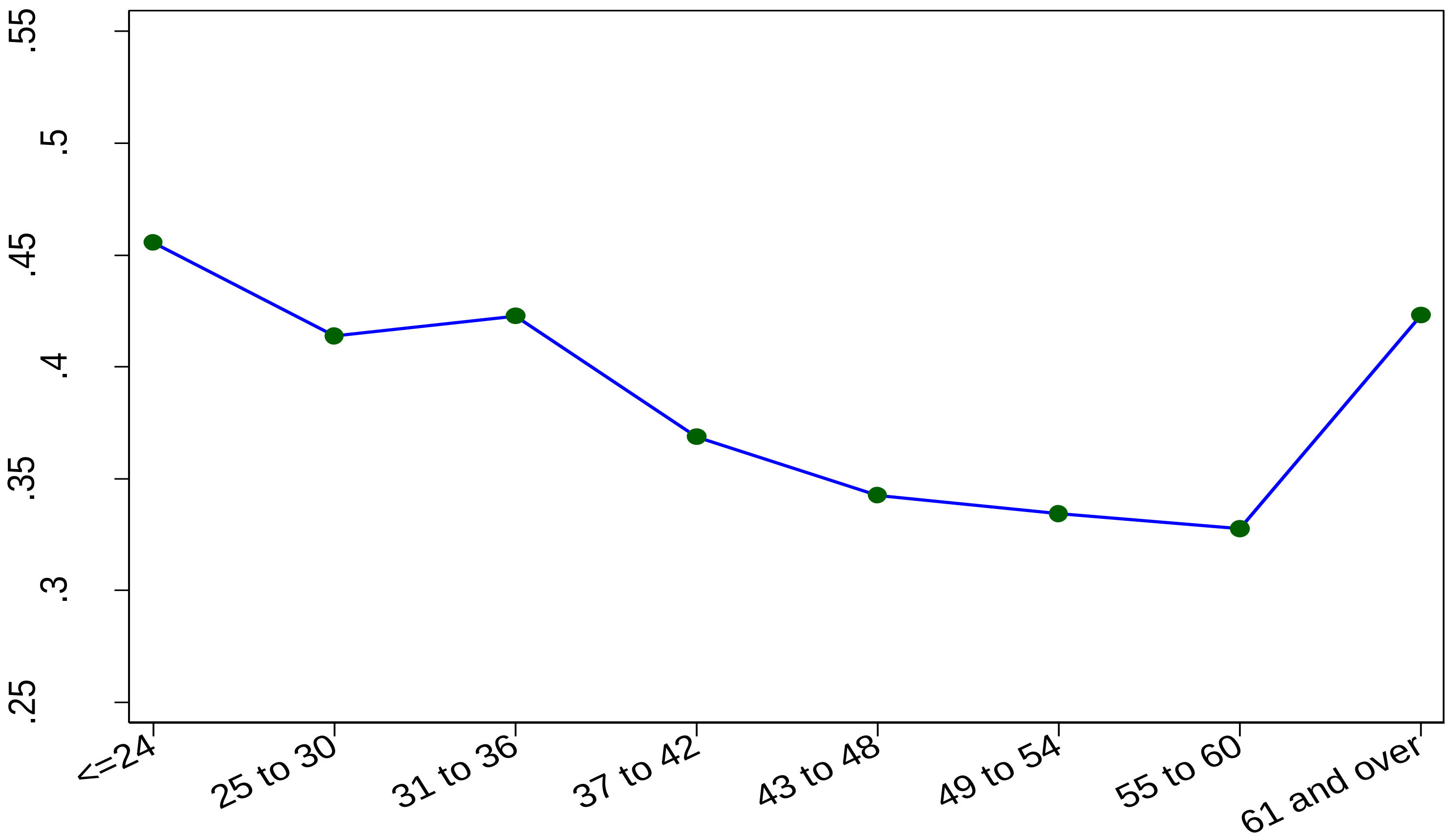


Figure 3. 6: Predicted probabilities and 95% CI of agreement for second hand smoking as a risk factor for MS by age.

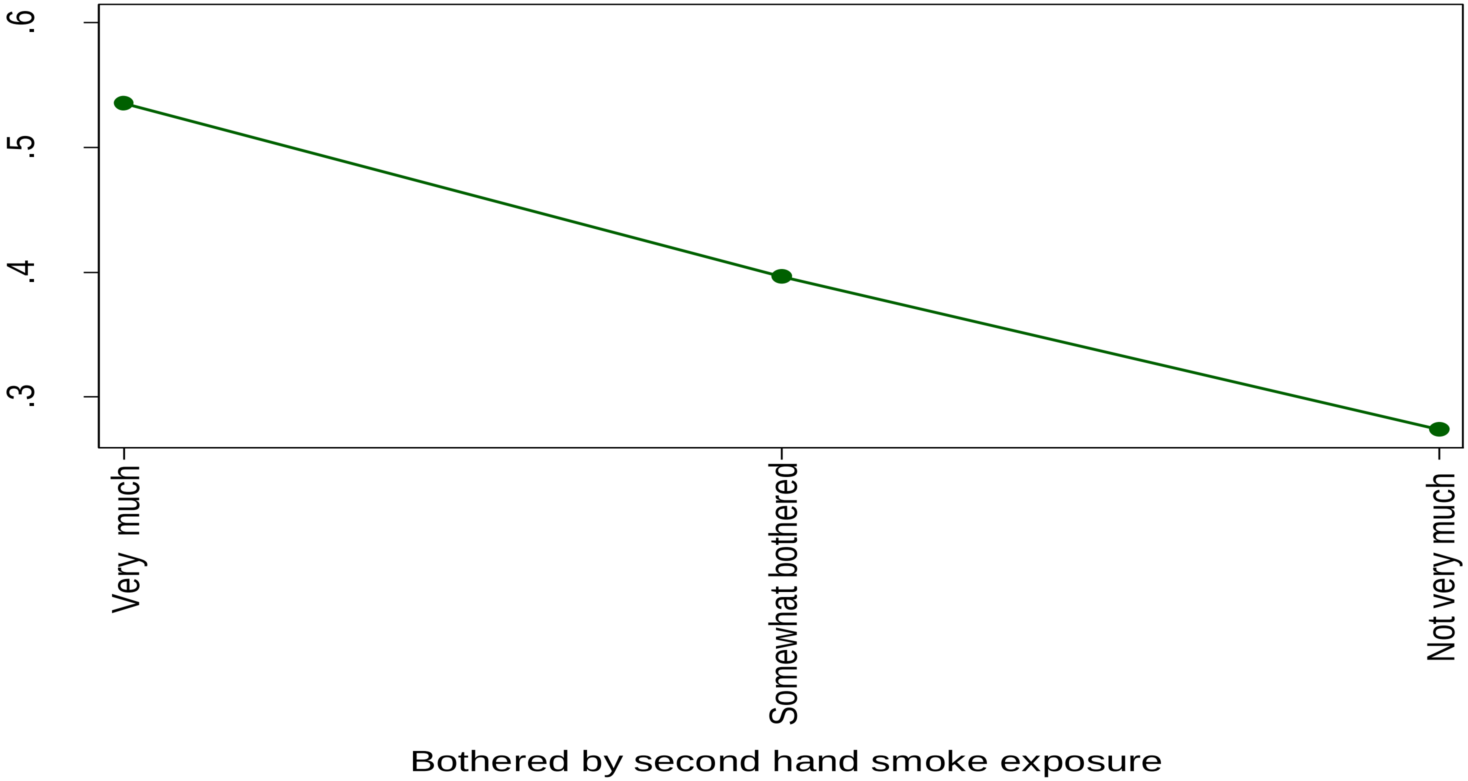


Figure 3.7:Predicted probabilities and 95% CI of agreement for second hand smoking as a risk factor for MS by whether respondent was bothered by second hand smoke exposure.

3.4.2 Results based on Multiple Imputation

The results based on the multiple imputation procedure was similar to the results from the complete cases analysis output (table 3-4 and table 3-5). All of the variables which were screened in the univariate analysis were significant and were included in the multivariate analysis model building process. Table 3-4 shows the output for the univariate analysis based on multiple imputation procedures. In the model building process, number of people living in the household, marital status, whether members of the household smoked, whether there were children in the household younger than 18 years of age, the frequency of breathing in second hand smoke and smoking status were removed based on a p-value of 0.05, however all were included back into the model due to the variables being confounders.

Based on the comparison between models, the model based on complete case analysis explained a larger portion of the total variance (1.9%) in people's responses to the question on second hand smoke exposure than the model based on imputation procedures (1.3%). Based on the results of the ROC analysis, the final model based on complete cases analysis correctly classified 70% of people on their perception of second hand smoke exposure, however the model based on the imputation procedures correctly classified 65% of people on their perceptions of second hand smoke exposure. The AIC was 7,832 for the multiple imputation model, which is larger compared to the model with complete case analysis AIC= 5,201. After comparison of the models and fit of the data, the model based on complete case analysis was better compared to the model based on the imputation procedures.

Table 3.4:Descriptive statistics and univariate analysis for perception of second hand smoking as a risk factor for MS based on multiple imputations (N=7,166).

Variables	OR	95% CI	P-value
Sex			p<0.001*
Male	Ref		
Female	0.75	0.69-0.88	p<0.001
Age			p<0.001*
≤24	Ref		
25 to 30	0.70	0.56-0.89	0.003
31 to 36	0.70	0.57-0.88	0.002
37 to 42	0.57	0.46-0.70	p<0.001
43 to 48	0.47	0.38-0.58	p<0.001
49 to 54	0.46	0.37-0.57	p<0.001
55 to 60	0.46	0.36-0.57	p<0.001
≥61	0.57	0.47-0.69	p<0.001
Marital status			p<0.001*
Married or living as a couple	Ref		
Single	1.17	1.03-1.33	0.017
Widowed	0.85	0.68-1.07	0.179
Separated	0.96	0.71-1.29	0.777
Divorced	0.62	0.49-0.79	p<0.001
Education			p<0.001*
Less than high school degree	Ref		
High school degree	0.73	0.62-0.86	p<0.001
More than high school but less than university	0.61	0.53-0.71	p<0.001
University degree or greater	0.48	0.40-0.57	p<0.001
Number of people living in household			p<0.001*
Less than 2 people	Ref		
Greater than 3 people	1.26	1.13-1.40	p<0.001
Do other members of your household smoke inside your home?			0.054
Yes	0.88	0.77-1.00	0.054
No	Ref		

Variable	**OR**	**95% CI**	**P-value**
Bothered by second hand smoke			p<0.001*
Very much	Ref		
Somewhat	0.72	0.63-0.83	p<0.001
Not very much/not at all	0.51	0.45-0.56	p<0.001
Smoking status			p<0.001*
Smoker	Ref		
Non-smoker	0.69	0.62-0.77	p<0.001
Children in household under age of 18			0.004*
Yes	1.17	1.05-1.31	0.004
No	Ref		
Frequency of breathing in second hand smoke			0.014*
Everyday	Ref		
Once to few times a week	1.20	1.06-1.37	0.005
Less than a month to 3 times a month	0.98	0.85-1.12	0.718
Never	1.04	0.81-1.33	0.778
Smoking restriction in workplace or restaurant or shopping malls			p<0.001*
Yes	0.70	0.58-0.78	p<0.001
No	Ref		

*Significance based on p<0.20

Table 3. 5:Multivariate analysis for perceptions of second hand smoke as a risk factor for MS based on multiple imputation.

Variables	**OR**	**95% CI**	**P-value**
Sex			p<0.001*
Male	1.57	1.34-1.83	p<0.001
Female	ref		
Age			p<0.001*
≤24	ref		
25 to 30	0.80	0.63-1.03	0.08
31 to 36	0.76	0.60-0.97	0.029
37 to 42	0.60	0.47-0.76	p<0.001
43 to 48	0.48	0.38-0.61	p<0.001
49 to 54	0.47	0.37-0.61	p<0.001
55 to 60	0.47	0.36-0.62	p<0.001
≥61	0.53	0.41-0.69	p<0.001
Marital status			0.30
Married or living as a couple	ref		
Single	1.00	0.86-1.17	0.98
Widowed	0.89	0.69-1.16	0.39
Separated	1.06	0.78-1.44	0.73
Divorced	0.78	0.60-0.99	0.045
Education			p<0.001*
Less than high school degree	ref		
High school degree	0.66	0.56-0.79	p<0.001
Greater than high school diploma but less than university degree	0.53	0.45-0.62	p<0.001
University degree or greater	0.38	0.32-0.46	p<0.001
Number of people living in household including themselves			0.28
Less than 2 people	ref		
Greater than 3 people	1.09	0.93-1.27	0.28
Do other members of your household smoke inside your home?			0.81
Yes	ref		
No	1.02	0.8-1.18	0.81

Variable	**OR**	**95% CI**	**P-value**
Bothered by second hand smoke			p<0.001*
Very much	2.05	1.75-2.41	p<0.001
Somewhat	1.46	1.26-1.69	p<0.001
Not very much/not at all	ref		
Smoking status			0.0003*
Smoker	ref		
Non smoker	1.40	1.16-1.67	p<0.001
Children in household under age of 18			0.62
Yes	1.04	0.88-1.32	0.62
No	ref		
Frequency of breathing in second hand smoke			0.061
Never	ref		
Everyday	0.96	0.73-1.27	0.793
Once to few times a week	1.07	0.82-1.40	0.619
Less than a month to 3 times a month	0.87	0.67-1.14	0.312
Smoking restriction in workplace or restaurant or shopping malls			0.0004*
Yes	0.77	0.67-0.89	p<0.001
No	ref		
Interaction of Sex and Smoking status			0.037*
Male×smoker	0.79	0.63-0.94	0.037

*Significance at p<0.05

3.5 Discussion

The main objective of this study was to determine the demographic, socioeconomic and personal predictors associated with people's level of agreement to whether they think that second hand smoking is a risk factor for MS. Based on the results of this research it was evident that demographic factors were associated with people's perceptions of whether second hand smoking is a risk factor for MS. As a secondary objective we explored whether this perception varied based on the province of residence to find out if there is a macro level effect. The complete case analysis indicated that 1.9% of the variability in responses in the dependent variable was explained by province in which the person resided. One of the reasons for this variability could be due to taxes on cigarettes and the tax hike that occurred in certain provinces over the years.[15] Another reason for this variability could be due to effects of stop-smoking campaigns in the provinces and the frequency in which messages about the harms of second hand smoking are shown in advertisements.

In this study, 39% of people agreed that second hand smoke causes MS while 61% of people disagreed to second hand smoke causing MS. The low prevalence of people in Canada who agree to second hand smoke being a risk factor for MS development shows the lack of awareness of MS risk factor. Males were more likely to agree that second hand smoke causes MS in comparison to females. The prevalence of smoking among males globally is 4.4 times greater in comparison to females.[16] However an interaction effect was seen whereby male non-smokers were more likely to agree that passive smoke exposure causes MS as opposed to male smokers. Similar interaction effect was found for female non-smokers compared to female smokers. Therefore smoking status plays a role in people's perceptions since smokers were more likely to disagree to harmful effects of passive smoking as oppose to non-smokers.

Having household members who did not smoke was associated with greater odds of people agreeing that passive smoking is dangerous. This finding was similar to a study conducted in Oregon whereby households with non-smokers or with at least one smokers, fully banning household smoking was associated with a greater awareness of the harms of smoke exposure.[17] This shows the importance of banning smoking in households and it's impact on people's perceptions.

Age was a contributing factor in opinions for second hand smoke and MS development in that older individuals were more likely to agree that second hand smoke causes MS as opposed to younger people when looking at comparisons between age categories. A study done on the prevalence of passive smoking found that a higher prevalence of passive smoking was evident in the older population as opposed to the younger population.[18] This suggests that older individuals may have experience with the harms of second hand smoke exposure and may be aware of the harms associated with it as opposed to the younger generation. With age comes more life experiences in terms of having friends or family members who have gone through problems with MS. Therefore they would have a better understanding of risk factors of primary and secondary smoking and its effect on health. In addition to this older individuals may be more inclined to quit smoking or reduce the harms of passive exposure based on advice received from clinicians so that they can improve their quality of life.[19]

Individuals who had greater levels of education such as high school degree or greater were less likely to agree to second hand smoke exposure being a risk factor for MS. These findings were consistent with a study that investigated the sociodemographic characteristics and second hand smoke exposure among women.[20] In this study it was found that that women who had lower levels of education were more likely to be exposed to second hand smoke exposure.[20] The findings from this study suggest that having higher levels of education doesn't necessarily mean that a person has more awareness and that perception of risk factors may be due to personal experiences.

This study had many strengths. This was the first multilevel study that assessed people's knowledge on whether they think that second hand smoking is a risk factor for MS development. Secondly the model correctly classified 70% of people on their perceptions of whether second hand smoke causes MS indicating a good model fit. The sample used was representative of the Canadian population since the major provinces were surveyed. Some of the limitations of this study is response bias. Survey respondents may assume that second hand smoke exposure may causes MS because of the way in which the question was asked and might answer in a desirable manner. Non-response bias is also present in this survey due to the high number of missing observations. Since this was a cross sectional study, a cause and effect relationship cannot be assumed. Another limitation was the high number of smokers in the survey which could have biased the results of the study, since smokers are more likely to disagree that smoking is detrimental to health, they would be more inclined to disagree to the question of whether second hand smoke exposure could increase risk of MS.

Limitations also exist with regards to the survey question. Since only one survey question was asked and it didn't have a definition of what MS was, there could be problems with people understanding the health condition before answering the question. Another limitation is that the survey is more than 10 years old, the knowledge of second hand smoking has increased and the levels of smoking in the general population has declined, therefore the results of this study and the recommendations made may differ in today's population. In addition to this, the survey was conducted through telephone interviews which may lead to higher number of non-responses if individuals are not available during the time the call was placed.

Public health awareness about the risks of second hand smoke exposure is needed. There have been two studies that have shown the impact of second hand smoke exposure and how it increases the risk of developing MS among children and adults.[3,5] In order to reduce the exposure in public places, legislative bans need to be more restrictive in terms of specifying where people can't smoke.

Public smoking bans in Canada has been effective in reducing the prevalence of smoking and have been effective in reducing rates of illnesses such as acute myocardial infection in Saskatoon.[21–23] However, in terms of MS, not many people are aware that second hand smoke exposure can trigger relapses in MS, therefore patient and public education is important. One way to educate people about second hand smoking and MS is through advertisements on television or on buses.

Advertisements about the harms of cigarette smoking and it’s effect on lung cancer or on alcohol use and impaired driving have been effective in raising awareness in these two areas and can also be effective for diseases such as MS.[24,25] Creating stop smoking campaigns which includes messages about harmful effects of second hand smoking and it effects on neurological conditions such as MS would also be effective in reducing smoking and second hand smoking.

Patient and family education about the risk factors for MS is important so they can be better informed as to what triggers to avoid. Since second hand smoke exposure could be avoided, physicians should communicate to caregivers about risk factors and give out educational materials such as pamphlets or books about MS. A study on the effect of a website that provides in depth information about beta interferon therapy found it to be useful for many patients.[26] Websites such as this could show information regarding risk factors such as second hand smoke exposure and its effect on MS. Another study by Kopke et al. (2014) found that patients who were in the educational program showed more risk knowledge which was beneficial for immunotherapy uptake. Educational programs on second hand smoke exposure and its impact on people living with MS could be beneficial to the public.[27]

Since sociodemographic factors were associated with people's perceptions about second hand smoke exposure and MS, educational programs that raise awareness on this topic need to be created. In addition to this stop smoking campaigns need to incorporate messages about the various health problems that second hand smoke exposure could cause in children as well as in adults. Lung cancer, chronic obstructive pulmonary disease and heart disease are the main problems which are normally advertised as health problems associated with second hand smoking, other illness such as MS are left out and should be incorporated into stop smoking campaign messages.

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CHAPTER 4: PSYCHOSOCIAL FACTORS ASSOCIATED WITH PAIN IN PEOPLE WITH MS

Abstract

Objective: Pain is a common problem in MS. Risk factors associated with pain may include individual's cognitive thinking process, emotional and behavioural response to pain and amount of social support. The primary objective of this study was to determine the association between amount of social support and its association with odds of pain among individuals with MS.

Methods: The Survey on Living with Neurological Conditions in Canada (SLNCC) 2011-2012 linked to the Canadian Community Health Survey (CCHS) 2010-2011 was used to carry out a logistic regression model for this analysis. The factors that were assessed were psychological factors, problems with sleeping, self-perceived general health, self-perceived level of stress , number of years living with MS, as well as social factors (someone to confide/talk to, someone to do something enjoyable, someone to take you to the doctor and someone to help you in an emergency). The outcome variable was presence of pain.

Results: The amount of social support was found to be significant in that individuals who had 3 or less types of social support were 3.02 times more likely (95% CI 1.06 to 8.59) to be in pain as opposed to individuals who had 4 types of support.

Conclusion: The results indicate that caregivers may not be available to help with all type of activities, therefore home care services are very important. Reducing cost of home care services would be beneficial for people living with MS.

4.1 Introduction

Pain is a common problem in people living with MS.[1] The prevalence of pain in MS patients is 50%, and 75% of patients report having pain within one month of their assessment.[2] The presence of pain among patients with MS is associated with increasing age, the longer duration of their illness, depression and increased functional impairment and fatigue.[3] Pain causes changes to occur in the central nervous system (CNS) and affects the emotional processing area of the brain.[4] When there is damage to the peripheral or CNS, neuropathic pain occurs. Pain caused by MS can be explained by cognitive behavioural model which suggests that there are both disease and non-disease factors that trigger pain.[5]

In MS, pain may be headaches, back pain, neuropathic pain and or spasms.[6] Non-disease factors associated with pain include the individual's cognitive thinking process, emotional and behavioural response to pain and amount of social support. Biopsychosocial model of pain recognizes that psychological, social and environmental factors play a role in pain.[7] Figure 4.1 shows the biopsychosocial model of pain. Earlier models of pain looked at the role of social support and emphasized the importance of a transactional model where pain causes a problem and it effects mood or behaviour which then leads to more support from others.[8] However this model now has been further explored and scientists believe that physical pain is connected to social psychological pain.[8]

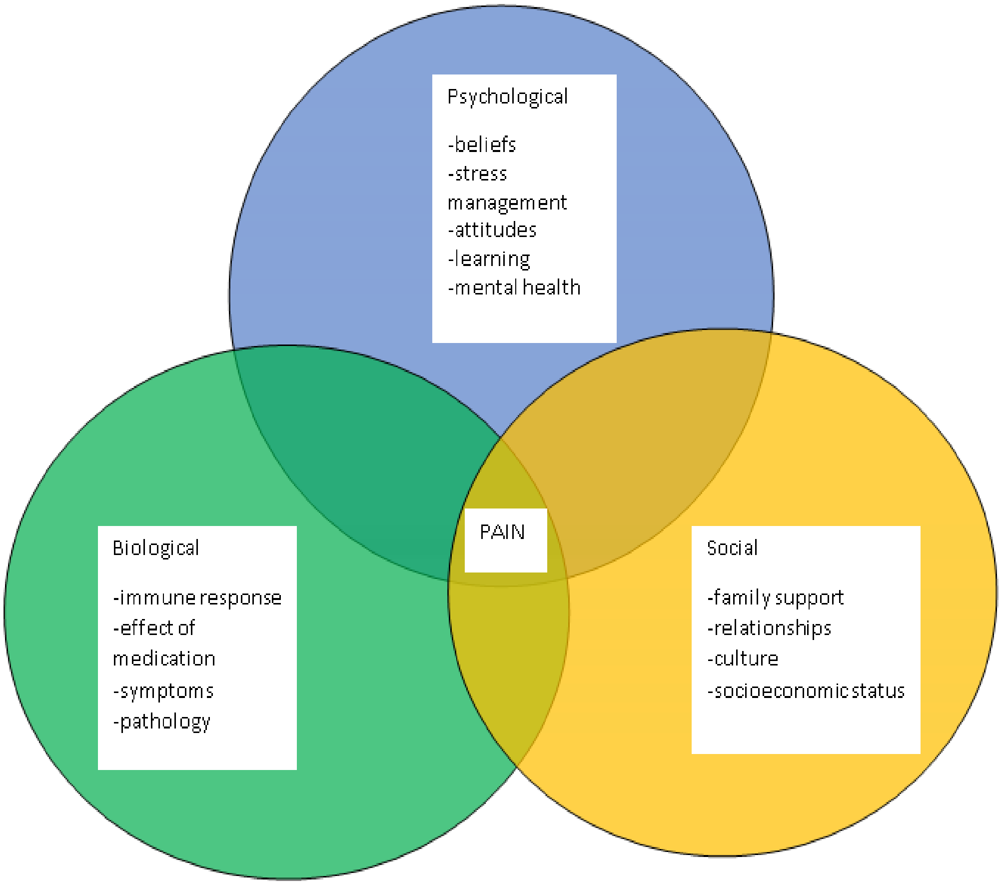

Figure 4.1: Biopsychosocial model of pain recognizes that psychological, social and environmental factors play a role in pain. Adapted from (Gatchel et al.,2007).[7]

Several studies have stated that the effect of chronic pain in MS patients is linked to depression and is mediated by fatigue, anxiety and sleep.[2,9–11] Since coping with MS is difficult, not having the support one needs could impact the emotional well-being of MS patients and exacerbate health problems.[3,12] This could then lead to a domino effect where emotional stress could impact sleep conditions and increase pain levels. Some studies that have looked at the association between social support as a predictor of mental health among MS patients found that social support made a significant contribution to the mental health dimension of their quality of life.[13,14]

Social support helps in three areas: the first is it provides emotional support such as love and affection, the second is instrumental support such as lending a helping hand to someone and the third is informational support such as from a physician or nurse.[15] Learning to cope with the illness is also important in reducing disease burden. There are two types of coping strategies such as problem focused coping and emotion focused coping.[16,17] Problem focused coping involves ways to change the problem that one is dealing with while emotion focused coping is related to managing the emotional distress of the situation. Each coping strategy is dependent on the person as well as the situation that they are dealing with.[17] Social support is an important aspect of coping and whether lacking in one type of social support could lead to pain is an understudied area.

In a study done on the psychological factors associated with chronic pain in people living with disabilities found that the perception of social support was associated with less pain and better psychological functioning. [18] Several studies have also shown that higher levels of social support are associated with higher levels of health related quality of life and lower levels of depression. [13,14,19,20] There have been few studies that have investigated the risk factors associated with pain and the emotional well-being of people living with MS. The majority of studies have focused on a single category of social support. The main objective of this study is to determine the association between amount of social support and it’s association with odds of pain among individuals with MS. The second objective of this study is to determine if there is an interaction between psychological factors and amount of support on pain.

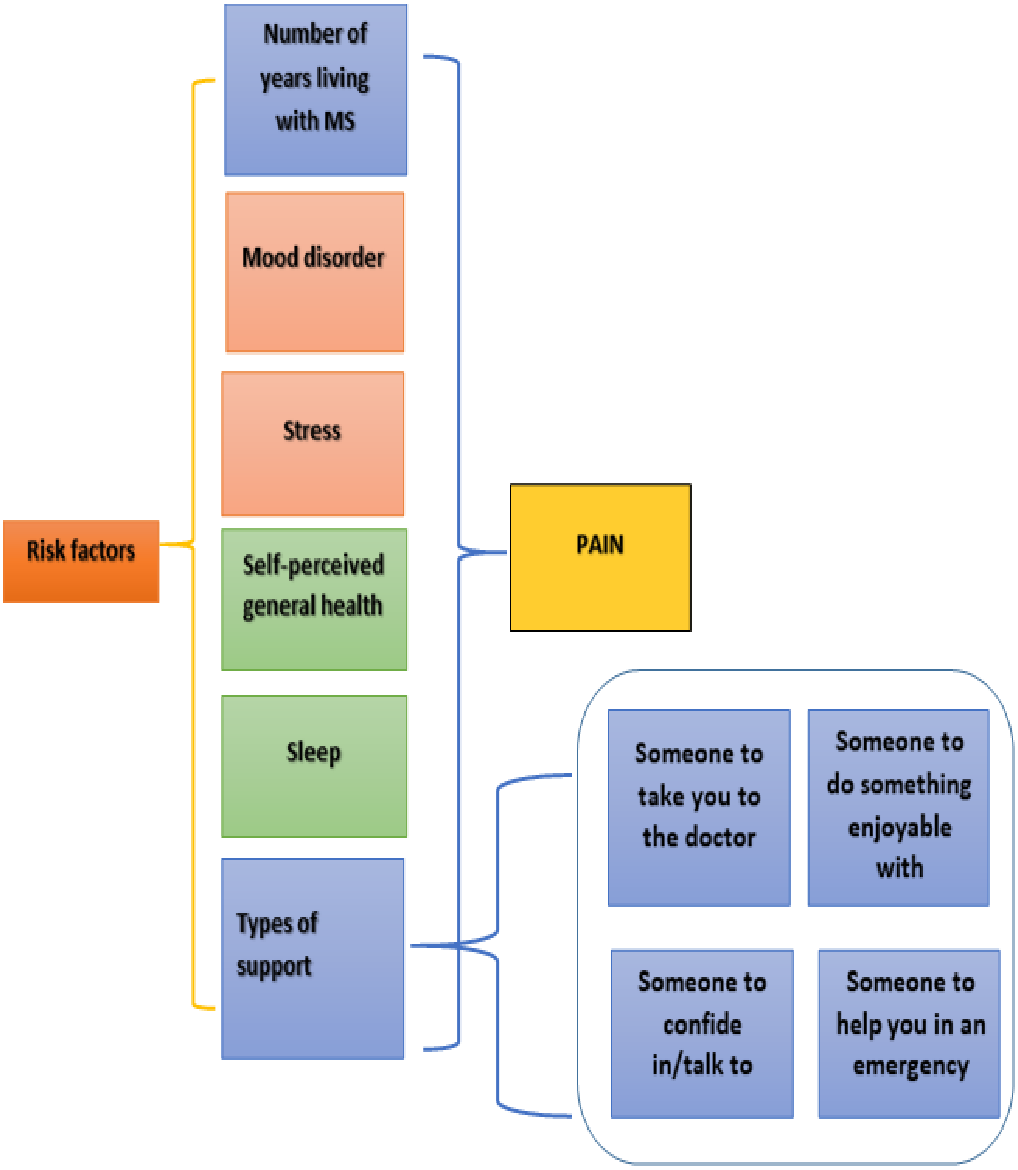

Figure 4. 2: Pain Model. This diagram shows the variables which are considered in the model building process for pain.

4.2 Methods

4.2.1 Data Source

The Survey on Living with Neurological Conditions in Canada (SLNCC) 2011-2012 linked to the Canadian Community Health Survey (CCHS) 2010-2011 was used for this analysis.[21] The SLNCC is a cross sectional survey that collected information on Canadian's experiences of living with chronic neurological conditions.[21] There were 18 neurological conditions which were included in the 2010 and 2011 Canadian Community Health Surveys.[21] The sample surveyed for the SLNCC survey were drawn from all CCHS respondents and household members who were 15 years of age and older living in the provinces being surveyed and who had one of the 18 neurological conditions.[21]

4.2.2 Variables assessed

Individuals 15 years and older were used in the analysis. The factors that were assessed were psychological factor (mood disorder such as depression, bipolar disorder, mania or dysthymia), problems with sleeping, self-perceived general health (poor or fair health, good, very good/excellent health), self-perceived level of stress (not at all or not very stressful, a bit stressful, quite a bit to extremely stressful), number of years living with MS (less than 10 years, 11 to 21 years, greater than 22 years), as well as social factors (someone to confide/talk to, someone to do something enjoyable, someone to take you to the doctor and someone to help you in an emergency).

There were 4 types of support questions asked following the prompt "people sometimes look to others for companionship, assistance or other types of support", "how often is each of the following kinds of support available to you if you need it?".[21] Following this statement, the respondent was asked 4 questions"…someone to confide in or talk to about yourself or your problems?", the second question was "….someone to do something enjoyable with?", the third was "…someone to take you to the doctor if you needed it?" and the fourth was "…someone to turn to help in an emergency?" the responses were "none of the time, a little of the time, some of the time, most of the time and all of the time".[21]

The outcomes were recoded as “none”, “little/some”, “most/all” in order to have enough number of observations in each category.[21] These 4 questions and the responses were combined together to create one support variable (someone to confide/talk to, someone to do something enjoyable, someone to take you to the doctor and someone to help you in an emergency) and categorized as either having less than 4 types of support or the second category being having all 4 types of support. The outcome variable was pain health status for which there were 5 categories (no pain or discomfort, pain prevents no activities, pain prevents a few activities, pain prevents some activities and pain prevent most activities). These categories were collapsed to either presence or absence of pain.

4.3 Analysis

In order to take into account the survey design, replicate sampling weights along with bootstrapped variance estimation were used which were recommended by Statistics Canada.[22] A set of (n=500) replicate weights were used in order to account for population estimates and non-responses. For the SLNCC linked data set, the bootstrap replicates are the sub samples which were drawn in order to estimate the variance of the CCHS estimates. All analyses was conducted at the Research Data Centre at the University of Saskatchewan using STATA IC 15.[23] Figure 4.2 shows the model for this analysis.

Univariate analysis using a p-value of 0.20 was used as a cut point for the entry of a variable for multivariate analysis. A logistic regression model was built using the backward method based on a p-value of 0.05. Variables that were not included in the model were tested as confounders based on whether the addition of the variable changed the other estimates in the model by more than 20%. Receiver operating curve and the goodness of fitness test was to determine model fit.

4.4 Results

There was a total of 78,623 respondents in the survey. Majority of respondents, 42% were living with MS for 11 to 21 years while 35% were living with MS for less than 10 years. There were 51% of individuals who reported pain while 49% reported no pain (Figure 4.3). Based on the univariate analysis, years living with MS, self-perceived general health, mood disorder, problem with sleep and amount of family support were significant in the model (table 4-1). Stress was not significant in the univariate analysis and was not included in the multivariate analysis. Initially health and amount of family support were the significant variables in the final model. However after testing for confounders, all variables which were removed initially were found to change the parameter estimates of the final model by 20% and were included back into the model.

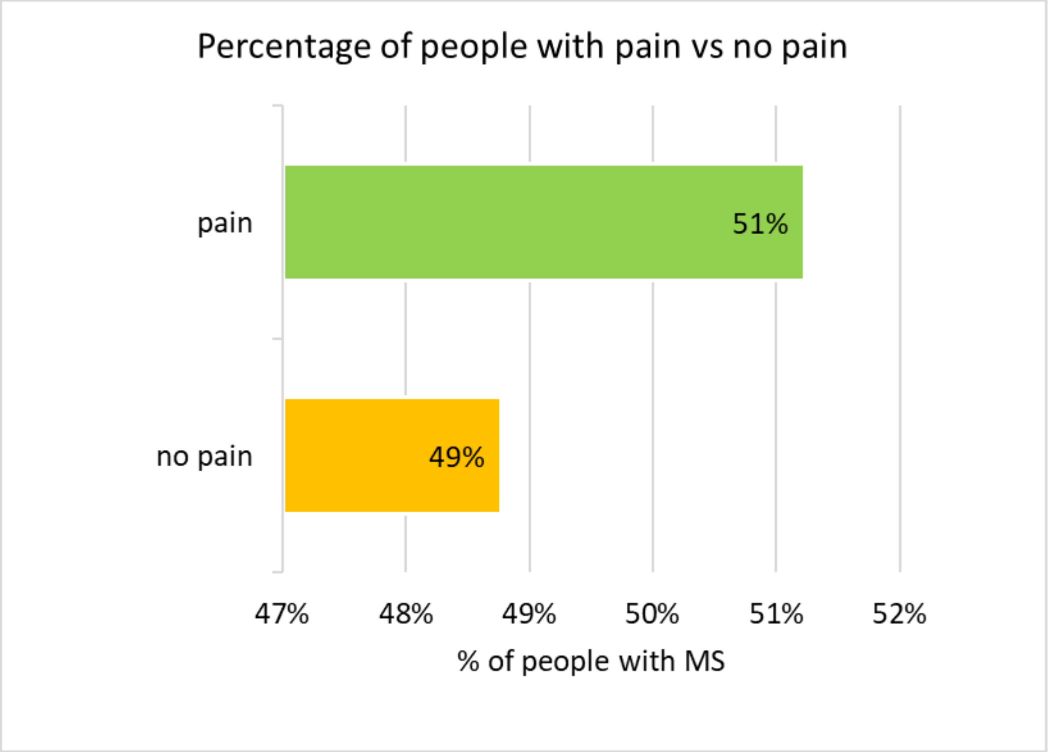

Figure 4.3: Percentage of people with pain vs no pain.

Table 4. 1: Descriptive statistics and univariate analysis of predictors associated with pain.

Variables	OR	95% CI	P-value	N
Number of years living with MS			0.112*	
11 to 21 years	1.88	0.95-3.71	0.07	32696
Greater than 22 years	1.85	0.90-3.82	0.10	18055
Less than 10 years	Ref			27872
Self-rated general health			p<0.001*	
Poor/fair	6.46	3.13-13.32	p<0.001	26444
Good/excellent	Ref			52179
Mood disorder			0.120*	
Yes	1.93	0.84-4.40	0.12	16785
No	Ref			61837
Problem with sleep			0.010*	
Yes	2.50	1.25-5.00	0.01	52903
No	Ref			25719
Self-rated stress			0.389	
Not at all/not very	Ref			33746
A bit	1.29	0.64-2.62	0.47	21300
Quite a bit to extreme	1.83	0.77-4.33	0.17	23577
Amount of support from family or friends			0.028*	
<4 types of support	2.98	1.13-7.88	0.03	6592
4 types of support (someone to confide/talk to, someone to do something enjoyable, someone to take to the doctor and someone to help in emergency)	Ref			72030

*significance is based on p-value <0.20

From the results of the multivariate analysis, individuals who had poor/fair health were 5.86 times more likely (95% CI 2.64 to 13.05) to have pain as opposed to individuals who had good health/excellent. The amount of social support was found to be significant in that individuals who had less than 4 types of social support were 3.02 times more likely (95% CI 1.06 to 8.59) to be in pain as opposed to individuals who had all 4 types of support (table 4.2).

Table 4. 2: Multivariate analysis of predictors association with odds of pain in people with MS.

Variables	**OR**	**95% CI**	**p-value**
Number of years living with MS			0.15
11 to 21 years	2.06	0.95-4.44	0.06
greater than 22 years	1.71	0.78-3.73	0.18
less than 10 years	ref		
Self-rated general health			p<0.001 *
Poor/fair	5.87	2.63-13.05	p<0.001
Good/excellent	ref		
Mood disorder			0.67
Yes	1.17	0.56-2.409	0.67
No	ref		
Problem with sleep			0.33
Yes	1.47	0.68-3.18	0.33
No	ref		
Amount of support from family or friends			0.04*
<4 types of support	3.02	1.06-8.59	0.04
4 types of support (someone to confide/talk to, someone to do something enjoyable, someone to take to the doctor and someone to help in emergency)	ref		

*significance based on p-value of <0.05.

Interactions were tested between mood disorder and family support and between health condition and family support. Based on the univariate analysis, both interactions were found to be significant. However when included in the multivariate analysis there were not found to be significant. Therefore both interactions were not included in the final model. Table 4.2 shows the results of the final model. The area under the curve gave a value of 0.75 which indicated that this model was a good model and the goodness of fit test indicated a value of 0.94 which indicated that the model was significant.

4.5 Discussion

The results of the study indicate that all types of social support are needed for managing pain in MS patients. Lacking in one types of support increases the odds of pain among individual's with MS. Therefore having someone to talk to about problems that they may have, having someone to do something enjoyable with allow for a sense of belonging. One study on coping and psychological adjustment among people with MS found that people with MS were less likely to seek out social support.[24] In another study done on investigating the needs of people with MS found that socio-environmental support such as household adaptation, better transport and rehousing was the category that was most frequently suggested.[25]

Many people with MS who are in the later stages of MS cannot carry out activities of daily living need support from their family or friends, therefore the burden of caregivers is increased as disability progresses. This becomes a problem because the caregivers usually tend to be the spouse of the person with MS and all activities such as bathing or moving the person from wheelchair to bed cannot be carried out by a spouse. Therefore the person with MS may lack the support they need if they are financially unstable to hire help from an organization. In a study done by Akku (2010) on caregivers and their level of stress in taking care of someone with MS found that the major predictors of feeling overburdened were feeling hopelessness, conflicts in decision making, not having enough time for leisure activities and social isolation.[26] In addition to this, some people with MS may have loss of mobility which increases pain when carrying out even the simplest of tasks. Therefore lacking in one type of support would increase pain.

A study that examined the impact of walking impairment in people with MS found that among the 1011 people with MS, 41% reported having difficulty walking, with 70% stating that walking was one of the most difficult aspect of having MS and 74% stated that it disrupted their activities of daily living.[27] In addition to this, 39% of people with MS stated that they never or rarely discussed the problem they have about difficulty with walking to their family doctor.[27]

However not all caregivers will seek the support they need. In a study done on caregivers of people with MS experience of support found that some caregivers tend to reject support from other family members or friends because they did not want to face the reality that someone they love had MS.[28] In other cases, rejecting help was also associated with wanting more control of the situation.[28] Other reasons for not asking for help was the caregivers thought that no one knew the care recipient well enough to take care of them and though it was their responsibility to do it themselves.[28] Some caregivers were not satisfied with the support services since it did not meet the needs of the care recipient.[28]

It is important for caregivers to seek support when needed and talk to their doctors about getting the proper services. Having support workers, visiting nurses, home maintenance services, workplace or vehicle modification can improve quality of life of both the person living with MS as well as their caregiver.[29] The results of the study also indicate that having poor health is associated with increased odds of pain among individuals with MS. MS is a condition that occurs with other conditions such as migraine headaches, back pain, depression, spasms etc. Therefore those who have MS may be in more pain because of these conditions and may have been overlooked in the diagnosis or they may not seek help for their conditions.

A similar study done on self-rated health and association with pain have found similar results.[30] Other studies have pointed to self-efficacy as a predictor for self-rated health.[31] Self-efficacy is the ability of someone to adjust to the condition they have which would allow them to cope more effectively.[31] It is linked to self-esteem and how much control a person has.[31] There are 4 ways to improve self-efficacy: 1) experience of accomplishing a behaviour; 2) vicarious learning or modelling the behaviour; 3) through encouragement or support from others; and 4) through physiological arousal such as anxiety which is connected to the behaviour.[31] Other studies have also showed that self-efficacy is a significant predictor of self-reported physical, cognitive and social functioning in MS.[32]

The strength of this study is that an association between lack of support for people living with MS and pain outcomes were determined, in addition to this, the study highlights the importance of having support in helping patients with MS and the need for more affordable home care services for people living with MS. One of the limitations of this study was that the type of MS was not available as a variable which could have helped in determining whether pain levels varied based on type of MS.

The support variable question which was asked did not specify whether it was informal or formal support, however it can be assumed that the question is asking about informal support (from family or friends) since the question prompt was “people sometimes look to others for companionship, assistance or other types of support”.[21] However since the questions was not specific and didn’t given examples of the type of support, respondents may have answered based on formal support (organizations, agencies) they received.

The role of caregivers is important to the well-being of people living with MS. Therefore it is important that they get the help they need in order to reduce burnout. The results of this research will inform clinicians about the importance of caregiver support and how to help their patients seek out quality services that can help them with their needs. An example of resources that clinicians can give to caregivers is caregiver educational materials. The MS society of Canada has an information and resource page on their website which provide webinars to caregivers, peer support group and caregiver guides.[33]

The MS society of Canada also has resources to help with respite services which provide primary caregivers a break from their duties by providing them with a personal care worker to come in and help the patient.[29] In addition to this self-efficacy is important when overcoming many illnesses and people with MS should seek help if they cannot cope with their illness. The results of this study will also inform health care organizations on ways to improve home care services for people with MS especially in lower income neighbourhoods or on reserves.

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CHAPTER 5: USING COMPLEMENTARY/ALTERNATIVE TREATMENTS (CAMS) REDUCE ADHERENCE TO MS MEDICATION

Abstract

Objective: Appropriate use of prescribed medications are crucial to preventing relapses from occurring, however do to the side effects of many medications, many people turn to complementary and alternative medicine (CAM) treatments. The objective of this study was to examine the predictors associated with MS medication use. The two categories that were investigated were various alternative treatments as well as comorbid health conditions.

Methods: The Survey on Living with Neurological Conditions in Canada (SLNCC) 2011 was used to carry out the analysis. The outcome variable was whether or not the individual used medication for MS during the course of their illness. Logistic regression model was used to carry out the analysis.

Results: Individuals who did not take CAMs were more OR=5.44 95% CI (1.37-9.29) likely to use medication for MS as opposed to those who used CAMs. Having a mood disorder was associated with greater use of medications for MS while back problems were associated with lower odds of medication use.

Conclusion: The use of complementary treatment is associated with lower odds of MS medication use. Efforts should be taken by health care practitioners to inform patients about the benefits of disease modifying medications and why it should never be substituted with other treatments.

5.1 Introduction

Multiple sclerosis (MS) is a demyelinating diseases of the central nervous system which has no cure.[1,2] However, there are a wide range of disease modifying treatments, primarily medications that have been effective in slowing down the disease and reducing relapses from occuring.[3] The main drugs are Beta Interferons, Glatiramer Acetate, Mitoxantrone, Natalizumab, and Fingolimod that can shorten the duration of attacks, decrease the frequency and provide symptomatic relief.[4] In addition, medications can reduce disease progression, lower the number of emergency department visits and in general improve overall quality of life. Medication use benefit the patient as well as the clinician, health care system and society as a whole.

The importance of early treatment initiation in MS has been found in many studies.[3,5,6] Patients who had started treatments later in the clinical course of the disease had a greater risk of reaching a level 4 on the Expanded Disability Status Scale (EDSS) which indicates significant disability. The hazard ratio was 1.07 (95% CI 1.05 to 1.10).[5] Earlier treatments were associated with better clinical outcomes.[5] However one of the main reasons patients stop taking medication is because medication for MS is not a cure and although it prevents relapses from occurring, patients still have a wide range of symptoms and side effects such as bladder dysfunction, chronic pain, cognitive decline as well as mobility problems.[7] Disease modifying medications (DMTs) can help to slow down the progression of the disease but they cannot reverse the lesions that have already taken place.[8]

DMTs may need to be stopped if there are serious adverse side effects that are life threatening.[6] Some side effects may occur such as with the drug fingolimod which increases the risk of opportunistic infections in patients and causes low lymphocyte count in peripheral blood.[6] In order to reduce symptoms such as spasticity, antispastics such as baclofen, tizanidine, diazepam and clonazepam could be used, however there are adverse effects associated with this line of medication such as postural instability and vertigo.[9]

Up to now there hasn't been many studies that have been conducted on whether using complementary/alternative treatments (CAMS), rehabilitation therapy or other conditions impact medication adherence in positive or negative way. Due to adverse side effects of medication use people often turn to complementary/alternative medicine treatments (CAMS) such as natural health products, herbs, homeopathic medicine, vitamins, acupuncture or exercise.[10] Another type of auxiliary treatment is rehabilitation which is an understudied area whereby rehabilitation helps with walking or balance but whether rehabilitation impacts MS medication use has yet to be explored. Rehabilitation interventions has been considered beneficial in the earlier phases of MS. It is used to reduce symptoms and help improve the quality of life of people with MS.[9] The most important aspect of rehabilitation is that patients can have various types of difficulties from physical, behavioural or cognitive but rehabilitation programs can help the patient by altering the treatment regimen in order to better serve the needs of the patient.[9]

Having one or more conditions may also affect whether or not individuals take medication for MS. Chronic diseases may co-exist together because of chance or patients may be diagnosed with another disease because of frequent use of health care services.[11,12] In other cases, diseases may co-exist together because of genetic susceptibility to immune disorders, environmental factors and independent factors such as age, obesity and diet.[11,12] Diseases may co-exist together because they are a product of another undiagnosed disease.[11] Psychiatric illnesses may influence medication use or may hinder it but studies are lacking in this area. Some studies have shown that psychiatric disorders such as depression and anxiety are common among individuals with MS.[13–15]

Cognitive behavioural therapy has been shown to help patients cope with MS and improve overall quality of life. Majority of CBT's focus on treating depression, however whether it reduces disease progression has yet to be studied. Other areas include mindfulness based interventions which were found to be effective in helping patients be aware of present experiences and reduce emotional distress.[16] A review on mindfulness based interventions found that stress could lead to disease progression for MS patients and that mindfulness could be used to accept the presence of the disease and to look for a better outcome on life.[16]

There are a vast number of social behavioural models that have been found to be effective in helping patients adhere to medications.[17] Models such as the health belief model, information motivation behavioural (IMB) skills model, situated IMB model of care Imitation and maintenance, social cognitive theory, self-regulations theory, theory of planned behaviour, protective motivation theory, trans theoretical model, chronic care model, self-management theory, Anderson behavioural model and ecological/socio-ecological framework/ model has been found to be effective for helping patients to change their behaviour.[17]

For example the health belief model is commonly used to change ones behaviour with regards to compliance to medications. One of the main features of this model is that the patient has the choice and are able to decide what is best for their health.[18] It is dependent on whether the patient thinks that they are at a risk for an illness, whether they think the health condition has consequences, whether there is a course of action for the illness and whether the benefits of taking the action outweigh the costs.[18] There are six main concepts to the model which are perceived susceptibility, perceived severity, perceived benefits, perceived barriers, cues to action and self-efficacy.[18]

In a study done by Kamran et al. (2014) to determine whether the health behaviour model was effective in helping patients adherence to hypertension medication, it was found that adhering to medication was low because patients perceived susceptibility, perceived severity and perceived benefits were inadequate and they had poor lifestyle factors.[18] Therefore it was concluded that patients perceptions of medications needed to be improve and that proper education was important.[18] The results of the study indicated that based on the health behaviour model when pieces of the model are missing, the model isn’t effective in changing the persons behaviour. Therefore an effective approach for behaviour change that takes into account the social and behavioural factors of the patient need to be determined for effective behaviour modification to take place. The main objective of this study was to examine the individual level predictors such as having chronic conditions has an effect on medication use as well as whether types of CAMs and auxiliary treatments were associated with medication use in people who have MS.

5.2 Methods

5.2.1 Data Source

The Survey on Living with Neurological Conditions (SLNCC) was used to perform the analysis. The SLNCC was linked to the Canadian Community Health Survey (CCHS).[19] The SLNCC is a cross sectional survey that collected information on Canadian's experiences with chronic neurological conditions. This survey is a cross-sectional survey of a set of 18 neurological conditions. The sample for the SLNCC survey was drawn from the CCHS respondents and household members who were aged 15 years of age and older.[19] These respondents had to have at least one of the following 18 neurological conditions listed. [19] Only individuals who had MS were included in the study (N=267). As recommended by Statistics Canada, in order to take into account the survey design, replicate sampling weights and bootstrapped variance estimation were used in the analysis.[19] A set of (n=500) replicate weights were used in order to account for non-responses. For the SLNCC linked data set, the bootstrap replicates are the sub samples that were drawn and used to estimate the variance of the CCHS estimates.[20]

5.2.2 Variables assessed

Demographic factors such as age, sex, income and education were assessed. Age was categorized as 22 to 30 years, 31-40, 41-50 and greater than 51 years. Income was categorized as 5,000-39,999, 40,000-59, 9999, 60,000-89, 9999 and 90,000 and greater. Education was categorized as less than secondary school, secondary school or grater and some post-secondary school or greater. The type of treatment were assessed in the model were complementary/alternative medical treatments, rehabilitation therapy and counselling/psychotherapy. Mood disorder was examined as the psychological factor in the model. Individuals were asked whether they had mood disorder or anxiety disorder for which there were 2 responses either yes or no.

Other chronic conditions that were tested for were back problems, arthritis, heart disease and blood pressure and the responses were either "yes" or "no". The age of first diagnosis of MS was also used in the screening process and was categorized as 31 to 40, 41 to 50 and greater than 51 years of age. The outcome variable was whether or not the individual with MS had taken medication to treat their MS with a binary response of "1= yes" and "0=no".

5.3 Analysis

A logistic regression model analysis was carried out for this study in order to determine whether each of the predictors were associated with medication use. These predictors were selected based on previous theories on this topic. Figure 5-1 shows the hypothetical model for the analysis. Unadjusted and adjusted odds ratios with 95% CIs with p-values were computed. Univariate analysis was conducted using a ($p < 0.20$). Manual backward selection was used to build the multivariable model based on ($p < 0.05$). A complete case analysis was conducted in which only variables with complete values were used in the model and missing values were removed. Cofounders were tested in the final model and were retained if the addition of that variable changed the coefficients of the other variables by more than 20%. All possible interactions were assessed and added to the model if they were significant at ($p < 0.05$). The effectiveness of the final model was assessed using receiver-operating characteristics (ROC). The analysis was performed using STAT IC 15.

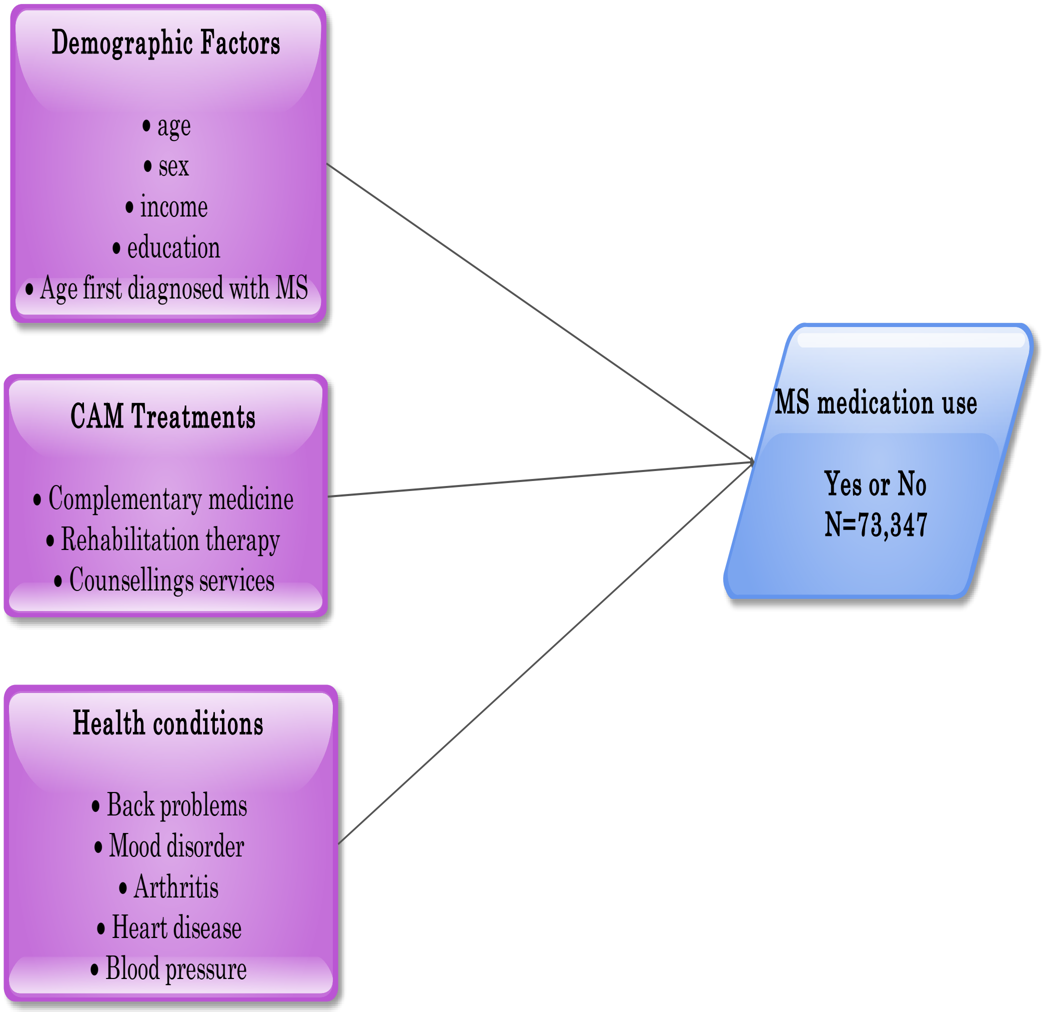

Figure 5. 1: Model for MS medication use.

5.4 Results

There were 306 individuals diagnosed with MS in the Survey of Living with Neurological Conditions in Canada (SLNCC) 2011 and of those 267 were included in the analysis. The final sample consisted of 73,347 weighted observations. There were 49,770 individuals who used medication to treat MS and 23,577 individuals who didn’t use medication. Based on the weighted percentage, 50% of individuals with MS were those who were 51 years of age and older, 33% were those who were 41-50 years of age, 12% were those 31-40 years of age and 5% were 22-30 years of age. 75% of individuals with MS were females while 25% were males. Figure 5-2 shows the age categories. Figure 5.2 shows the age categories. Based on Figure 5.3 the majority of respondents were in the lower income bracket of 5,000 to 39,999. In terms of education, the majority of respondents had some postsecondary education or more, however education was not significant not having an impact on whether a person used medication for MS (Figure 5.4). In the final model age and sex were controlled for. Although counselling/psychotherapy services and rehabilitation were not significant in the univariate analysis, they were tested for in the final multivariate analysis based on ($p<0.05$).

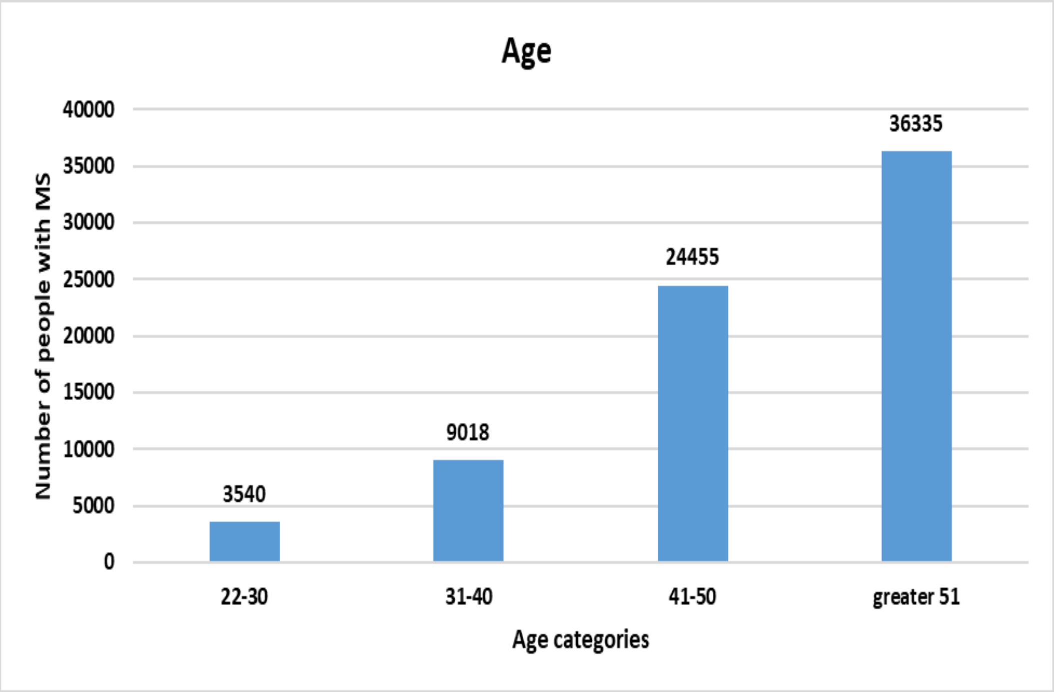

Figure 5. 2: Number of people living with MS based on age categories.

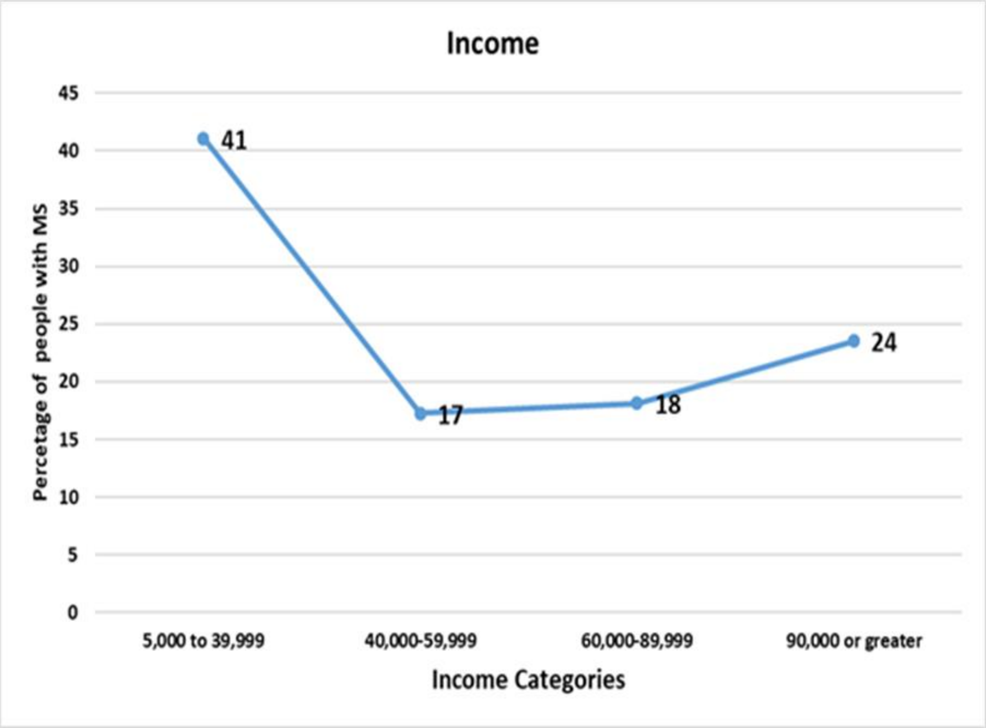

Figure 5. 3: Percentage of people living with MS based on income categories.

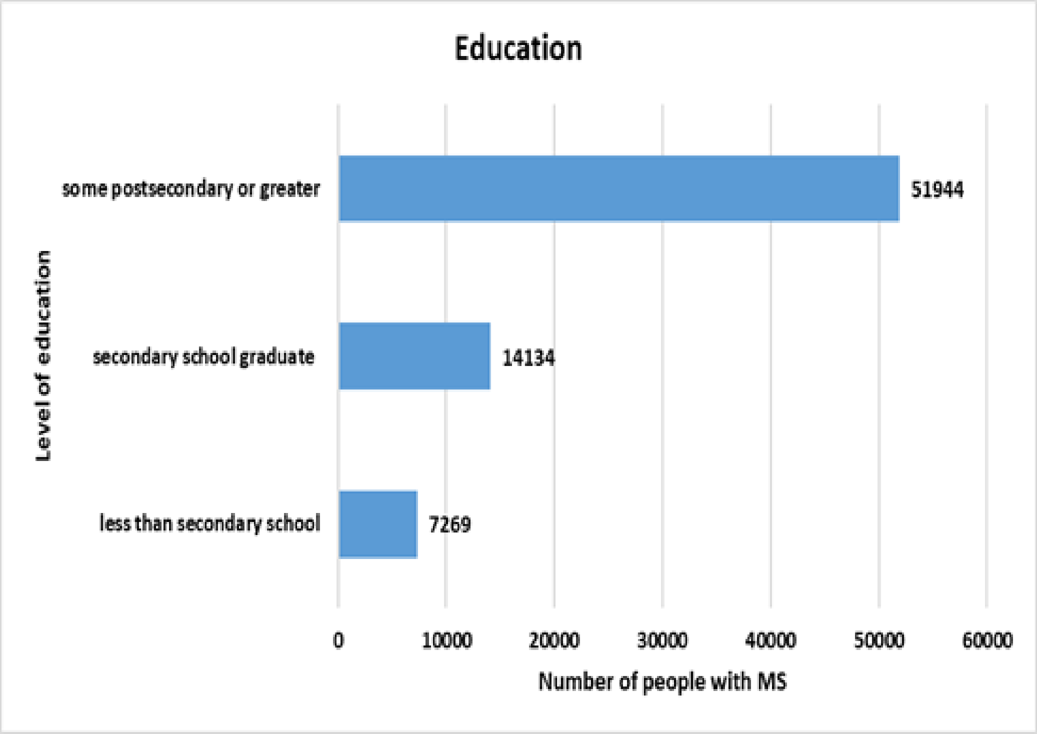

Figure 5. 4: Education level of respondents with MS.

Based on the univariate analysis (see table 5.1), individuals who had an income of 60,000 to 89,999 were more likely to take medications as opposed to those who had an income of 5,000 to 39,999 OR=5.63 95%CI (1.50-21.2). Individuals who had back problems as a co-morbid conditions with MS were less likely to take medication as opposed to those without back problems OR=0.38 95% CI (0.15-0.98). Individuals who had a mood disorder were more likely to take medication for MS as opposed to those who didn’t have a mood disorder OR=5.39 95%CI (1.60-18.17).

Table 5.1: Univariate analysis for predictors associated with medication usage.

Variables	**Odds Ratio**	**P-value**	**95% CI**	**N**	**percentage**
Age		0.80			
22-30	ref			3540	5
31-40	2.96	0.41	0.23-38.7	9018	12
41-50	3.21	0.33	0.31-33.1	24455	33
greater 51	2.65	0.36	0.33-21.5	36335	50
Sex		0.20			
Female	1.97	0.20	0.693-5.61	55361	75
Male	ref			17986	25
Income		0.07*			
5,000 to 39,999	ref			30133	41
40,000-59,999	1.17	0.76	0.43-3.23	12658	17
60,000-89,999	5.63	0.01	1.50-21.2	13302	18
90,000 or greater	1.90	0.33	0.52-6.99	17255	24
Education		0.95			
Less than secondary school	ref			7269	10
Secondary school graduate	0.81	0.79	0.163-4.01	14134	19
Some post-secondary education or greater	0.81	0.75	0.214-3.03	51944	71
Back problems		0.04*			
Yes	0.38	0.05	0.146-0.98	16905	23
No	ref			56442	77

Variables	Odds Ratio	P-value	95% CI	N	percentage
Mood disorder		0.01*			
yes	5.39	0.01	1.60-18.17	12155	17
no	ref			61192	83
Arthritis		0.23			
Yes	0.52	0.23	0.17-1.51	15286	21
No	ref			58062	79
Heart disease		0.91			
Yes	1.09	0.91	0.25-4.70	3226	4
No	ref			70122	96
Blood pressure		0.94			
Yes	0.97	0.94	0.42-2.24	14888	20
No	ref			58460	80
Complementary medicine		0.08*			
Yes	0.40	0.08	0.15-1.12	15405	21
No	ref			57942	79
Counselling services		0.20			
Yes	2.74	0.20	0.58-12.9	15966	22
No	ref			57381	78

Variables	**Odds Ratio**	**P-value**	**95% CI**	**N**	**percentage**
Rehabilitation therapy		0.25			
Yes	1.86	0.25	0.65-5.34	28013	38
No	ref			45335	62
Age first diagnosed with MS		0.23			
<31	ref			21839	30
31 to 40	1.70	0.37	0.53-5.40	26811	37
41 to 50	2.02	0.28	0.56-7.28	16497	22
Greater than 51	0.58	0.35	0.18-1.84	8201	11

* shows significance at p-value of <0.20
Numbers were rounded either up or down due to weights and bootstrapping procedures.

Based on the multivariate analysis and cross comparison chart (see table 5-2 and 5-3) individuals who did not take complementary medicine treatment were more likely to take MS medication as opposed to those who used complementary/alternative medicine treatment OR=5.44 95% CI (1.37 -9.29). Individuals with a mood disorder were more likely to take MS medication as opposed to those who did not have a mood disorder OR=5.5 95% CI (1.18-25.7). Individuals with MS who had back problems were less likely to take MS medication than those who did not have back problems OR=0.32 95%CI (0.11-0.95). Interactions were not found to be significant and were not included in the final model. In the model diagnostics, the ROC curve showed that the logistic regression model correctly classified 75% of people who used MS medication indicating that the multivariate model was a good one. The goodness of fit statistics which shows whether the observed and expected observations for the final model are good fit gave a value of 0.23 indicating good model fit.

Table 5. 2: Multivariate analysis of predictors associated with medication usage.

Variables	**Odds Ratio**	**95 % CI**	**P-value**
Age			0.745
22-30	ref		
31-40	0.95	0.06-15.26	0.97
41-50	2.22	0.21-23.29	0.51
Greater than 51	2.15	0.25-18.28	0.45
Sex			0.098
Male	ref		
Female	2.65	0.84 - 8.14	0.96
Income			0.06
Less than 39,999 (<5,000 to 39,999)	ref		
40,000-59,999	1.32	0.30-5.89	0.71
60,000-89,999	7.72	1.37-43.6	0.02
90,000 or greater	4.03	1.15-14.1	0.03
Health conditions			
Back problems, excluding scoliosis, fibromyalgia and arthritis			0.04*
Yes	0.32	0.11-0.95	0.04
No	ref		
Mood disorder			0.03*
Yes	5.49	1.18-25.7	0.03
No	ref		
Types of alternative medicine			
Complementary/alternative medicine			0.016*
Yes	0.18	0.05 - 0.73	0.02
No	ref		
Rehabilitation therapy			0.099
Yes	3.17	0.80-12.51	0.09
No	ref		
Counselling or Psychotherapy services			0.42
Yes	2.05	0.35-11.95	0.42
No	ref		

* shows significance at p-value of <0.05

Table 5. 3: Comparisons of odds ratios based on significant variables from the multivariate analysis based on p-value of <0.05.

Variables	**no vs yes**	**OR**	**95% CI**
Complementary/alternative medicine treatments		5.44	1.37-9.29
Mood disorder		0.18	0.04-0.85
Back problems		3.12	1.05-9.29

5.5 Discussion

This study aimed to show the predictors that were associated with medication use for MS among patients in Canada. Sociodemographic factors were not associated with medication use. This finding is in agreement with a similar study that found sociodemographic differences were not a factor in differences between complementary medication use and MS medication use among individuals diagnosed with MS.[21] In the multivariate analysis sociodemographic factors were not associated with medication use however in the univariate analysis, increased income was associated with greater likelihood of medication use.

From the analysis it was evident that using complementary and alternative treatments (CAMs) was associated with lower medication use and this was reported by many studies that were done on complementary medicine.[22] Another study examining the frequency and characteristics of complementary and alternative medicine use among patients with MS found that 67.3% of patients were currently using one or more complementary and alternative treatments.[21] The patients who used complementary treatments were more severely affected by MS than non-users and had a greater duration of the illness.

Studies have reported that the most common reason for using (CAMs) was the desire by MS patients to use holistic health care which looked at treatments that recognized the mind, body and spirit aspects and dissatisfaction with conventional medicines. The most frequent (CAMs) used were herbs followed by massages and acupuncture.[22] similar studies have reported use of vitamins, essential fatty acids and minerals. [23] Complementary and alternative medicine (CAM) are used frequently by MS patients because they experience improvements in their symptoms.[24]

In some cases, patients decided to use complementary medicine instead of using conventional treatments because of the side effects associated with medications and they believed that concentrating on getting rid of the stress and using acupuncture helped them feel better over the years.[24] Another study indicated that a patient had worsening of their symptoms after using β-interferons and had become disabled because of paralysis of arms, legs and blindness in one eye.[24] Although doctors had stated that it was due to the progression of her disease, she decided to use CAM which consisted of dopamine, noradrenaline, acetylcholine and serotonin in addition to diet and supplements which improved her symptoms.[24]

Homeopathic medicine were used by majority of patients with MS who used complementary medicine followed by acupuncture, healing, yoga and dietary supplements.[25] Another reason for turning to CAM was the dissatisfaction with medical treatments with regards to lack of support from health care professionals and having lack of control on medications being prescribed.[25]

Comorbid health conditions are common among individuals with MS. Mood disorders and back problems were found to be associated with whether or not a person who had MS were likely to take medication. Mood disorders consisted of major depressive disorder, dysthymic disorder, bipolar disorder, panic disorder, and generalized anxiety disorder.[26]

The results of our study stated that individuals with mood disorder were at a greater odds of medication use. This is consistent with the study which researchers examined the effect of comorbidities on disease modifying therapy (DMT) use in MS in which patients with depression were 13% more likely to initiate DMT compared to those who did not have depression.[27] One of the reasons for this could be that individuals with depression may have had more active MS as opposed to those did not have depression and this could be a reason for initiating DMT treatment.[28]

Depression has also been correlated with fatigue caused by MS.[29,30] Fatigue is a problem that has been overlooked over the years but new studies indicate that 50-90% of patients report fatigue as one of the symptoms of MS and affects many aspects of the person's life.[31] The lifetime prevalence of depression in MS patients is 50%.[32] Therefore physicians prescribe Modafinil which is a type of medication that is used to promote wakefulness and reduce fatigue.[29] This could be one of the reasons for the increase use of MS medication use among individuals who have mood disorder since Modafinil could be one of the prescribed medications along with first line medications for MS. Patients who have both MS and mood disorder may be more inclined to take their medication in order to reduce their fatigue which they may believe is the cause of their mood disorder. Psychiatric onset in MS and whether early signs of psychiatric illness could help with diagnosing patients as having MS has also been studied. It has been suggested that psychiatric episodes may occur before MS onset.[33] This could be an explanation for why patients who have mood disorder are more likely to use medications.

Back problems are a common problem in patients with MS due to painful spasms. In order to reduce painful spasms caused by MS, patients turn to massage therapy or acupuncture. Our study indicated that those with back problems had a lower adherence to MS medication than those without back pain. One of the reasons for this is that disease modifying medications for MS don't target pain. Therefore patients turn to CAM in order to help relieve the symptoms. In a study done on why patients use CAM, it was found that CAM helped them relax, reduced tension and reduced pain in addition to improving overall quality of life.[34] Another study indicated that pain is managed poorly in the treatment course of MS and many patients have turned to opioid medication, benzodiazepines, massage therapy, marijuana and hypnosis treatments.[35]

One of the problems with adhering to medication is that when many medications are prescribed, the patient may find it difficult to manage them all. One example of an effective model is the health behaviour model. However the effectiveness is not based on the model that one chooses, but is based on tailoring the model to suit the person's needs based on the type of illness they have, operationalize the factors such that the factors that motivate the person are identified and then to use the model based on these changes.[17] In a study done by Kaluer et al. (2008) on compliance, adherence and the treatment of MS, researchers state that a comprehensive model of treatment adherence should integrate patient, therapist, illness, treatments factors as well as the external factors from the social environment. Therefore interventions needs to be tailored to the specific deficits of the patient. The main goal for interventions is to encourage the patient to take responsibility for their treatment which is self-commitment to change.[36] Having good communication between the patient and health care providers is important for better progress in treatment.

This study had several strengths. This is the first study that examined the association associated with medication use and assessed different type of treatments such as CAMs as a risk factor. The study highlights the problems that many individuals with MS face which is desperation to find a treatment that works regardless of safety. It provides awareness to primary care providers about CAM use by patients so that they can direct patients to counselling services that can help patients cope with MS. The limitation of this study is that it was a cross sectional survey, therefore a cause and effect relationship cannot be determined. Since the variables for medication and complementary and alternative medicine did not have specific types of medications used, it was difficult to state what specifically each respondent used and how it affected their overall health. The results of this research indicate that individuals who did not use complementary treatment were more likely to adhere to medication. Having other health conditions such as back problem and mood disorder were associated with medication use.

It is important to create targeted medication education programs for patients in order to help them understand the advantages and disadvantages of medication use as well as the potential harms of complementary treatments use alone without medication. Health care professionals should also look at comorbidities that patients with MS have so that drug interactions don’t take place with prescribed medication and patients can have tailored treatment for their specific conditions.

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CHAPTER 6: THE EFFECT OF EXERCISE, YOGA AND PHYSICAL THERAPY ON THE QUALITY OF LIFE OF PEOPLE WITH MULTIPLE SCLEROSIS: SYSTEMATIC REVIEW AND META-ANALYSIS.

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I contributed to the entire study design, data collection, quality assessment, data analysis, data interpretation and manuscript writing. This chapter includes total standard mean difference of combined intervention scores which were excluded in the published study.

Abstract

Objectives: People living with MS have a poor quality of life (QOL) because of the symptoms caused by the disease and there are various types of treatments to manage the symptoms aside from medication.

Methods: A systematic review with meta-analysis was conducted using PubMed Medline and Scopus from 1990 to 2017. Standard mean differences were computed.

Results: Eighteen studies met the inclusion criteria for this meta-analysis. Aerobic exercise was effective in improving satisfaction with physical functioning, d=0.35 (95% CI=0.08 to 0.62), mental functioning d=0.42 (95% CI=0.11 to 0.72), and social functioning d=0.42 (95% CI=0.15 to 0.69). Physiotherapy was also found to be effective for physical functioning d =0.50 (95% CI 0.19 to 0.80), mental functioning d =0.44 (95% CI 0.14 to 0.75) and social functioning d =0.60 (95% CI 0.21 to 0.90).

Conclusion: These findings suggest that aerobic exercise and physiotherapy improves the satisfaction of MS patients with their physical, mental/emotional and social role functioning strengthening the need for this kind of complementary treatment to include as normal practice in the treatment of MS.

6.1 Quality of Life and MS

Multiple sclerosis (MS) is a chronic autoimmune disease.[1] This disease affects the myelinated axons in the central nervous system leading to neurological deterioration over time.[1] MS is more common among individuals of Northern European descent.[2] It is usually diagnosed between the ages of 20 to 50 years of age.[3] The disease causes a wide variety of symptoms including muscle weakness, fatigue, ataxia, impaired speech, vision impairment, cognitive dysfunction and paralysis.[4]

Individuals with MS have consistently been shown to have lower quality of life (QOL) scores.[5] Improving the quality of life of MS patients has been recognized as important in secondary prevention of MS.[6–8] Quality of life (QOL) scales ensure the satisfaction of individuals with their physical, mental and social wellbeing. Health related QOL is based on the perspectives of the individual and how they feel in the various areas of their life such as their physical, mental and social health and is usually measured using a variety of questionnaires.[8]

Exercise training in general has been recognized as a useful intervention to alleviate some of the symptoms of MS.[9–14] Endurance training, resistance training and combination of both[15] are the main categories of exercise that have been investigated for their effectiveness with respect to MS in experimental studies. Meta-analysis studies that have investigated the possible association between exercise and quality of life among individuals with MS have focused on an overall quality of life score as opposed to investigating the different types of exercise methods and their impact on the various domains of quality of life.[4,16,17]

Yoga, a form of flexibility exercise that involves spiritual practice, breathing exercises and meditation has been used as a therapeutic method. It has been shown to help relieve stress and anxiety among individuals with neuropsychiatric disorders, however the impact of it among individuals with MS has not been systematically investigated across quality of life domains.[18] Esmonde and Long AF (2008) state that yoga is among the six most effective complementary therapies for managing MS patient's symptoms. It has its therapeutic effects on QOL by improving many of MS symptoms, including weakness, fatigue, mental impairments and helps reduce persistent pain, reduce stress and help in reducing the symptoms of cancer and prevention of cardiovascular disease[19–22] The different types of movements involved in yoga may improve quality of life by relieving spasticity, cognitive impairment and mental stress as well as increasing physical and motor functions.[23]

Physiotherapy interventions includes various types such as education, consultation, therapeutic exercise, and cardiorespiratory techniques.[24] Physiotherapy has been known to help in recovering from MS such as in balance and gait and for improving walking dysfunction in persons with MS.[25] It has also been used to help with urinary incontinence which is a common symptom of people living with MS.[26] However besides helping in balance and gait as well as in urinary incontinence, not much research has been done on the benefits of physiotherapy on individual domains of quality of life and whether there are more benefits to the mental and social domains.

Although systematic reviews on interventions to alleviate symptoms of MS has been conducted, the comparative effectiveness of various types of interventions have not been systematically assessed nor have studies that have looked at the impact of these intervention on specific domains of quality of life been systematically investigated. What this review adds new to the literature in an investigation on the comparative effectiveness of various types of interventions such as aerobic exercise, anaerobic exercise, mixed exercise, yoga and physiotherapy on the overall quality of life of individuals diagnosed with MS as well as looking at their specific effect on MS patients' physical, mental, and social quality of life domains.

6.2 Methods

6.2.1 Data sources and searches

We performed a comprehensive search using the databases PubMed/ Medline and Scopus using key words” multiple sclerosis" AND "exercise “OR "physical activity" OR "physical therapy “OR "aerobic" OR "anaerobic" OR "strength" OR "flexibility" OR "yoga" AND "quality of life" from 1990 to 2017. We started from 1990 in order to get the maximum number of citations possible for this study. The inclusion criteria were: 1) study must have either a randomized control design, pre-test post-test design, quasi experimental design or cross over design 2) should be testing the effectiveness of either exercise, physiotherapy or yoga interventions, and 3) should have a standard recognized QOL outcome measure including specific measures of the subdomains physical functioning, mental/emotional functioning and social role functioning domains.

Three researchers KA, YS and CD were involved with title and abstract screening and differences were resolved through discussions. Articles that had comparisons between a complementary therapy and control where the control had an exercise component were included in the meta-analysis as a separate study. Thus a single study could have 2 types of treatment. We excluded articles that did not have a measures of quality of life domains or those that did not have cases and controls. Systematic reviews, literature reviews, meta-analysis and case studies were also excluded. PRISMA and Meta-analysis of Observations Studies in Epidemiology (MOOSE) guidelines were adhered to.[27,28] The modified Pedro scale was used to assess study quality.

6.2.2 Effect sizes and statistical analysis

Quality of life was categorized into 3 categories: a) physical, b) mental and c) social health. Articles that did not have these components were not included in the meta-analysis. For each quality of life category, pooled standard mean differences were calculated as well as mean differences based on the type of exercise or therapy such as aerobic, anaerobic, flexibility, mix of aerobic and anaerobic, yoga or physiotherapy. We computed standard mean difference using Cohen's *d* for physical, mental and social health scores for each study.[29] The standard mean difference was calculated based on the mean difference between the treatment and control group divided by the pooled standard deviation. For randomized controlled trials we used the difference between the treatment and control group and for pre-test post-test studies we used the post-test as the intervention and used pre-test as the control.

The aggregated or pooled standard mean difference was computed using a random effects models where heterogeneity was found and weighted using the sample size for each study. Heterogeneity was evaluated using the DerSimonian and Laird I^2 statistics.[30] When heterogeneity was absent a fixed effect model was used. A standard mean difference (SMD) of 0.20 indicated a small effect, SMD of 0.50 indicated a medium effect and an SMD of 0.80 or greater indicated a large effect.[31]

In order to assess publication bias, funnel plots and Forest Plot 's test were used.[32] The assessment of study quality was conducted using the modified Pedro scale which can be found in Appendix B. Sensitivity analysis was carried out in order to assess the impact of each study on the overall estimates. This was done by removing each study one at a time and by recalculating the standard mean difference. Meta-regression was used to assess heterogeneity and study quality. All analysis was conducted using STATA IC 13.

6.3 Results

There were 1015 articles initially identified through database searches in PubMed/Medline and Scopus. After duplicate titles were removed 586 titles remained. Another 443 potential articles were removed after title review. After abstract review, full texts were reviewed for 84 articles and 18 articles were used in the analysis based on inclusion and exclusion criteria. Figure 1 shows the process in selection of the articles.

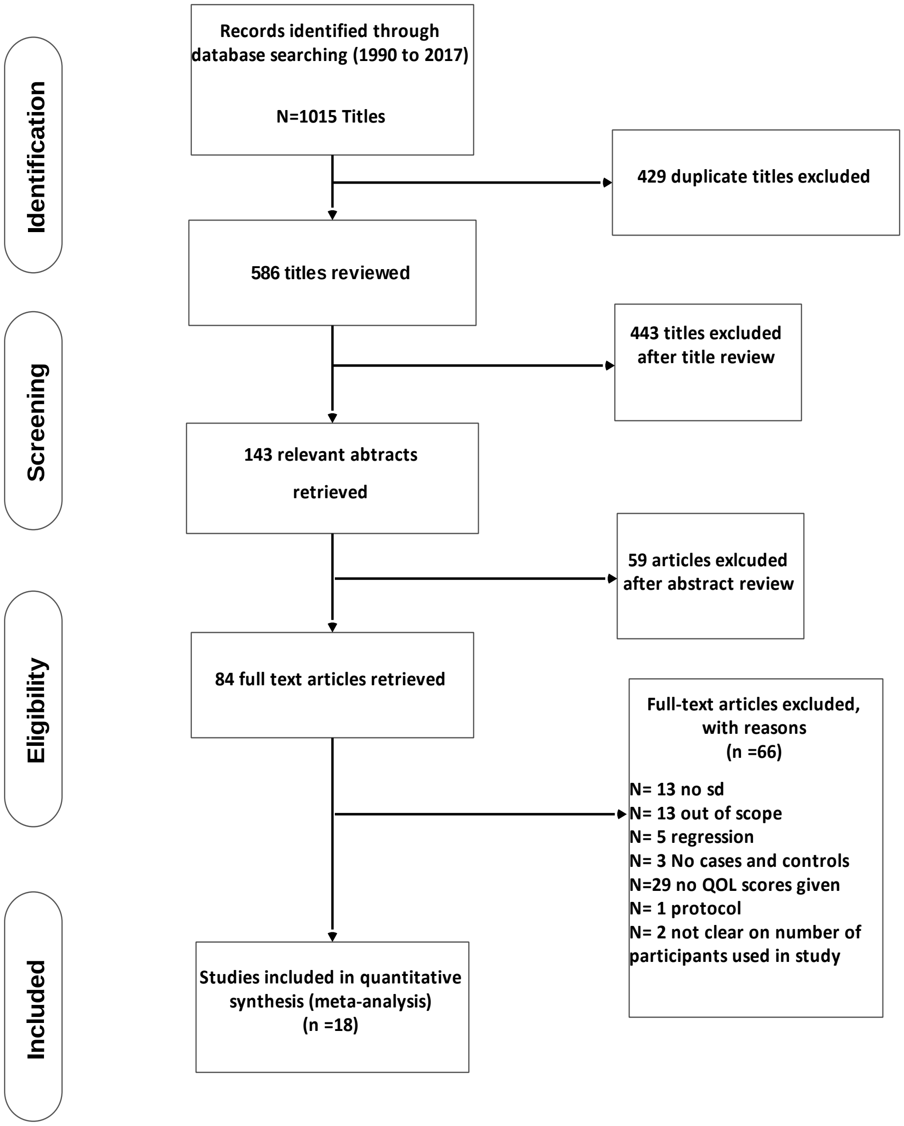


Figure 6. 1:PRISMA flow diagram for exercise, yoga and physical therapy on health related quality of life.

Table 6.1 shows the characteristics of the studies that were included in the meta-analysis. There were 4 different types of quantitative measures of quality of life: Medical Outcomes Survey Short Form-36, Multiple Sclerosis Quality of Life-54 Questionnaire (MSQOL-54), Multiple Sclerosis Quality of Life Inventory (MSQLI), Multiple Sclerosis Impact Scale-29 (MSIS-29) and World Health Organization Quality of Life BREF (WHOQOL-BREF). The majority of studies included in the analysis were carried out in USA and Australia with the common instrument used for the analysis being SF-36 and MSQOL-54.

In total there were 828 participants in the study. The majority of study designs used randomized controlled trials with some being pretest post-test and others being cross over design. Based on the modified Pedro scale, the majority of the studies ranges from 5 out of 9 to 8 out of 9 on the scale indicating good study quality. Appendix A shows assessment of studies based on the modified Pedro scale.

Table 6.1: Description of studies that were included in the meta-analysis.

	Author, Study year	**Country**	**N**	**Study design**	**Instrument Used**	**Participants and age**	**Type of MS**	**Main findings**
1	Ahmadi et al. 2010	Iran	10	RCT	Multiple Sclerosis Quality of Life–54 questionnaire (MSQOL-54)	Women with a mean age of 36.75 years	Participants with MS	Significant improvements shown on the physical function and physical health MSQOL-54 scores. Treadmill training improved balance and walking capacity, fatigue and quality of life (QOL) in people with mild to moderate MS.
2	Cakit et al. 2010	Turkey	23	RCT	Medical Outcomes Survey Short Form-36 (SF-36)	Men and women between age of 25 and 62 years of age.	Participants with MS	Significant improvements shown on the physical function and role physical functioning on the SF-36 scale.
	Cakit et al. 2010	Turkey	19	RCT	Medical Outcomes Survey Short Form-36 (SF-36)	Men and women between age of 25 and 62 years of age.	Participants with MS	Significant improvements shown on the physical function SF-36 scale.

	Author, Study year	**Country**	**N**	**Study design**	**Instrument Used**	**Participants and age**	**Type of MS**	**Main findings**
3	Cohen et al. 2017	USA	14	Repeated measures	Multiple Sclerosis Quality of Life Inventory (MSQLI),	Men and women between the ages of 18 to 64.	Participants with MS	Significant improvements shown on the mental score of the MSQLI but not for physical score.
4	Dodd et al. 2011	Australia	71	RCT	World Health Organization Quality of Life BREF (WHOQOL-BREF).	Men and women with a mean age of 47.7 ±10.8 for experimental group and mean of 50.4 ± 9.6 for control group.	Relapsing Remitting MS	Significant improvement on the physical health domain of the WHOQOL-BREF scale for relapsing remitting MS patients.
5	Gobbi et al. 2016	Italy	8	Pretest post test	Medical Outcomes Survey Short Form-36 (SF-36)	Men and women between the ages of 35 and 59 years of age	Participants with MS	Significant improvement shown on the role-physical and vitality HRQOL subscales.
6	Husinga et al. 2011	USA	26	Pretest post test	Medical Outcomes Survey Short Form-36 (SF-36)	Men and women with a mean age of 45.5 ±10.5	Participants with MS	Significant improvements shown on the physical function and social function scores of SF-36 scale.

	Author, Study year	**Country**	**N**	**Study design**	**Instrument Used**	**Participants and age**	**Type of MS**	**Main findings**
7	Jackson et al. 2012	USA	26	Single group repeated measures	Multiple Sclerosis Quality of Life-54 Questionnaire (MSQOL-54)	Men and women between the ages of 28 to 62 years	Participants with MS	Significant improvements in gait speed
8	Kargarfard et al. 2012	Iran	21	RCT	Multiple Sclerosis Quality of Life-54 Questionnaire (MSQOL-54)	Women with a mean age of 32.6± 8.0	Relapsing Remitting MS	Significant improvement shown on the physical and mental MSQOL-54 scores.
9	Kerling et al. 2015	Germany	18	RCT	Medical Outcomes Survey Short Form-36 (SF-36)	Males and females with a mean age of 40 for patient group and 44 years for control group.	Patient with MS (no specific type)	Improvements were shown for the physical functioning, social functioning and mental health scores on the SF-36.
	Kerling et al. 2015	Germany	38	RCT	Medical Outcomes Survey Short Form-36 (SF 36)	Males and females (mean age of 40 for patient group and 44 years for control group)	Patient with MS (no specific type)	Improvements were shown for the physical functioning, social functioning and mental health scores on the SF-36.

	Author, Study year	**Country**	**N**	**Study design**	**Instrument Used**	**Participants and age**	**Type of MS**	**Main findings**
10	Mutluay et al. 2008	Turkey	43	RCT	Multiple Sclerosis Quality of Life-54 Questionnaire (MSQOL-54)	Men and women between the age of 27-55 years	Relapsing Remitting MS or progressive type	Significant improvements noticed in the in physical scores for MSQOL-54.
11	Oken et al. 2004	USA	42	RCT	Medical Outcomes Survey Short Form-36 (SF-36)	Men and women with a mean of 49.8 ± 7.4	Participants with MS	Improvement in fatigue was found after 6 months of doing yoga.
	Oken et al. 2004	USA	35	RCT	Medical Outcomes Survey Short Form-36 (SF-36)	Men and women with a mean of 48.8 ± 10.4	Participants with MS	Improvement in fatigue was found after 6 months of doing aerobic exercise.
12	Patti et al. 2002	UK	111	RCT	Medical Outcomes Survey Short Form-36 (SF 36)	Men and women with mean age of 45.2 ±12.0 for treatment and 46.1±6.0 for control	Primary and secondary progressive MS	Significant improvements on physical functioning, and mental health functioning scores of the SF-36.

	Author, Study year	**Country**	**N**	**Study design**	**Instrument Used**	**Participants and age**	**Type of MS**	**Main findings**
13	Pilutti et al. 2016	USA	10	RCT	Multiple Sclerosis Quality of Life-54 Questionnaire (MSQOL-54)	Men and women between the ages of 18 to 60.	Progressive MS	Significant improvements on physical functioning and mental health functioning scores of the MSQOL-54 questionnaire.
14	Ray et al. 2013	USA	21	Quasi experimental before after trial	Medical Outcomes Survey Short Form-36 (SF-36)	Men and women with a mean age of 50.9 ±5.7 for experimental group and 56.2±8.8 years for control group.	Participants with MS	Significant changes were not found for physical functioning and social functioning scores on the SF-36 scale but was found for emotional being scores.
15	Romberg et al. 2005	Finland	91	RCT	Multiple Sclerosis Quality of Life-54 Questionnaire (MSQOL-54)	Men and women between the age of 30 and 55 years of age	Participants with MS	Improvements were noticed for the social functioning score.
16	Salgado et al. 2013	USA	22	Pretest post test	Medical Outcomes Survey Short Form-36 (SF-36)	Men and women with a mean age of 48.1±10.5	Participants with MS	Significant improvements in functional strength,

	Author, Study year	Country	N	Study design	Instrument Used	Participants and age	Type of MS	Main findings
17	Solari et al. 1999	Italy	54	RCT	Medical Outcomes Survey Short Form-36 (SF-36)	Men and women between the age of 18 and 65 years	Primary progressive, relapsing remitting or secondary progressive	Significant improvements noticed in the mental health component of the MSQOL-54 questionnaire.
18	Sutherland et al. 2001	Australia	22	RCT	Multiple sclerosis quality of life instrument (MSQOL)	Men and women with a mean age of 47.18 ±4.75 for exercise group and 45.45±5.05 for control group	Participants with MS	Significant improvements in physical functioning score.

* Some ages are reported in mean and standard deviation (mean±SD).

* Participants with MS: anyone who had MS regardless of type.

6.3.1 The Effect of Aerobic, Anaerobic, Mixed Exercise, Yoga and Physiotherapy on Physical, Mental and Social Domains of Quality of Life

The pooled analysis of aerobic, anaerobic, mixed exercise, yoga and physiotherapy on the physical quality of life are shown in Figure 6.2. There were physical (20), mental (16) and social health (11) articles found and regardless of the type of exercise there was an overall positive effect of exercise on physical health[18,33–51] (d= 0.19, 95% CI=0.06 to 0.32, p=0.004, I^2 =15.2%), mental health[18,33–36,39,40,44,47–51] (d= 0.39, 95% CI=0.13 to 0.65, p=0.003, I^2=65.7%) and social health[18,35,36,38,41,44,47,48,50,52] (d= 0.26, 95% CI=0.02 to 0.49, p=0.03, I^2=42.9%). Figure 6.3 shows the forest plot for pooled effects of all complementary therapies on the mental health quality of life domains. Egger's test and funnel plot indicated that there was no small study effect bias for physical, mental health and social health (p=0.18, p=0.06, p=0.99).

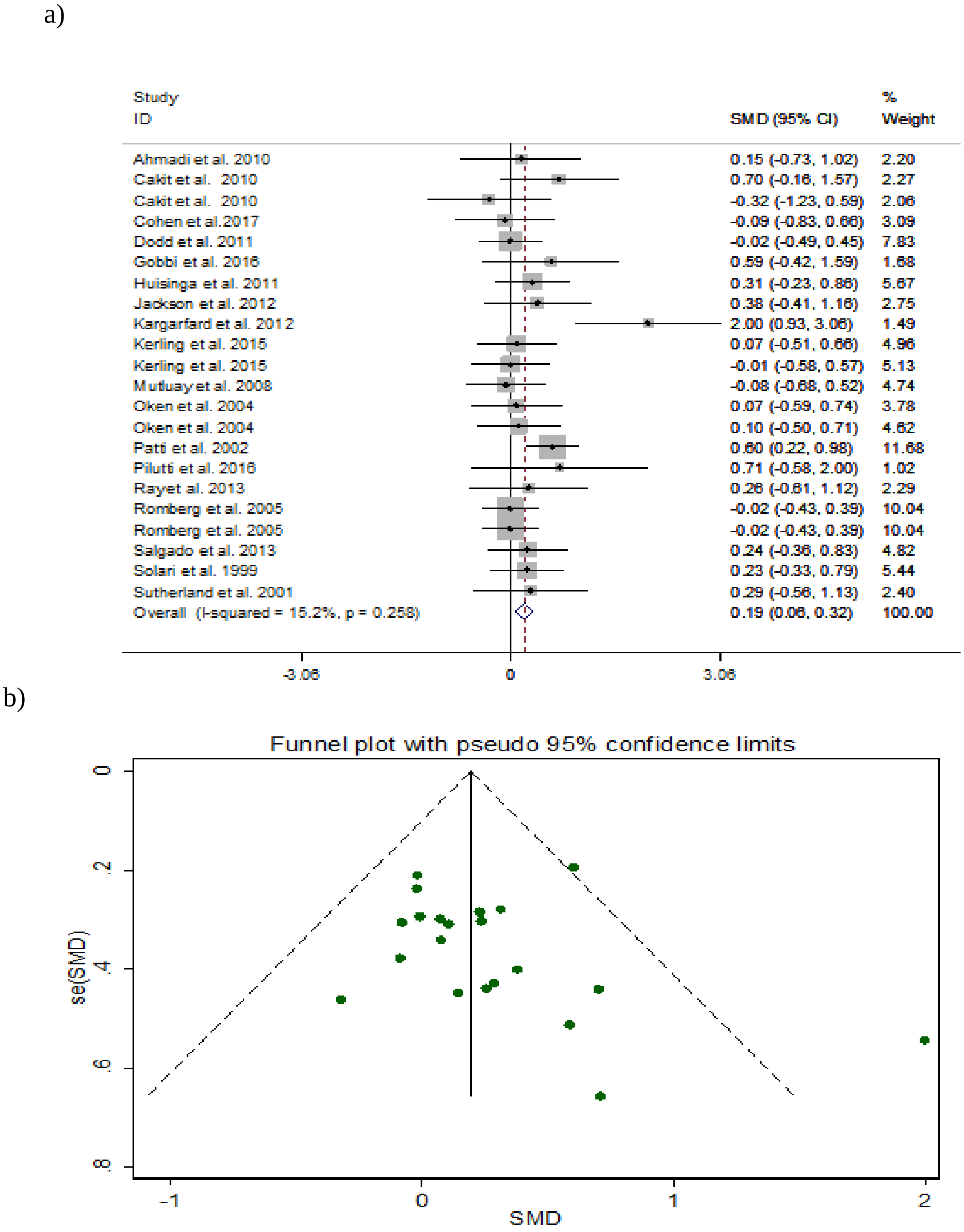
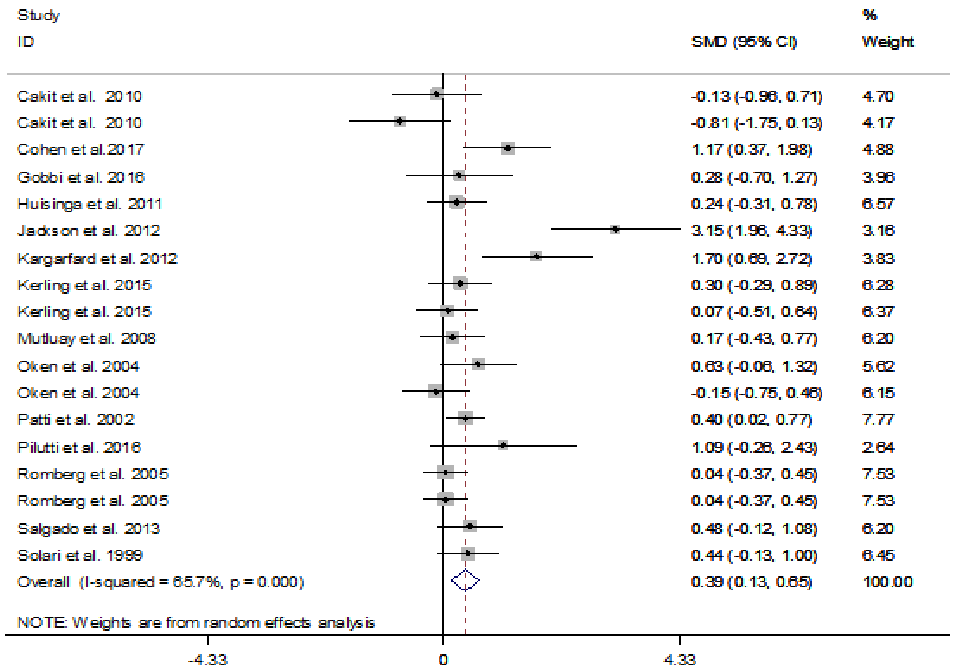


Figure 6.2: a) The effect of all types of complementary therapy on the physical health of people living with MS. b) Funnel plot with pseudo 95% confidence limits for all types of complementary therapy.

a) Effect of all types of complementary therapy on the mental quality of life



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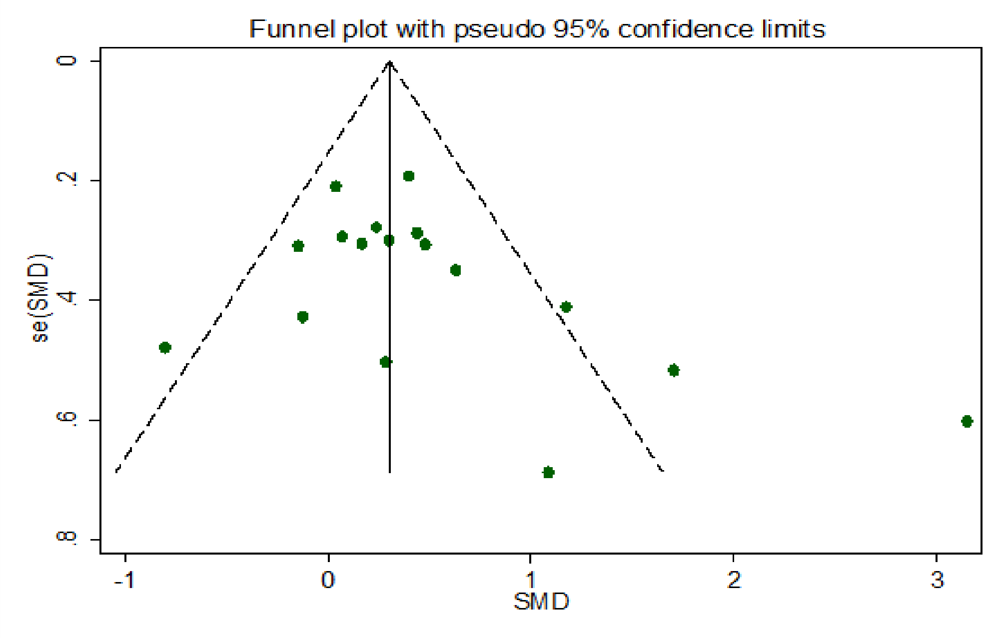


Figure 6.3:a) The effect of all types of complementary therapy on the mental health of people living with MS. b) Funnel plot with pseudo 95% confidence limits for all types of complementary therapy.

a) Effect of all types of complementary and alternative therapy (CAM) on the social quality of life of people living with MS

b)

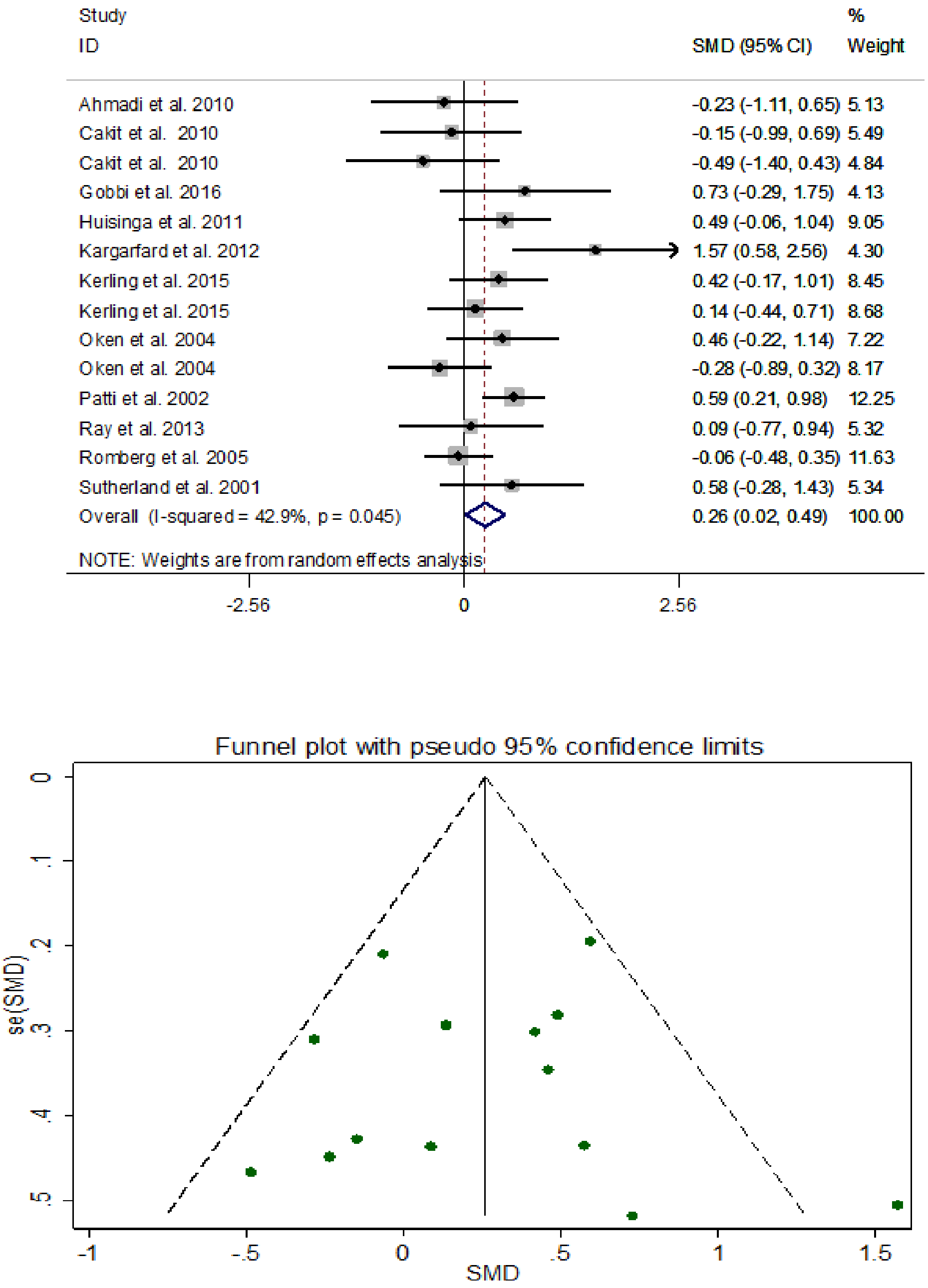


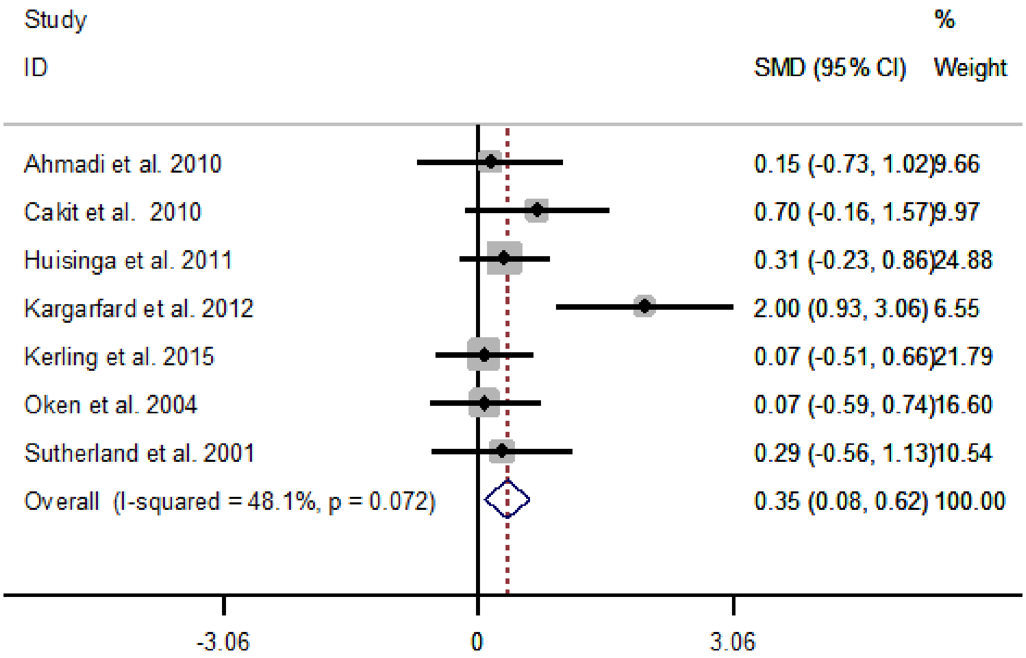
Figure 6.4: a) The effect of all types of complementary therapy on the social health of people living with MS. b) Funnel plot with pseudo 95% confidence limits for all types of complementary therapy.

6.3.2 Aerobic Exercise

There were seven studies of aerobic exercise interventions (low to high intensity such as walking, cycling, running etc.) with physical QOL health scores,[18,33,38,44,48–50] five studies which had mental health scores[18,44,48–50] and seven studies with social health scores.[18,33,38,44,48–50] Aerobic exercise intervention studies showed that aerobic exercise had a small effect on physical health of MS patients. These studies reported a standard mean difference SMD of d=0.351 (95% CI=0.08 to 0.62, p=0.012, I^2=48.1%). A funnel plot and Egger's test showed no small study effect bias (p= 0.100).). Figure 6-5 shows the forest and funnel plot for this analysis.

a)

Effect of aerobic exercise on the physical quality of life



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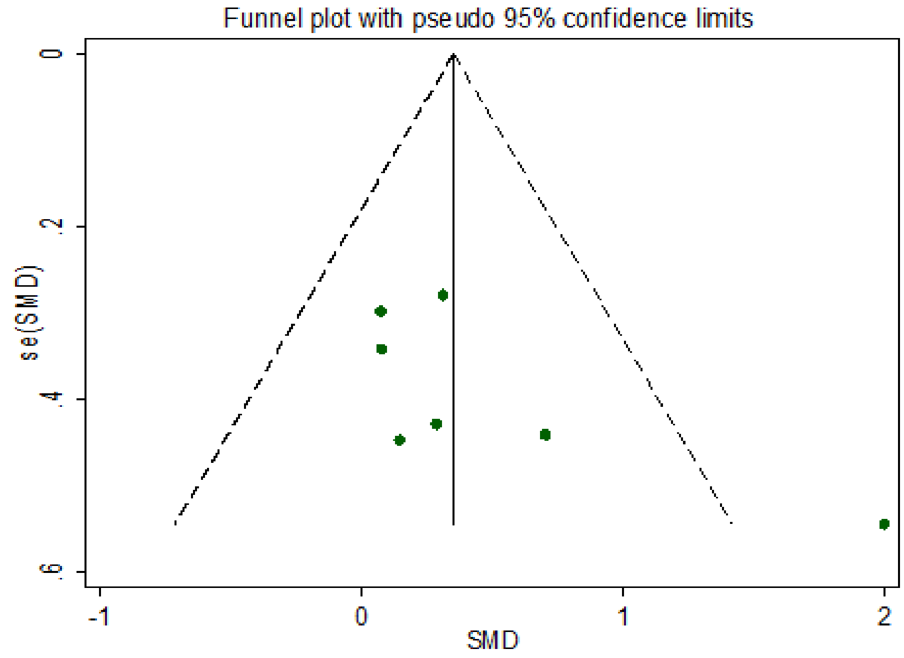

Figure 6.5: a) The effect of aerobic exercise on the physical health of people living with MS. b) funnel plot with pseudo 95% confidence limits for aerobic exercise.

A small effect found was found for the impact of aerobic exercise on mental health, *d*=0.417 (95% CI=0.112 to 0.721, p=0.007, I^2=54.2%). The funnel plot and Egger's test showed no small study effect bias (p=0.315).

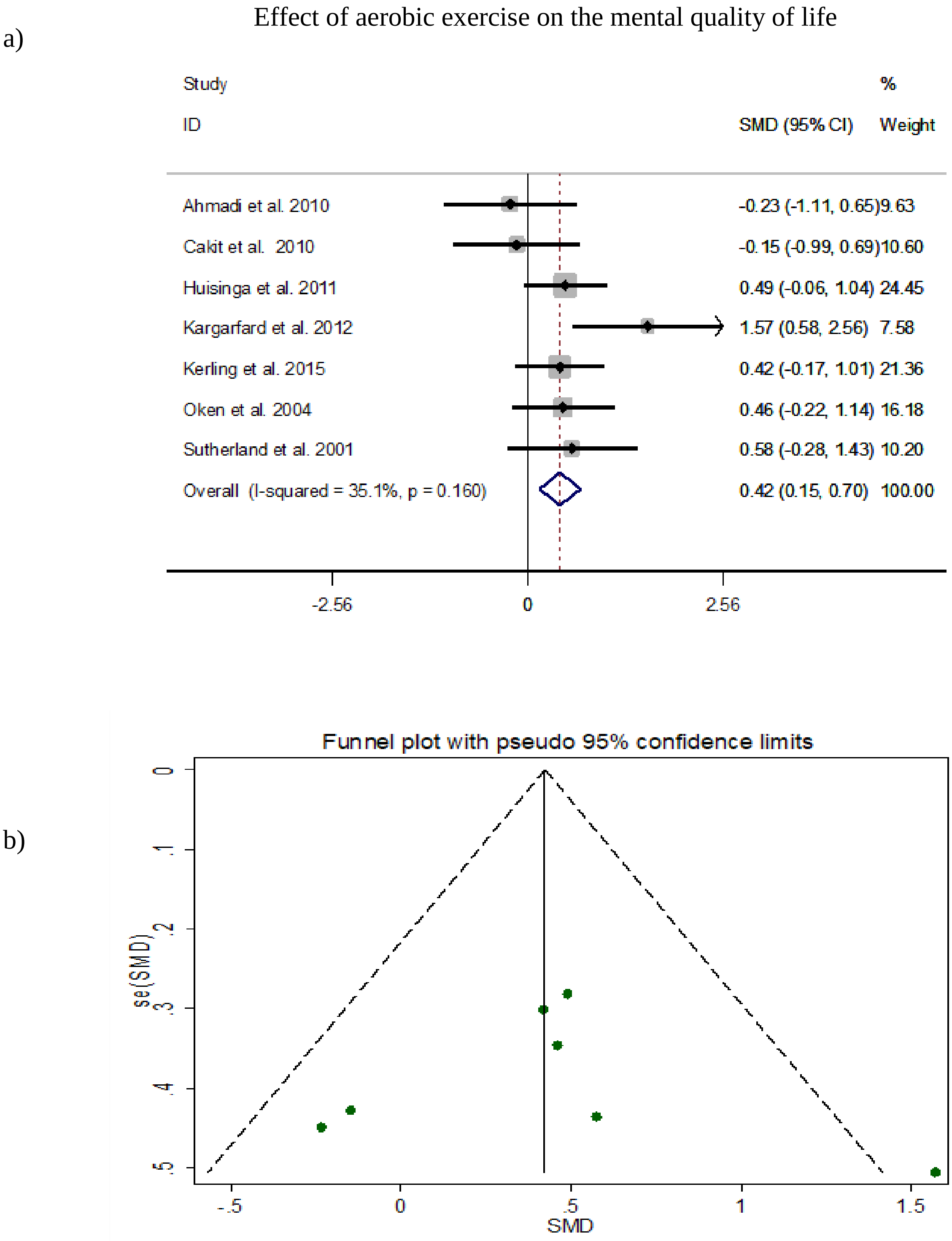

Figure 6.6: a) The effect of aerobic exercise on the mental health of people living with MS. b) funnel plot with pseudo 95% confidence limits for aerobic exercise.

Aerobic exercise also had a small effect on social health with an SMD of *d*=0.423 (95% CI=0.15 to 0.69, p=0.002, I^2=35.1%). Again the funnel plot and Egger's test did not show a small study effect bias (p=0.851). These combined results clearly show that aerobic exercise has a significant impact on the physical, mental and social health of MS patients. Figure 7 shows the forest plot along with the corresponding funnel plots.

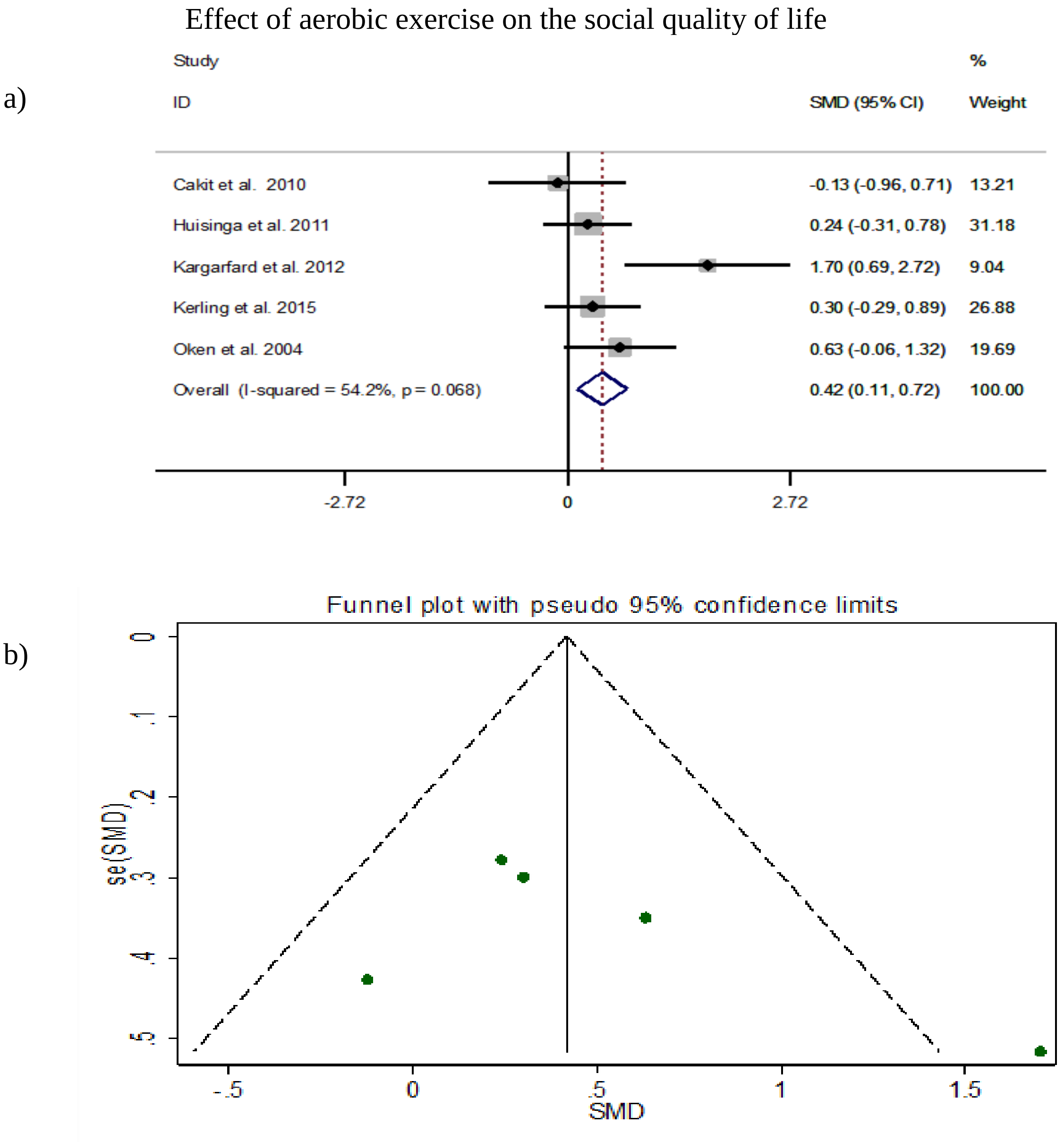

Figure 6.7: a) The effect of aerobic exercise on the social health of people living with MS. b) Funnel plot with pseudo 95% confidence limits for aerobic exercise.

6.3.3 Anaerobic Exercise

There were four anaerobic exercise studies that had physical health QOL scores [36,41,44,46], two studies reported mental health scores[36,44] and two studies reported social health scores.[41,44] Anaerobic exercise in MS patient groups did not have a significant effect on either physical, mental or social health. The SMD scores were for physical health quality of life was *d*=-0.02 (95% CI=-0.30 to 0.26 p=0.90, I^2=0%), mental health: *d*=-0.10 (95% CI=-0.47 to 0.28, p=0.61, I^2=61.5%) and social health: *d*=-0.18 (95% CI=-0.81 to 0.45, p=0.573). Funnel plots and Egger's did not show any small study effect bias (p=0.94) for the physical QOL studies.

6.3.4 Yoga

Three studies examined the effect of yoga interventions on physical health of MS patients.[18,37,45] Yoga did not have a significant effect on physical health *d*=0.11 (95% CI=-0.26 to 0.48, p=0.57, I^2=0%). A funnel plot and Egger's test showed no small study effect bias for yoga on physical health (p= 0.247). The three studies that assessed the effect of yoga on mental health found no significant effect *d*=0.46 (95% CI=-0.24 to 1.17, p=0.19, I^2=70.2%). A funnel plot and Egger's test showed no small study effect bias (p=0.398). The one yoga intervention study that reported social health scores found that there was no effect d=-0.28 (95% CI= -0.89 to 0.32, p=0.36).[18]

6.3.5 Physiotherapy

Three studies used physiotherapy as an intervention and reported on physical and mental health outcomes.[34,42,43] Physiotherapy did have a significant medium effect on physical health *d*=0.50 (95% CI=0.19 to 0.80 p=0.001, I^2=0%). An Egger's test and funnel plot showed no small study effects bias (p=0.945). Similarly physiotherapy was found to have a significant effect on mental health outcomes *d*=0.44 (95% CI=0.14 to 0.75, p=0.004, I^2=0%). Egger's tests and funnel plot indicated that there was no small study effect bias for mental health (p=0.174). The one physiotherapy intervention study that reported social health scores found that physiotherapy had a medium to large effect *d*=0.60 (95% CI = 0.21 to 0.9, p=0.002).[42] Figures 6-8 and 6-9 shows the forest and funnel plot for the analysis.

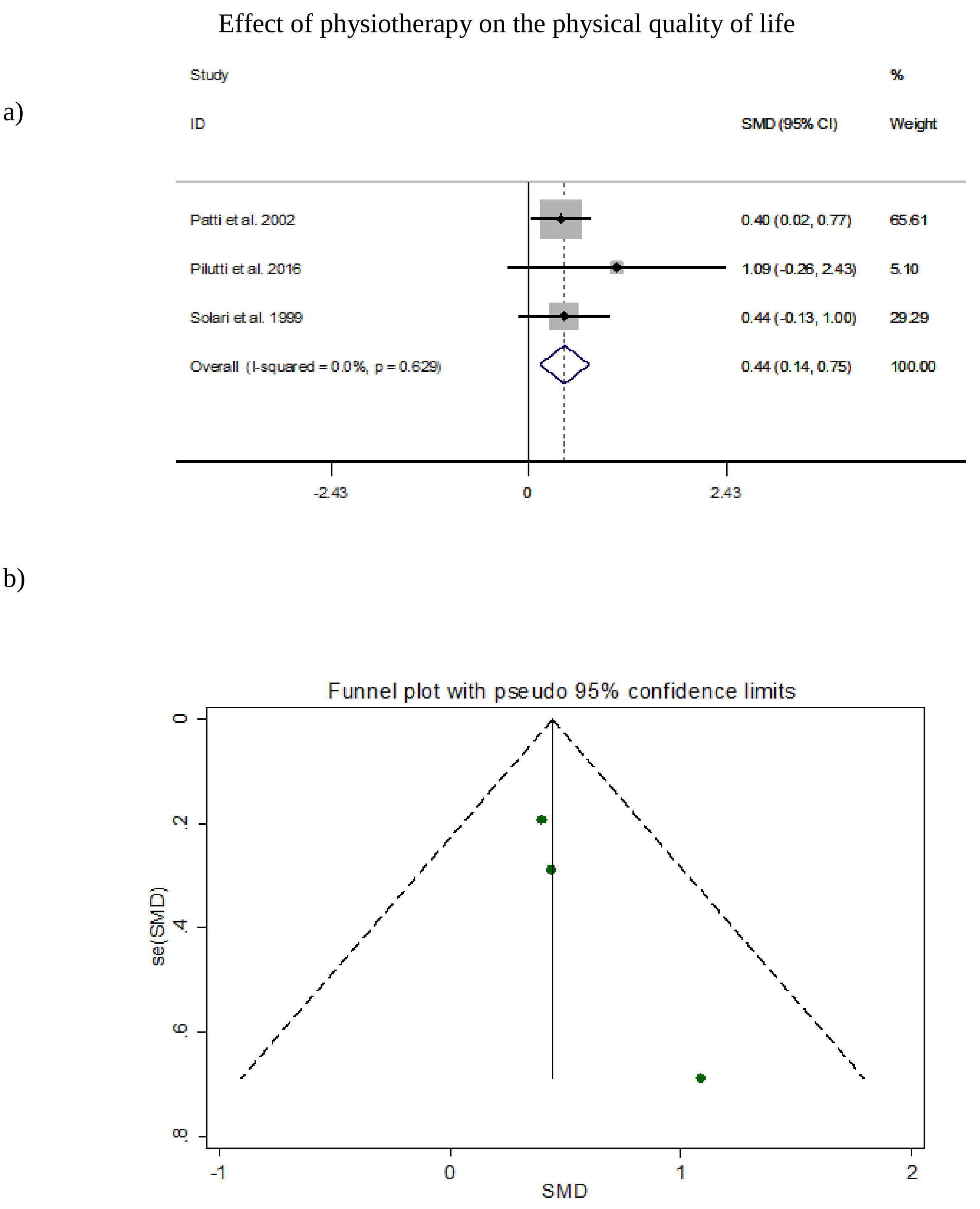

Figure 6. 8: a) The effect of physiotherapy on the physical health of people living with MS. b) Funnel plot with pseudo 95% confidence limits for physiotherapy.

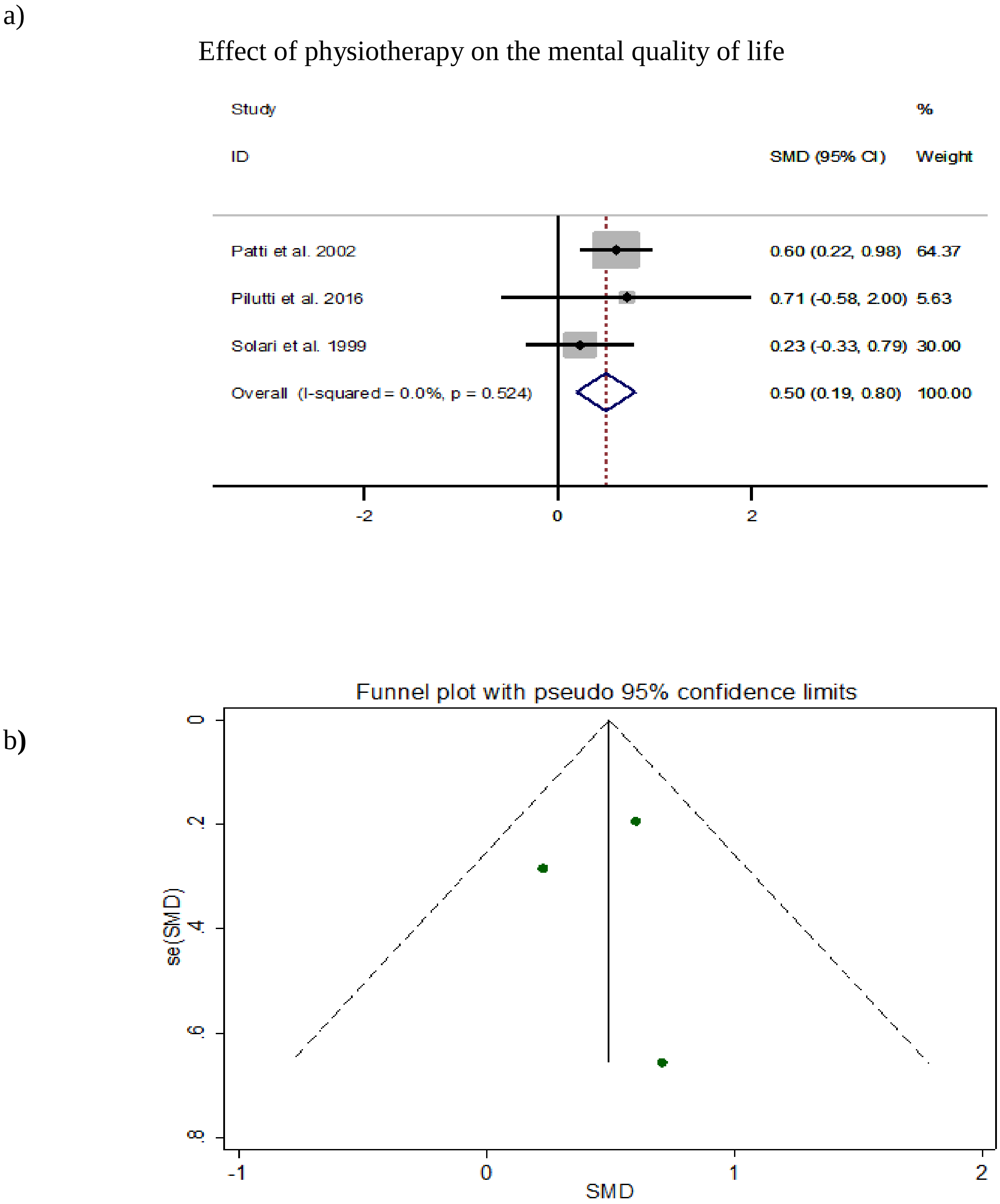

Figure 6. 9:a) The effect of physiotherapy on the mental health of people living with MS. b) Funnel plot with pseudo 95% confidence limits for physiotherapy.

6.3.6 Combination of exercises

There were five studies of combination of exercise interventions with physical and mental health QOL scores [36,40,47,50,51] and three studies reporting social health scores.[36,47,50] Combination of exercises has a combination of various types of aerobic, anaerobic and flexibility or strength training exercises. No significant effect was found for the combination exercises on physical health QOL; *d*=0.06 (95% CI=-0.21 to 0.32, p=0.66, I^2=0%), mental health QOL: *d*=0.59 (95% CI=-0.15 to 1.33, p=0.12, I^2=83.7), or social health QOL: *d*=0.07 (95% CI=-0.24 to 0.39, p=0.65, I^2=4.1%). Funnel plots and Egger's tests showed no small study effect bias for physical (p=0.08) and mental scores (p=0.14) but did show for social scores (p=0.01).

Based on the sensitivity analysis, there was no significant change made to the combined results by any single study indicating that the results were reliable. Meta-regression did not find specific variables that caused heterogeneity, but there could be other factors associated with the heterogeneity present in the study such as methodological issues with randomization within individual studies. However random effect models were used when heterogeneity was present in our study. The study quality was assessed using the modified Pedro scale (Appendix B). Based on the scale, the studies ranged from 5 to 9 with the majority of the studies in the 9's. This indicated that the majority of studies that were selected were of high quality.

6.3.7 Summary of Results

Table 2 summarizes the impact in terms of effect size of each treatment type on MS patients QOL domains. For all domains of QOL, aerobic exercise was found to have a small significant effect. Anaerobic exercise, combinations of exercises and yoga did not have a significant effect on QOL. Physiotherapy was found to be most effective for the physical, mental and social domains in comparison to other types of complementary treatments.

Table 6. 2**:**Effect size estimates for interventions based on domains of quality of life.

Domains	Type of Intervention	No of studies	Cohen’s d	95% CI	p-value	Effect
Physical	Aerobic	7	0.35	0.08-0.62	0.01	Small effect
	Anaerobic	4	-0.02	-0.30-0.26	0.90	
	Combined	5	0.06	-0.21-0.32	0.66	
	Physiotherapy	3	0.50	0.19-0.80	p<0.001	Medium effect
	Yoga	3	0.11	-0.26-0.48	0.57	
	All types of interventions	20	0.19	0.06-0.32	0.004	Small effect
Mental	Aerobic	5	0.42	0.11-0.72	0.007	Small effect
	Anaerobic	2	-0.10	-0.47-0.28	0.61	
	Combined	5	0.59	-0.15-1.33	0.12	
	Physiotherapy	3	0.44	0.14-0.75	0.004	Small effect
	Yoga	3	0.46	-0.24-1.17	0.19	
	All types of interventions	16	0.39	0.13-0.65	0.003	Small effect
Social	Aerobic	7	0.42	0.15-0.69	0.002	Small effect
	Anaerobic	2	-0.18	-0.81-0.45	0.57	
	Combined	5	0.07	-0.24-0.39	0.65	
	Physiotherapy	1	0.60	0.21-0.90	0.002	Medium to large effect
	Yoga	1	-0.28	-0.89-0.32	0.36	
	All types of interventions	11	0.26	0.02-0.49	0.03	Small effect

$p<0.05$ was used to identify significance

6.4 Discussions

This systematic review and meta-analysis extends previous findings by showing aerobic exercise interventions in MS patients had a small effect size in improving patients physical mental and social QOL. These results were consistent with a previous systematic review conducted on the effect of exercise as a treatment for multiple sclerosis that found aerobic exercise helps with depression.[53] In general, studies have shown that aerobic exercise such as jogging, swimming, cycling, walking reduce anxiety and depression in individuals. It is hypothesized that exercise stimulates activity in the sympathetic nervous system (SMS) and activates the parasympathetic nervous system activity (PNS) which causes acetylcholine to be released resulting in a calming effect.[54]

Studies have also shown that exercising in general allow for social interactions to take place and alleviate symptoms of social isolation.[54] Our results are consistent with previous reviews where aerobic exercise have been found to improve physical health since it decreases fatigue and pain which are two main symptoms of MS.[4,42,55] Endurance training was also found to help in improving aerobic capacity that MS patients lack.[56] Recent literature has shown that endurance training for 3 months improved the quality of life of people living with MS.[8]

Physiotherapy was also found to be beneficial in improving the physical and mental quality of life of people living with MS where it was found to have a medium effect on physical quality of life and small effect on mental health. This was consistent with a randomized controlled trial that assessed the effect of physiotherapy at home vs an outpatient vs no therapy program. Based on the study, it was found that physiotherapy improved mobility, subjective wellbeing and mood in people living with MS.[57]

Smedal et al. (2006) investigated the benefits of physiotherapy for MS found similar results in that physiotherapy helped to improve balance and gait.[58] In a summary of systematic reviews, incorporating therapeutic exercise into physiotherapy programs was found to be beneficial for people living with MS as well as other neurological conditions.[59] Our pooled analysis of all types of complementary and alternative treatment (CAM) it was found that there was a small significant effect on improving the quality of life of people living with MS. Individuals who uses CAM reported that their overall stress was reduced and found improvements in their overall wellbeing. One of the main reasons for using CAM was the ineffectiveness of conventional medical treatments in not providing symptom relief and worsening of symptoms.[60] In addition to this, the longer people use CAMs the less satisfied they were of conventional medicine.[61]

The strength of this systematic review and meta-analysis is that it looks at the effects of a variety of complementary therapies on specific quality of life domains and provides an estimate of the impact of those therapies on QOL in terms of effect size. A limitation of the analysis is that some studies could not be included in the meta-analysis because they either did not report physical, mental and social quality of life scores or were published in languages other than English. Some articles did not report mean and standard deviations needed to calculate SMD and where therefore excluded.

The exclusion criteria also did not allow for the use of other types of quality of life scales such as fatigue impact scale which may have reduced the number of articles included in the meta-analysis. There was also some heterogeneity that were found in some of the analysis which indicated variation in the degree of association between the type of intervention and its effect on the physical, mental and social health of individuals with MS. When heterogeneity was present a random effects model was used for the analysis. Publication bias that was present when assessing the effect of combination of therapies on social health was due to having only three studies in the analysis with one study being an outlier. Another limitation was some confidence intervals were wider, but this is due to the small sample sizes in the study.

This systematic review indicates that physical activity particularly aerobic exercise and physiotherapy had the greatest impact on physical, mental and social health as opposed to anaerobic, combination or yoga. This review provides strong evidence for the inclusion of aerobic exercise and physiotherapy programs as part of the regular treatment of patients with multiple sclerosis. Further studies need to be conducted in CAM treatments in terms of amount of treatment necessary in order for improvements to be noticed in physical, mental and social aspects of quality of life. The combination of CAM with traditional medications needs to be explored in order to determine the overall effectiveness of these treatments in relieving symptoms of MS.

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CHAPTER 7: CONCLUSIONS

This thesis covers several areas in MS research. The first area examined was to understand the public awareness of an important risk factor, second hand smoke exposure on MS development. The second was to understand how social factors play a role in pain experiences in people living with MS. The third objective was to understand the factors associated with MS medication adherence. Lastly the thesis identified the various types of complementary treatments such as types of exercise on various domains of quality of life (physical, mental and social). This concluding chapter discusses the relevance of the findings.

7.1 Summary of Findings

The thesis explored various areas in MS research from prevention of risk factors such as second hand smoking to promotion of medication use and intake of aerobic exercise. The chapters each touch on difference aspects of MS from prevention to promotion. The results presented in this thesis can help in the development of policies and inform health care professionals about the problems that many patients with MS face. Chapters 3 assessed awareness of second hand smoke exposure and it effect on MS while chapters 4, 5 and 6 looked at improving overall quality of life.

Chapter 3 is the first study that examined the factors associated with Canadian's public perceptions of second hand smoke exposure on MS development. The sociodemographic variables that were investigated were age, sex, marital status and education level. Other variables include number of people living in the household, whether other members of the household smoked, whether they were bothered by second hand smoke, smoking status, the number of children in the household under the age of 18, frequency of breathing in second hand smoke and whether there were smoking restrictions in workplaces, restaurants or shopping malls.

Through multilevel modelling the results of the study showed that the province of residence impacted the odds of a person agreeing to whether second hand smoke exposure could cause MS. The methodology used in this study used a multivariate multilevel mixed effects model which took into account the interaction effects of sex and smoking status and its effect on people's perceptions based on the province in which they reside in Canada. The results of this study indicated that sex, age, education level, having household members smoke in the home and if the individual was bothered by second hand smoke exposure was associated with increased odds of people agreeing to second hand smoke exposure being a risk factor for MS development.

Based on the multilevel mixed effects model, the province of residence of the respondent was also associated with perceptions about second hand smoke exposure on MS development with Newfoundland having (24%) and Ontario (23%) of people out of 1,639 people agreeing to the statement. This chapter explored the knowledge gap in MS and second hand smoke exposure and highlighted the need to strengthen the stop smoking campaign and to introduce messages about the harmful effects of second hand smoke exposure to the public.

Chapter 4 explored the psychosocial factors associated with pain in people with MS. The Survey of Living with Neurological Conditions in Canada 2011 was used for this chapter. This chapter looked at health promotion and prevention. Pain is a problem with many conditions, however in MS it is one of the primary symptoms that many people face. Many studies explore pain from a biological standpoint, however the social aspect of pain has not been explored well in MS research. This chapter focused on social support and its association with pain in people with MS. The methodology used for the analysis used a logistic regression model to understand whether social factors were associated with pain among individuals with MS. This chapter drew attention to a hidden problem that many individuals with MS face which is having lack of support. Based on the results of the study all types of social support are needed in order to reduce pain outcomes and that lacking in either one of the 4 (someone to take you to the doctor, someone to do something enjoyable with, someone to confide/talk to and someone to help in an emergency) is associated with increased probability of pain. Having someone to talk to or do something enjoyable allows for a sense of belonging which helps in promotion of positive mental health. Having someone to take you to the doctor if needed or for help in case of emergencies allows the person to reduce their stress because they know that there will be someone to help them when there is a medical emergency. When one of these supports are missing, the odds of pain increases.

The results of this research indicate the importance of affordable access to health care services for individuals with MS. Not all individuals will have support from caregivers, therefore it is important to create programs that are affordable for individuals living with disabilities. The role of self-efficacy is also important since learning to cope with the problem at hand can help reduce pain and give a positive outlook to life. Therefore having social support is important for psychological health but at the same time is needed for help in case of emergencies.

Chapter 5 investigated the factors associated with MS medication adherence using the Survey of Living with Neurological Conditions in Canada (SLNCC) 2010 to 2011 cycle. This is the first study that used a logistic regression model to understand the factors that promote medication use and factors that reduce medication use. Medication for MS is beneficial in order to stop relapses from occurring, however due to side effects of medication many people reduce the frequency of medication use or stop taking it altogether. Complementary/alternative treatment (CAM) such as exercise, herbal products, homeopathic medicine, vitamins, acupuncture, massage and meditation is beneficial when used with disease modifying MS medications, however when taken alone it can cause many problems to the overall health of the person with MS. This chapter showed the hidden factors that influence a person’s decision to take MS medications such as comorbid health conditions and the use of social behavioural models as a tool to help patients adhere to medications.

The analysis in chapter 6 which used systematic review and meta-analysis examined the effect of various types of interventions such as exercise (aerobic, anaerobic, mixed, yoga) and physiotherapy on the quality of life (physical, mental, social) of individuals diagnosed with MS. Overall quality of life was categorized into 3 categories: a) physical, b) mental and c) social health. Aerobic exercise such as treadmill training, elliptical exercise and aquatic exercise was beneficial for all domains of health. Physiotherapy was also found to be beneficial in improving the physical and mental quality of life of people living with MS. This chapter draws attention to patient's quality of life and how each domain such as physical, mental and social health can be improved by doing aerobic exercise. The results of this study will reinforce physicians' awareness of the benefits of exercise programs and how they could be incorporated into treatment regimens for patients. In addition to this, physiotherapy was also found to be beneficial for people living with MS and could also be used as a complementary treatment approach. However further studies in this area are needed in order to provide stronger evidence for these interventions.

7.2 Practical Implications

Based on the findings of this research more educational programs on the harmful effects of second hand smoking for people living with MS need to be created. In addition to this advertisements about second hand smoke exposure and its effect on MS need to be included on television or on public transportation services in order to increase public health awareness. The findings of this research also indicate a need for more affordable home care services for people living with MS especially for individuals who live in low income neighbourhoods.

Primary care providers need to also direct caregivers and MS patients on nursing or home care services available in their area. In terms of medication used, low adherence is a problem that often goes unnoticed by primary care providers. The results of the chapter on medication adherence highlight the desperation that people living with MS face as they turn to CAMs to reduce their symptoms. It also shows that poor health literacy and lack of knowledge in the area of MS medications among people living with MS is a problem. In order to increase medication adherence rates, patient education programs in hospitals need to be created that stress the harms of using CAMs and the benefits of medications. Primary care providers need to be aware of behavioural modification models that patients can use and should refer patients to counselling services that can help them cope with MS. The results of this dissertation also indicate that aerobic exercise such as walking, cycling, running and physiotherapy are beneficial for physical, mental and social health and should be incorporated into MS treatment regimens.

7.3 Limitations

The primary limitation of this study was the lack of data that was available on Multiple Sclerosis. Chapters 3, 4 and 5 relied on cross sectional surveys such as the Health Canada: Smoking Survey and the Survey on Living with Neurological Conditions in Canada (SLNCC), therefore a cause and effect relationship could not be stated. Since these surveys are self-reports they are prone to information bias and recall bias. In addition to this the cross sectional surveys were not repeated in consecutive years, therefore a cross year comparison could not be performed.

There were limitations in using the Health Canada: Smoking Survey since it only surveyed 5 provinces (Saskatchewan, Ontario, Newfoundland, Quebec and British Columbia) which left out many people in the population, thus reducing the sample size. There were limitations in the SLNCC data set with regards to the descriptions of the types of treatments that were used by people with MS. Types of medications were not mentioned clearly in the data set and specific complementary treatments were not clearly identified in the Statistics Canada Survey. Therefore it was difficult to distinguish between specific types of treatments. In addition to this there were some variables which were missing such as the types of MS that individuals had which could have given a clearer picture when carrying out the analysis. For the meta-analysis in Chapter 6 the limitations of the study was that the long term effects of each type of complementary treatments could not be determined since the immediate effect after the intervention was not measured.

7.4 Future Work

Based on the results of this thesis, future studies could look into assessing the level of knowledge that people have about risk factors for MS. This could help to understand how messages about risk factors could be spread to the public in order to increase awareness. Chapters 3 and 4 used the SLNCC data set since there weren’t any surveys that measured information about people living with MS in Canada. Since this was measured only once, it would be better if surveys were conducted every 2 years so that researchers could have access to MS data and a longitudinal study could be conducted. In addition to this surveys need to ask specific questions with regards to the type of MS the person has and the type of medication they used.

The results of the study in Chapters 4 about lack of social support and having a greater probability of pain inform caregivers about the amount of support that a person with MS needs. This research can be built on by further delving into the area of how caregiver support can be managed stress free and whether programs need to be created in order to better educate caregivers on ways to help take care of their loved ones with MS.

The results of Chapter 5 talk about using complementary treatment and its effect on medication use. Research on other factors associated with not complying to medication need to be examined such as the side effects of certain medications and what doctors can do to help patients. In addition patients and caregivers need to be better informed about the role of therapists in helping patients adhere to medications and how social behavioural models could be used as a tool to manage medications better. Medication should be the primary line of treatment, however complementary treatments could also be used after consultation with the physician.

The results of the study in chapter 6 examined how beneficial complementary treatments were in the various domains of quality of life. Aerobic exercise and physiotherapy was found to be more beneficial, however further research on the type of exercise regimens that is beneficial for the different types of MS need to be assessed. Research on whether targeted aerobic exercise programs are beneficial in the long run need to be examined as well.

APPENDIX A: Additional file for Chapter 6

Assessment of study quality using modified Pedro scale.

Modified Pedro scale

Study	Eligibility Criteria Specified	Random allocation of participants	Allocation concealed	Groups similar at baseline	Assessors were blinded	Outcome measure for more than 85% of subjects	Intention to treat	Reporting of between group statistical comparison	Point and variability for that measure reported	Total score out of 9
Ahmadi et al. 2010	1	1	0	1	0	1	1	1	1	8
Cakit et al. 2010	1	1	1	1	1	1	0	1	1	8
Cohen et al.2017	1	0	0	1	0	1	0	1	1	5
Dodd et al. 2011	1	1	1	1	1	1	0	1	1	8
Gobbi et al. 2016	1	0	0	1	1	1	0	1	1	5
Huisinga et al. 2011	1	0	0	1	0	1	0	1	1	5
Jackson et al. 2012	1	0	0	1	0	1	0	1	1	5
Kargarfard et al. 2012	1	1	1	1	1	1	1	1	1	9
Kerling et al. 2015	1	1	1	1	0	1	1	1	1	8
Mutluay et al. 2008	1	1	1	1	1	1	0	1	1	8
Oken et al. 2004	1	1	1	1	1	0	0	1	1	7
Patti et al. 2002	1	1	1	1	1	1	0	1	1	8
Pilutti et al. 2016	1	1	1	1	0	1	0	1	1	7
Ray et al. 2013	1	0	0	1	0	1	0	1	1	5
Romberg et al. 2005	1	1	0	1	0	0	1	1	1	6
Salgado et al. 2013	1	0	0	1	0	1	1	1	1	6
Solari et al. 1999	1	1	1	1	1	1	1	1	1	9
Sutherland et al. 2001	1	1	0	1	0	1	0	1	1	6