CHILDREN OF MULTIPLE SCLEROSIS: IMPACT OF CHRONIC DISEASE IN PARENTS ON CHILD AND ADOLESCENT DEVELOPMENT

by

Neda Razaz

M.P.H., The University of British Columbia, 2010

B.A., Simon Fraser University, 2006

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF

THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

in

THE FACULTY OF GRADUATE AND POSTDOCTORAL STUDIES

(Population and Public Health)

THE UNIVERSITY OF BRITISH COLUMBIA

(Vancouver)

January 2016

Abstract

Approximately 10% of children live in households where a parent has a chronic illness and many children are exposed to a parent coping with a potentially disabling chronic condition, such as multiple sclerosis (MS). However, few methodologically rigorous studies have evaluated the impact of parental MS on child development. The purpose of this thesis was to fill this knowledge gap by studying the association between parental MS and child and adolescent development.

The studies in this dissertation were based on population-based health databases from Manitoba and British Columbia. The cohorts followed in these population-based studies included all individuals with MS who had a child with a completed Early Development Instrument (EDI) school readiness assessment, and matched parent-child dyads of unaffected parents. Parents with MS were identified using a validated algorithm, as those with ≥3 records related to MS in hospital admission, physician visit or prescription claims. Mental and physical morbidity in parents and children were also identified through a combination of hospital, physician and drug claims.

In Manitoba, children in kindergarten with an MS parent were similar to matched children of unaffected parents on all developmental domains as assessed by the EDI. However, in the larger population-based cohort from British Columbia, children of mothers with MS had lower rates of vulnerability on the social competence domain (odds ratio 0.62, 95% confidence interval [CI] 0.44-0.87).

Overall, mental health morbidity, such as anxiety and depression, was significantly more common among MS parents compared with MS-unaffected parents. Additionally, such parental mental health morbidity mediated the association between maternal MS and mood and/or anxiety disorders in children. Incidence rates of psychiatric disorders were significantly higher in children and adolescents with an MS parent who were exposed to parental MS since birth, compared with children and adolescents of MS-unaffected parents (hazard ratio 1.37, 95% CI 1.05-1.78).

In summary, the presence of parental MS was not independently associated with adverse developmental health in kindergarten-aged children. However, MS was associated with substantially higher levels of mental health morbidity in parents and such morbidity was associated with adverse child and adolescent psychiatric morbidity.

Preface

This statement certifies that the work presented in this thesis was conceived, conducted, and written by Neda Razaz. All studies conducted in British Columbia were approved by the British Columbia Ministry of Health and were conducted after receipt of ethics approval from the University of British Columbia Research Ethics Board (Certificate No.: H1103477) and the Vancouver Coastal Health Authority (Certificate No.: V11-03477). In Manitoba, the University of Manitoba Health Research Ethics Board (Certificate No.: HS15285 [H2012:157]) sanctioned the study, and the Manitoba Health Information Privacy Committee (HIPC#: 2012/2013-07) approved data access.

Chapters 2 to 6 of the dissertation are each composed of manuscripts, which have been published or have been submitted for publication in a peer-reviewed journal. I was responsible for developing the study proposal, conceptual framework, and analytic approaches for all analyses. For this, I received assistance from my thesis supervisor, Dr. K.S. Joseph, my thesis committee members Dr. Helen Tremlett (co-supervisor), Dr. Thomas Boyce, Dr. Martin Guhn and my research collaborators Dr. Ruth Ann Marrie, and Dr. Barry Forer. I conducted all analyses, and wrote all of the statistical analysis code with the assistance of Dr. K.S. Joseph and Dr. Helen Tremlett. I wrote the first draft of all manuscripts. My supervisor, thesis committee members and research collaborators made contributions to the study design, analysis and interpretation of data and revised each article for intellectual content. My contribution was >90% for each manuscript of this dissertation.

CHAPTER 1. A section of this chapter was published in a peer-reviewed journal.

Razaz N, Hertzman C, Marrie RA, Tremlett H, Boyce WT. Children of chronically ill parents: The silence of research. *Child Care Health Dev* 2013;40:753-754.

CHAPTER 2. A version of this chapter has been published in a peer-reviewed journal.
Razaz N, Nourian R, Marrie RA, Boyce WT, Tremlett H. Children and adolescents adjustment to parental multiple sclerosis: A systematic review. *BMC Neurol* 2014;14:107.

CHAPTER 3. A version of this chapter has been published in a peer-reviewed journal.
Razaz N, Tremlett H, Boyce WT, Guhn M, Joseph KS, Marrie RA. Impact of parental multiple sclerosis on early childhood development: a retrospective cohort study. *Multiple Sclerosis Journal* 2015; 21:1172-83.

CHAPTER 4. A version of this chapter is under review by a peer-reviewed journal.
Razaz N, Joseph KS, Boyce WT, Guhn M, Forer B, Carruthers R, Marrie RA, Tremlett H. Relationship between parental multiple sclerosis and childhood developmental health.

CHAPTER 5. A version of this chapter is under review by a peer-reviewed journal.
Razaz N, Tremlett H, Boyce WT, Guhn M, Marrie RA, Joseph KS. Incidence and determinants of mental health disorders in children of parents with multiple sclerosis.

CHAPTER 6. A version of this chapter is under review by a peer-reviewed journal.
Razaz N, Tremlett H, Marrie RA, Joseph KS. Peripartum depression in parents with multiple sclerosis and psychiatric disorders in children.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

ADHD – Attention-Deficit Hyperactivity Disorder

ATC - Anatomical Therapeutic Chemical system

BCMS - British Columbia Multiple Sclerosis (database)

CI – Confidence Interval

DIN - Drug Identification Number

EDI – Early Development Instrument

EDSS – Expanded Disability Status Scale

HR – Hazard ratio

ICD-9 – International Classification of Diseases - Ninth revision

ICD-10CA – International Classification of Diseases - Tenth Revision, Canadian version

MS – Multiple sclerosis

MSP – Medical Services Plan

PHIN – Personal Health Identification Number

PHN – Personal Health Number

PEN – Personal Education Number

OR – Odds ratio

SES – Socioeconomic status

Acknowledgements

This dissertation was made possible by the exceptional support and contribution of my thesis supervisor, committee members, our co-authors and the agencies that provided critical data access and support. I want to thank my thesis supervisory committee, Drs. Thomas Boyce and Martin Guhn for their mentorship, support and guidance. My co-supervisor, Dr. Helen Tremlett has been an outstanding source of mentorship and guidance throughout my studies. Her endless support and her enthusiasm and passion for research and teaching have been both contagious and admirable and I offer her my heartfelt thanks. I also extend my gratitude to Dr. K.S. Joseph, who during the rough patches of my training gave me the opportunity to thrive as a student, by giving me his undivided attention and coherent answers to my endless questions. I deeply value his hard work in helping me develop as an independent investigator. I would also like to thank Dr. Ruth Ann Marrie who was an inspiration to me and who provided me with resources and direction when facing methodological challenges and other obstacles. Finally, I would like to remember and acknowledge my late supervisor, Dr. Clyde Hertzman, whose passion for improving child health and creating a better society instilled in me the desire to pursue my PhD, and whose memory will always be a driving force in my career and professional life.

Beyond my colleagues, special thanks are owed to my parents, Ahmad Razaz and Farideh Rahmanian, who have supported me throughout my years of education and have always showered me with unconditional love and patience.

This work was supported by a Canadian Institutes of Health Research operating grant (MOP-119393) and the MS Society of Canada Doctoral Studentship. Data access and data analyses were carried out with the help of Population Data BC and the Manitoba Population Health Research Data Repository.

Dedication

To my wonderful parents, my little sister, my Kalu and in loving memory of my brother, Babak

Chapter 1: Introduction

1.1 Children of chronically ill parents: The silence of research

Childhood experiences can have profound and enduring effects on subsequent physical, social and psychological development of children, and affect a child's future competence, coping skills, and health.[1-3] Families are the proximal source of experience for most children and family factors are typically the best predictors of child development.[4] In Western societies, 4% to 12% of children and adolescents live in households where a parent has a chronic illness.[5-7] Whereas a great deal of research has been conducted on the ill child, few studies have focused on the children of chronically ill parents.[8] There is little information in the literature on how chronic illness in parents affects child development.

Recent studies focusing on adolescents with parents affected by chronic medical conditions have shown that such children are at increased risk for anxious and depressive behaviour, stress and low school peformance.[6] This increase in problem behaviours among adolescents is believed to be due to the daily adversities ('hassles') encountered in families with a chronic disease and the quality of parent-child attachment.[6,9] As the number, intensity, and duration of stressors increase, the child is likely to have more difficulty resuming his or her developmental trajectory in the emotional and interpersonal domains. Furthermore, the impact of such stressors may not be fully appreciated until adolescence, when it may be too late to intervene. Most research in this field has focused on the consequences of cancer in parents, and within this disease group, many studies have focused on mothers diagnosed with breast cancer and their adolescent offspring.[5] Studies on the effects of other chronic illnesses in parents, the

impact of parental chronic disease on younger children and the effects of chronic illness among fathers are lacking.

1.2 Why multiple sclerosis?

Multiple Sclerosis (MS) is a chronic inflammatory disorder of the central nervous system, primarily affecting the white matter in the brain and spinal cord. It is the most common non-traumatic cause of neurological disability in young adults in the Western world.[10] Symptoms of MS include changes in sensation, muscle weakness and spasms, physical disability, as well as neuropsychiatric symptoms, such as depression, anxiety, and cognitive impairment.[11] The diagnosis of MS rests on the demonstration of a 'dissemination of neurologic signs and symptoms in space and time'. Although the diagnostic criteria for MS have changed over time, the time (2 or more attacks) and space (2 or more objective clinical symptoms) criteria are fundamental to the clinical diagnosis of MS. The Poser criteria were promulgated in 1983 for research purposes and incorporated paraclinical information including cerebrospinal fluid examination.[12] In 2001 these criteria were supplanted by the McDonald criteria, which incorporated magnetic resonance imaging findings into the diagnostic criteria.[13] Other potential diagnoses have to be excluded as well.[14]

The disease course and prognosis of MS is highly variable; roughly 10-15% of people with MS have 'primary progressive MS' which is characterized by a lack of distinct attacks but steadily worsening symptoms from the onset of symptoms.[15] Another 85-90% have 'relapsing-remitting MS' (also known as a 'relapsing-onset MS'), with a disease course characterized by intermittent attacks of MS ('relapses') with partial or full return to previous function between

episodes. Over time, virtually all individuals with relapsing-onset MS will eventually accumulate disability progressively in what is known as 'secondary progressive MS'.[16]

Approximately 100,000 Canadians have MS, yielding a prevalence rate in Canada that is 9 times higher than the global average. British Columbia represents a high-risk region for MS[17] and the mean age at onset of MS (30.6 years)[18] in this province coincides with the mean age of first pregnancy (30.3 years).[19,20] MS is thought to predominantly affect people of northern European ancestry and most people with MS (approximately 75%) are women.[16] Clinical symptoms characteristically manifest in early adulthood, when individuals are of reproductive age. The etiology of MS is not well-understood, but is believed to involve an interplay between an individual's genetic susceptibility and several suspected environmental factors including (but not limited to) serum vitamin D levels, sunlight exposure, viral illnesses (e.g., Epstein-Barr virus) and cigarette smoking.[21]

1.3 Associations between parental multiple sclerosis and child development

The disease course of MS is largely unpredictable. The uncertainty over future disability constitutes a potential threat to a patient's mental health and makes MS a particularly challenging illness.[22] Furthermore, due to an array of potential health effects, including physical and cognitive disability, and the caregiving tasks MS imposes on the family members, the disease may compromise parenting and cause considerable stress and anxiety on patients and their families.[23,24] Indeed, childhood anxiety is a common factor identified in the sparse literature examining children of parents with MS.[24-26] From the few cross-sectional studies that were published before this dissertation was initiated, it appears that children with an MS parent are at risk for adjustment disorders, particularly internalizing difficulties, which

could cause depressive disorders later in life.[23,27,28] Nevertheless, not all such experiences result in negative impacts: studies have associated parental chronic illness, such as MS, with positive outcomes such as pro-social behavior and higher personal competence.[29,30] Additionally, some studies have shown no significant differences in psychosocial adjustment among children with a parent with MS relative to children with parents not affected by MS.[31]

1.4 Study rationale

A review commissioned by Health Canada in conjunction with the MS Society of Canada in 2002 reached the unanimous conclusion that 'more research is needed about the children of parents with MS.'[8] As highlighted by this report, very little is known about how children with an MS parent are affected by the parental illness. Even in the intervening years between 2002 when this report was published and this dissertation was initiated, very few studies in the literature specifically investigated the effects of parental chronic illness and MS-specific clinical factors on early developmental health (other than studies focusing on disease inheritance). Most studies on such issues have focused on older children,[25,27,32,33] partly because objective data collection in early childhood is challenging. However, it is important to study the effects of parental MS on children's health in the early and crucial formative years, when the potential for remedial measures still exists.

Although the few studies examining the impact of parental chronic disease on children's development and health represent important first steps, many have serious methodological limitations, including: a) sub-optimal data collection, for example, the use of self-report or questionnaires potentially open to recall bias; b) use of outcome measures with low reliability or validity; c) failure to account for important confounding or explanatory factors such as

socioeconomic status; d) failure to consider the role of gender of either the child or the parent with MS; e) failure to consider important MS-specific factors such as disease duration, level of disability and presence of comorbidity, all of which could impact a child's adjustment in different ways; f) small study size, e.g., most studies have included around 20 - 50 children, with the largest to date having 170 children; and g) absence of a theoretical framework.

These issues highlight the need for conducting detailed and methodologically rigorous studies that focus on the children of chronically ill parents, such as children whose parents have MS. While previous research contributes to our broader understanding of this issue, important questions remain unanswered. It is unknown whether i) parental MS and MS-related clinical factors, such as the presence of mental and physical comorbidity, disability level, disease duration and the gender of both the child and the affected parent, influence a child's early developmental health; ii) the incidence and the pattern of mental health disorders in children and adolescents with parental MS are unknown; and iii) the timing of parental mental health comorbidity, and its role on psychiatric disorders in children have not been explored.

Population-based longitudinal studies are required to address these knowledge gaps in the literature and to overcome some of the limitations of previous studies. Such an approach should exploit information from large databases in order for the study to accrue sufficient numbers of parents with MS, and to make gender-specific analyses feasible. The linkage of prospectively collected information from disease registry databases on MS with data on child development from education-related databases is currently the best recourse for answering questions related to parental MS and child development. Towards this end, this dissertation is based on studies that used population-based data from British Columbia and Manitoba,

Canadian provinces which have compiled and maintained large, population-based linked health administrative and education-related databases to which researchers have access. The linkage of health and education data provides the best opportunity for using prospectively collected accurate data to investigate factors that support or undermine children's health and development across the early life course. The use of validated measurement tools, such as the Early Development Instrument (EDI)[34] for assessing child development, is an important strength of the studies in this thesis, as measures on child development are from standardized teacher-reports.

1.4.1 Factors potentially associated with developmental vulnerability in children with a parent with multiple sclerosis

To address the deficiencies in the literature, in this dissertation I consider four key factors related to parental MS that could potentially influence a child's developmental health. These include the presence of physical and mental comorbidity in the MS affected parent, the level of disability, MS disease duration, and the gender of both the child and the MS affected parent. These four factors were motivated by the following observations:

First, comorbidity is relatively common in MS; over one-third of MS patients report at least one physical comorbidity that adversely influences health-related quality of life, health care utilization, disability progression and mortality.[35-38] Further, depression and anxiety affect individuals with MS at more than twice the frequency observed among people without MS.[37,39] Parental mental illness is an important predictor of child adjustment and has been associated with detrimental effects on children's early behavioural and emotional development.[40]

Second, studies of somatically ill parents have found that the extent of children's distress is correlated with the severity, phase and the incapacity caused by the illness.[26,27,41] Although research on the impact of a parent's physical disability on children's well-being is scant,[42] the limited literature on this topic suggests that disability in a parent may disrupt parenting and inhibit or delay accessing care for the child.[42,43] As the disease changes over time and disability progresses, the family may experience more conflict and less cohesion; thus, there is a possibility that parents pay less attention to the child's needs.[44,45]

Third, the relationship between MS disease duration and the impact on a child's developmental well-being may be complex. The prior literature suggests that caregiving demands imposed on children because of parental MS can lead to behavioural and psychosocial problems in some families and to positive outcomes such as self-perceived maturity and strengthened relationships in other families.[46]

Finally, studies indicate that the child's gender can influence behavioural responses to parental MS, the coping strategy adopted, and ultimately the child's developmental health.[29,47] Typically, daughters appear to cope better than sons.[28,47] However, the findings related to the child's gender have been inconsistent, with one study suggesting that girls might be at the highest risk for maladjustment.[48] The gender of the sick parent may also be influential; studies from the wider literature suggest that men with MS score better on self-reported health-related quality of life and role-emotional functioning compared with women with MS.[49,50]

Understanding the factors that influence the impact of a highly complex chronic illness such as MS on the patients' family is necessary in order to derive strategies that might alleviate the family burden. Findings of this dissertation may also help to spur research on the associations between other chronic illnesses and children's developmental health.

1.5 Conceptual framework

Relatively little work has been done in establishing a conceptual framework to guide research on the issue of parental MS and child development. One study[41] used the Lazarus & Folkman stress and coping theory,[51] while another [52] focused on the Family Ecology Framework[53] to test a conceptual model of the effects of parental illness on youth and family functioinning. Given the paucity of studies on this topic, the original hypotheses of this disseration were based on previous emipircal work and were not derived from a specific theoretical framework. However, I have developed a conceptual framework to describe pathways and mechanisms through which parental MS may affect children and youth's mental health, based on the findings of studies in this dissertation (Chapter 7).[54]

1.6 Causal language

The literature relating parenting and early childhood development is almost exclusively non-experimental and epidemiologic in nature. Non-experimental epidemiologic studies have documented associations between caregiver characteristics and behavior and child development and these associations may or may not be statistically and clinically significant.[55] If a study fails to demonstrate a statistically significant association between parental MS and adverse child development, this suggests either a lack of a causal relationship between parental MS and child development or a possible false negative result due to a lack of power to detect a

meaningful difference. On the other hand, if a study does show a statistically significant association between parental MS and adverse child development, this does not necessarily imply a causal relationship between the parental MS and child development. For causality to be inferred there are several criteria that need to be satisfied including temporality and proper control of confounding, among others. Nevertheless, a positive study does satisfy the first requirement for inferring causality, namely the demonstration of a statistically significant association.

The question posed in this dissertation regarding the relationship between parental multiple sclerosis and child development is a causal question. Towards this end, an attempt is made to control for confounding factors that may be responsible for a biased association. In the same vein, analyses are carried out to identify potential modifiers of the effects of parental multiple sclerosis on adverse child outcomes. Words such as effect, risk factor, impact, contribute, and influence, which imply causality, are used throughout and especially in the Discussion sections to indicate that that the global picture provided by the studies suggests causality. Usage of such language should be understood to mean that I am merely speculating, suggesting or inferring the existence of a causal relationship. It does not imply that a causal relationship has been proven.

1.7 Dissertation objectives

The primary purpose of this doctoral thesis was to describe the impact of parental MS on child and adolescent developmental health and to determine the role of factors, such as parental mental and physical comorbidity, disease duration, the level of disability, and the gender of both the child and the affected parent.

The specific objectives of the dissertation were to:

1) Systematically review the current scientific literature on child and adolescent adjustment to parental MS, to critically assess the methodological quality of these studies, and to synthesize the findings into the best knowledge on developmental health of children with parental MS.
2) Examine the effect of parental MS on early childhood development at 5 years of age, and to investigate the role of MS-related clinical factors, such as the presence of mental and physical comorbidity, disability level, disease duration and the gender of both the child and the affected parent, on child development.
3) Quantify the incidence of mood or anxiety disorders in children and adolescents with and without parental MS and to identify risk factors (e.g., parental physical and mental morbidity and the gender of the affected parent) for the development of mood or anxiety disorders in such children.
4) Determine the frequency of peripartum depression in parents with MS and its potential effect on child and adolescent psychiatric disorders among children exposed to parental MS.

1.8 Data sources and linkage

The data used in this dissertation were obtained from Manitoba and British Columbia, where publicly funded provincial health care programs are available for all residents. The index study cohort consisted of parents affected by MS and their children and the matched reference cohort comprised of parents unaffected by MS and their children.

Data on the study subjects were obtained from several different population-based health and education databases. All data in each province were anonymized to ensure privacy and confidentiality, and linked through an encrypted unique identifier to further ensure anonymity. The province-wide databases included: (a) physician billings data covering all fee-for-service claims including service date, and associated diagnoses based on the International Classification of Disease codes (ICD-9) from April 1, 1990 onwards in British Columbia and March 1, 1979 in Manitoba;[56] (b) hospital discharge abstracts, containing admission and discharge dates, and diagnoses codes, recorded using ICD-9 and ICD-10 codes from April 1, 1984 to March 31, 2012 in Manitoba and from April 1, 1985 and December 31, 2011 in British Columbia;[57] (c) the registration files (the Manitoba Health Insurance Registry in Manitoba and the Consolidation file in British Columbia),[58] providing demographic information e.g., sex, age, dates of health coverage, and enabling identification of the family for all individuals registered; (d) prescription information (the Drug Programs Information Network in Manitoba and PharmaNet[59] in British Columbia), capturing outpatient prescription drug dispensations since 1996, including date, drug name, Drug Identification Numbers (DIN) and the Anatomical Therapeutic Chemical (ATC) system;[59] (e) Vital Statistics birth data files, containing records of all births since January 1, 1985;[60] and (f) Early Development Instrument (EDI)[34] data, that provided information on childhood developmental health, which were accessed through linkage with the Healthy Child Manitoba Office in Manitoba (since 2006) and the Human Early Learning Partnership in British Columbia (since 2000).[61]

In Manitoba, two data sources were used to determine socioeconomic status of the child's family: the provincial Employment and Income Assistance data files (identifying individuals requiring social assistance) and Census data (providing mean household income in the area of

residence). In British Columbia the Census GeoData[62] files which provide Statistics Canada generated neighborhood income quintiles based on postal codes of residence were used as an indicator of socioeconomic status. The smallest geographical unit for which census profile data was available were dissemination areas composed of one or more neighbouring blocks with a population of 400-700 individuals.[63]

The British Columbia Multiple Sclerosis (BCMS) database, established in 1980, was used to obtain MS-related clinical information for a sub-set of individuals in the MS cohort. It contained clinical data on MS parents based on medical records of the responsible neurologist. This information was collected prospectively on an estimated 80% of MS patients in British Columbia.[64] The BCMS database has data for over 10,000 patients spanning over 30 years of prospective follow-up from the four MS clinics in British Columbia (Vancouver, Victoria, Kelowna, and Price George since 2004). Along with other personnel responsible for maintaining this database, I performed extensive patient chart reviews to enter and corroborate the data from the BCMS database and where necessary, consulted with the responsible physician to clarify unusual or missing data.

All data for the Manitoba component of this dissertation were linked by authorized personnel at the Manitoba Population Health Research Data Repository.[65] Data files used were anonymized, and linkage at the individual-level was performed via the scrambled personal health identification number (PHIN) identifying the person who received the service. Data in Manitoba were accessed up to March 31, 2012 and used for the study described in Chapter 3. In British Columbia, data extraction and linkage was facilitated by Population Data British Columbia. Linkage between databases occurred at the individual level via Personal Health

Number (PHN), a government-issued personal identifier common to all databases and unique to each resident of British Columbia. Parents were linked to their children using the birth registry and the Consolidation file via the unique Medical Services Plan Contract Number, Dependent Number and Age code. The Personal Education Number for each child was matched to his/her Personal Health Number, which enabled the identification of the relevant Early Development Instrument records for each child. Data from Population Data British Columbia up until December 31, 2011 were used for studies in chapters 4, 5 and 6.

1.9 Dissertation structure

The second chapter of this thesis provides a systematic review of the existing research examining children and adolescents' adjustment to parental MS and it critically assesses the methodological strengths and limitations of the available literature. Chapter 3 explores the effect of parental MS and the role of comorbidity and disease duration on child developmental health at kindergarten age in Manitoba. Chapter 4 builds on the work in chapter 3 by both replicating and extending the study using a larger study size in British Columbia. This study also provides detailed analyses of the influence of MS-related clinical factors, such as the presence of mental and physical comorbidity, disability level, disease duration and the gender of the affected parent, on the child's developmental health at kindergarten age. The fifth chapter is an exploratory analysis of the effect of parental MS on the incidence of mood or anxiety disorders in children and adolescents, and includes a discussion about whether parental mental health comorbidity could potentially explain the increase in the risk of mood or anxiety disorders in children. The sixth chapter presents the results of analyses carried out to determine if the timing of parental mental health morbidity, specifically peripartum depression in parents with MS, is associated with psychiatric disorders in children. Finally, the

Discussion chapter synthesizes the findings of the different studies, proposes a conceptual framework based, in part, on the results of this dissertation and highlights the significance of this thesis.

Chapter 2: Children and adolescents' adjustment to parental multiple sclerosis: a systematic review[1]

2.1 Synopsis

Background: Families are the primary source of support and care for most children. Exposure to early-life stressors, including financial stress, role overload, parenting stress, parental depression and parental chronic disease are believed to tax children's bodies and minds in ways that have the potential for altering gene expression leading to harmful changes in their long term social, emotional or behavioural functioning. Little is known about the child living with a parent who has Multiple Sclerosis (MS). I systematically reviewed the literature regarding possible effects of having a parent with MS on the child's or adolescent's psychosocial adjustment.

Methods: I accessed the following databases: MEDLINE, PsychInfo, CINAHL, EMBASE, Web of Knowledge, ERIC, and ProQuest Digital Dissertations. These were searched for relevant studies on this topic for the period 1806 to December 2012. References from relevant articles were also manually searched. Selected studies were evaluated using the Graphic Appraisal Tool for Epidemiology (GATE).

[1] A version of this chapter has been published as Razaz N, Nourian R, Marrie RA, Boyce WT, Tremlett H. Children and adolescents adjustment to parental multiple sclerosis: A systematic review. *BMC Neurol* 2014;14:107.

Results: The search yielded 3133 titles; 70 articles were selected for full text review and 18 studies met the inclusion criteria. Fourteen studies employed quantitative techniques; of these 13 were cross-sectional and one was longitudinal. Four studies were both qualitative and cross-sectional in design. Only 2 of 18 studies were rated as having high methodological quality. Overall, eight studies reported that children of MS patients exhibited negative psychosocial traits compared with children of healthy parents. Among adolescents, greater family responsibilities were linked to poor social relationships and higher distress. Three studies indicated that parental MS was associated with positive adjustment in children and adolescents, such as higher personal competence, while four found no statistically significant difference between children and adolescents of MS affected and MS unaffected parents.

Conclusion: Although having a parent with MS was often reported to have negative psychosocial effects on children and adolescents, there was a lack of consensus in the literature and some studies documented positive effects. However, few high quality studies were identified, and this precluded firm conclusions. There are potentially important, long-term health impacts of early life stressors, such as having a parent with a chronic disease such as MS and more extensive and higher quality research in this area is urgently needed.

2.2 Background and objectives

In Western societies, 4% to 12% of children and adolescents aged 18 years and under live in households where a parent has a chronic illness.[5-7] There is evidence in the literature to suggest that having a parent with a chronic condition can put children at a higher risk of developing emotional and behavioural difficulties due to changes in parent-child interactions.[7]

Multiple sclerosis is a chronic degenerative disease of the central nervous system and is the most common non-traumatic cause of neurological disability among young adults in the Western world.[10] MS typically manifests between the ages of 20 and 40 years, at a life stage when parenting is an important issue for many.[45] Reproductive decision-making by people with MS seems to follow the same pattern as that seem among healthy people in the population.[66] Consequently, many children are exposed to a parent trying to cope with a potentially disabling chronic condition. MS is a particularly challenging disease, and the unpredictable and variable clinical course can cause considerable stress and anxiety to patients and their families.[23,24]

While much research and considerable resources now focus on the child or adolescent who has MS, little is known about the child living with a parent who has MS.[8,29] I aimed to systematically review the literature to address the question - what are the effects on child and adolescent psychosocial adjustment of having a parent with MS? In doing so, I aimed to illuminate the impact of parental health issues on children's development, and open avenues for early identification and preventive interventions.

2.3 Methods

A comprehensive search of the literature was undertaken in December 2012, accessing the following databases: MEDLINE, PsychInfo (from 1806), CINAHL (from 1982), EMBASE (from 1974), Web of Knowledge (from 1900), ERIC (from 1966), and ProQuest Digital Dissertations (from 1980). Search terms included 'Multiple Sclerosis', 'family', 'Parents', 'Parent-Child Relations', 'Child of Impaired Parents', 'Nuclear Family' and 'Caregivers' (see Supplementary Table A.1 for detailed strategy). References from identified articles were also

hand searched for potentially relevant articles. Although I searched selected conference proceedings for emerging research, specifically the 2010, 2011 and 2012 proceedings from the annual meetings of the American Academy of Neurology and the European and American Committees of Treatment and Research in Multiple Sclerosis (the largest conferences covering MS research), I did not find any relevant abstracts to include in our data synthesis.

Only original full-text peer-reviewed published studies fulfilling the following criteria were included (1) school-aged children or adolescents, under the age of 18 years, were part of the study sample; (2) at least one parent was diagnosed with MS; (3) studies evaluated factors associated with parental MS and psychosocial adjustment in children and adolescents, regardless of the direction of findings (positive, negative or neutral); (4) study findings were reported using statistical or qualitative analysis; and (5) the papers were published in English. Clinical case reports and papers based on expert opinion were excluded (i.e. reviews, comments, experiences, case studies, or opinions).

Two individuals independently screened the titles and abstracts of all identified studies (N.R. & R.N.). All studies considered eligible underwent a full-text review by one reviewer (N.R.). Data extraction was conducted using a pre-piloted form, which captured: study design, sample size, duration of exposure to MS, outcomes measured, main findings and methodological quality (**Table 2.1**). Accuracy of data abstraction was cross-checked and confirmed, on a random sample of 10 studies out of the 70 studies that underwent full-text review, by a second reviewer (R.N.). The level of agreement between the two reviewers was 90% and disagreements were resolved through consensus.

No standard exists for conducting quality appraisals for observational studies in the context of a systematic review, so I adapted the Graphic Appraisal Tool for Epidemiology (GATE),[67] and supplemented this tool with topic-specific criteria (Supplementary Table A.2) to assess both qualitative and quantitative studies. Each study received a summary quality score of low, medium, or high. It should be noted that a low quality score does not negate the contribution of a given study, especially in an emerging field where methods may not be well developed, but reflects methodological rigor in the context of all observational studies.

Due to heterogeneity in outcomes and methodologies in the selected studies, a meta-analysis was not possible; therefore a narrative analysis of data was conducted, with studies broadly grouped into those finding a negative effect, a positive effect or no measureable effect on child outcomes among children living with a parent who has MS. Studies were also stratified by study design (e.g. quantitative vs. qualitative; studies which used a comparison group, etc.).

2.4 Results

The initial search returned 3133 citations, with 1114 remaining after duplicates were removed. Of these, 1044 articles were excluded at the title/abstract screening level for not fulfilling study criteria. Seventy articles underwent full-text review of which 52 were excluded for the following reasons: 1 included a population entirely outside the specified age range, 12 had a non-epidemiologic study design, 7 included parents with a range of chronic conditions, without separating out MS, 8 were dissertation abstracts and 24 articles did not focus on psychosocial outcomes. Eighteen studies met the inclusion criteria (**Figure 2.1**) and were published between 1959 and 2012.

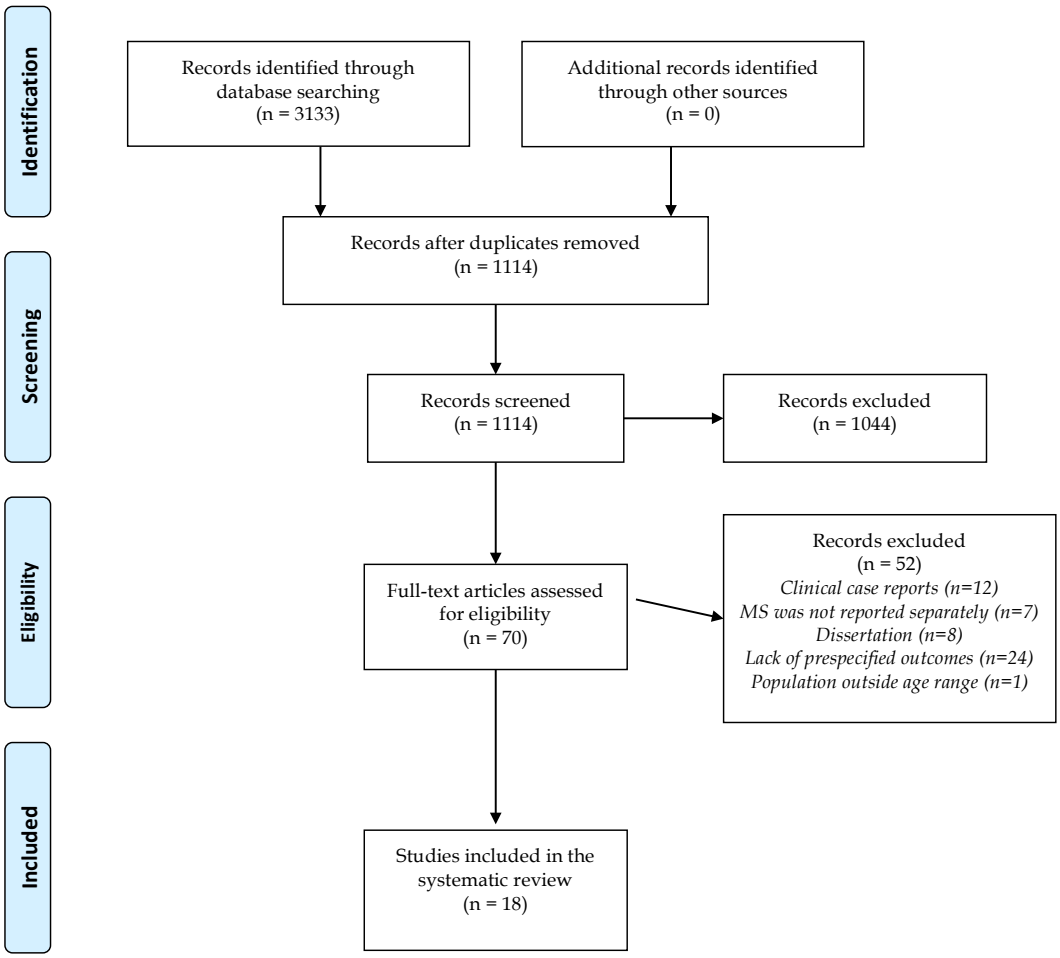


Figure 2.1. Search results and publication selection procedures

Of the 18 eligible studies (**Table 2.1**), locations of study participants were as follows: United States (n=4),[31,53,68,69] Canada (n=3),[30,70,71] Switzerland (n=2, 1 of which also included Germany and Greece),[24,72] Greece (n=2),[23,25] United Kingdom (n=1),[73] Israel (n=2),[74,75] Australia (n=4),[29,41,45,46] Cohort sizes ranged from 8 [29] to 281,[68] with a total of 2051 children or adolescents studied overall. There were a higher number of mothers with MS than fathers, which could be partly attributable to the higher prevalence of MS in females than males or to

mothers being more interested in participating in studies related to children. Most participants were of Caucasian/European-American descent.

None of the 18 studies evaluated in this review specified the diagnostic criteria used for ascertaining MS cases. All study participants were recruited mainly through university neurology departments or specific national or local MS society centres. MS-specific clinical information on the affected parent was noted in some studies, with 2 providing a quantitative measure of disability (based on Kurtzke's Expanded Disability Status Scale [EDSS] [76]), with the affected parent's score ranging from an EDSS of 2 to 7, indicating 'slight weakness' through 'restricted to a wheelchair.'[31,72] A further 9 studies provided other means of quantifying impairment, again with parent's scores ranging from minimal impairment to wheelchair bound disability. [23-25,29,30,41,46,53,73] In the two studies reporting the affected parents' disease course, most had relapsing-remitting MS.[45,73] Only six studies required a minimum time of exposure to parental MS before enrollment;[23,25,31,69,74,75] the rest did not specify or only mentioned parents' total disease duration.

Of the 18 studies included, 2 were considered of high quality, 7 of moderate quality and 9 of low quality. Fourteen studies employed quantitative techniques, of which 13 were cross-sectional and one was longitudinal (and prospective).[23-25,31,41,45,46,53,68-70,72,74,75] Four studies were both qualitative and cross-sectional in design.[29,30,71,73] Eight studies had a comparison group of children with healthy parents; [23,31,41,68-70,74,75] the remainder had no control group.

Table 2.1. Summary of studies examining exposure to parental multiple sclerosis (MS) and psychological adjustment in children and adolescents

Author/ Year	Country	Study design	Sample (age range of children)	A. Exposure to parental MS B. Parental MS duration	Outcomes measured	Evaluator	Main findings	*Quality[67]
Arnuad, 1959 [68]	United States	Quantitative/ Cross-sectional	60 children with an MS parent and 221 with a healthy parent (s) (7–16 years)	A. Mean = 7.2 years (SD: 2.5) B. Range: 3–17 years	[a] Psychological characteristics: (1) General anxiety (2) Body concern (3) Dysphoria (4) Hostility (5) Constraint in interpersonal relations (6) Dependency longings (7) False maturity	Third Party: Author	Children with a parent with MS scored higher in: Body concerns Dysphoric feelings, Hostility, Constraint in interpersonal relations, Dependency needs	Medium
Blackford, 1999 [71]	Canada	Qualitative / Cross-sectional	22 children with an MS parent. No comparison group.	Did not specify	Children's descriptions of life with a parent who has MS	Third Party: Author	Children with an MS parent described higher personal competence, hopefulness, and spirituality. Negative factors that children encountered were attributable more to society than to their parent's condition.	Low
Bogosian, 2011 [73]	United Kingdom	Qualitative/ Cross-sectional	15 children with an MS parent (13-18 years). No comparison group.	Did not specify	Interviews were conducted asking ● What is it like for you to have a parent with MS ● How does your mum's/dad's MS affect your a. Social life? b. Family life?	Third Party: Trained Interviewer	Adolescents described both positive and negative experiences related to having a parent with MS. Benefits to having a parent with MS included reports of feeling more empathetic to others and more grown-up. Negative impacts included family tension, less time to spend with friends, and worries about the future.	High

Table 2.1. Summary of studies examining exposure to parental multiple sclerosis (MS) and psychological adjustment in children and adolescents

Author/ Year	Country	Study design	Sample (age range of children)	A. Exposure to parental MS B. Parental MS duration	Outcomes measured	Evaluator	Main findings	*Quality[67]
Brandt, 1998 [53]	United States	Quantitative/ Cross-sectional	174 children with an MS parent (7-17 years). Population norms as comparison group.	Did not specify	[b] Children's Mental Health	Parent without MS	25% of children in this study (45 of the 174) were classified as being "at risk" for a mental health problem compared to the prevalence rate in the general child population of 12% to 20%.	Low
Crist, 1993 [31]	United States	Quantitative/ Cross-sectional	31 girls with mothers with MS and 34 girls with healthy mothers (8-12 years)	A. Minimum = 2 years B. Range: 2 - 28 years	Mother-daughter interactions during a work task and a play task assessed as: receptiveness, directiveness, and dissuasiveness	Third party: Author	Mothers with MS were not more directive, less receptive or more dissuasive than healthy mothers.	Medium
DeJudicibus, 2004 [45]	Australia	Quantitative/ Cross-sectional	48 children with an MS parent (4–16 years). No comparison group.	B. Mean = 5.6 years (ranged: 1- 19 years)	[c] Children's emotional and behavioural well-being	Parent with MS	Children with an MS parent demonstrated more difficulties in how they related to others, the distress they experienced and how they managed their lives. However, they did not reveal higher levels of clinical symptoms requiring treatment.	Low
Diareme, 2006 [23]	Greece	Quantitative/ Cross-sectional	56 children with an MS parent and 64 with a healthy parent (s) (4–17 years)	B. Mean = 10.3 years (SD: 9.5)	[d, e] Children's emotional and behavioural problems	Child	Children whose parents, especially mothers, had MS presented greater emotional and behavioural problems than comparison children. Children's problems were positively associated with maternal depression and family dysfunction. Family dysfunction predicted children's overall and externalizing problems, while	Medium

Table 2.1. Summary of studies examining exposure to parental multiple sclerosis (MS) and psychological adjustment in children and adolescents

Author/ Year	Country	Study design	Sample (age range of children)	A. Exposure to parental MS B. Parental MS duration	Outcomes measured	Evaluator	Main findings	*Quality[67]
							the severity of impairment of the MS mother predicted children's internalizing problems.	
Kikuchi, 1987 [30]	Canada	Qualitative / Cross-sectional	32 children with an MS parent (6 - 17 years). No comparison group.	Did not specify (although at the time of MS diagnosis subjects ranged from newborns to 15 years; mean =6.5 years)	Child reported quality of life	Third Party: Trained Interviewer	For most part children reported a good quality of life. Although, children expressed limited knowledge of MS and feelings of fear, anger and sadness.	Medium
Olgas, 1974 [69]	United States	Quantitative/ Cross-sectional	124 children with an MS parent and 60 with a healthy parent (7–11 years)	A. Minimum = 2 years	[f] Body image	Child	Body image scores did not differ between groups Body image distortion tended to be greater in girls with MS mothers than girls with MS fathers or boys with MS mother	Low
Pakenham, 2006 [41]	Australia	Quantitative/ Cross-sectional	48 children with an MS parent and 145 with a healthy parent (10–25 years)	B. Mean = 9 years (SD:7; range: 4 months to 29 years)	Children's positive (benefit finding, life satisfaction and positive affect) and negative (distress and health status) adjustment	Child	Children with a parent with MS had poorer adjustment, greater family caregiving responsibilities and lower levels of life satisfaction and positive affect	Low
Pakenham, 2012 [46]	Australia	Quantitative/ Longitudinal	Time 1: 130 children with an MS parent (10-20 years) Time 2: (After 12 months): 91 children with an MS parent (10-20 years). No comparison group.	At time 1:B. Mean = 8.2 years (SD: 5.8; range: 4 months to 25 years)	[g] Children's negative (behavioural emotional difficulties, somatisation) and positive (life satisfaction, positive affect, prosocial behaviour)	Child; Parent with MS; Parent without MS	At time 1 higher total caregiving was associated with lower life satisfaction and higher somatization and total difficulties. Higher total difficulties were also associated with greater social-emotional care. At time 2, higher caregiving responsibility was associated with lower life satisfaction and	Low

Table 2.1. Summary of studies examining exposure to parental multiple sclerosis (MS) and psychological adjustment in children and adolescents

Author/ Year	Country	Study design	Sample (age range of children)	A. Exposure to parental MS B. Parental MS duration	Outcomes measured	Evaluator	Main findings	*Quality[67]
					adjustment		higher total caregiving was associated with increased prosocial behaviour. Further, time 1 instrumental and social-emotional care domains were associated with poorer time 2 adjustment.	
Paliokosta, 2009 [25]	Greece	Quantitative/ Cross-sectional	56 children with an MS parent (4-17 years). No comparison group.	B. Mean = 10.3 years (range = 2 months to 21 years)	[b] Children's mental health and behavior. Interviews were also conducted with the child and the parent about the amount of information regarding parental MS given to child	Third Party: Trained Interviewer; Parent with MS; Parent without MS; Child	Children and adolescents who had "partial information" about parental MS presented with higher scores in social difficulties and internalizing behaviours as well as higher total problems on the child behaviour checklist. They also presented with higher score on social problems.	Low
Peters, 1985 [70]	Canada	Quantitative/ Cross-sectional	33 children with a MS parent and 33 with a healthy parent (12–18 years)	B. Mean = 9.2 years (range: 1.6 - 17.7 years)	[h] Family cohesion, expressiveness, conflict, independence, achievement orientation, intellectual-cultural orientation, active-recreational, moral-religious emphasis, organization and control in the family	Child	Children of MS parents showed significant differences in the perception of their family environment vs children of healthy parents. Lack of 'feeling of togetherness' was reported	Medium
Steck, 2005 [72]	Switzerland	Quantitative/ Cross-sectional	41 children with an MS parent (6 – 18 years). No comparison group.	A. Mean = 3.5 years (for children < 12); mean = 8.2 years (for children >=12 years)	Children's indication for psychotherapy	Third party: Trained Interviewer	Half of the children were expected to benefit from individual psychotherapy aimed at enhancing ability to cope with the parental MS.	Low

Table 2.1. Summary of studies examining exposure to parental multiple sclerosis (MS) and psychological adjustment in children and adolescents

Author/ Year	Country	Study design	Sample (age range of children)	A. Exposure to parental MS B. Parental MS duration	Outcomes measured	Evaluator	Main findings	*Quality[67]
Steck, 2007 [24]	Germany, Greece, Switzerland	Quantitative/ Cross-sectional	192 children with an MS parent (Mean = 9.8 years; SD: 4.8). No comparison group.	B. Mean = 6.5 years for MS fathers; Mean =7.7 years for MS mothers	[b] Children's mental health and behaviour	Parent with MS; parent without MS; Child	MS parents, especially mothers, as well as depressed mothers, or depressed "healthy" parents evaluated their children's mental health problems with a higher prevalence within the internalizing spectrum. If two parents presented a depressive state, the prevalence of relevant psychological internalizing symptoms was twice or three times as high as the age norms.	Low
Turpin, 2008 [29]	Australia	Qualitative/ Cross-sectional	8 children with an MS parent (7–14 years). No comparison group.	Did not specify	Children's day-to-day lives, their perceptions of their parent's condition and their thoughts about the future	Third Party: Occupational therapist and a psychologist	Children described taking on additional roles and responsibilities that restricted their participation in developmentally appropriate occupations. Additional responsibilities can enhance children's skills and provide pride and stress.	High
Yahav, 2005 [74]	Israel	Quantitative/ Cross-sectional	56 children with an MS parent and 156 with a healthy parent (10–18 years)	A. >6 months	● A sense of personal concern and responsibility towards parents ● Degree of responsibility and active protection of parents ● Fear and anxiety about parents' future ● Burden of tasks and errands at home	Third Party: Trained Interviewer	Children of parents with MS felt more responsibility and obligation than children of healthy parents. They also exhibited higher degree of fear and anxiety related to MS, a greater sense of burden and greater degree of anger.	Medium

Table 2.1. Summary of studies examining exposure to parental multiple sclerosis (MS) and psychological adjustment in children and adolescents

Author/ Year	Country	Study design	Sample (age range of children)	A. Exposure to parental MS B. Parental MS duration	Outcomes measured	Evaluator	Main findings	*Quality[67]
					● Anger			
Yahav, 2007 [75]	Israel	Quantitative/ Cross-sectional	56 children with an MS parent and 156 with a healthy parent (10–18 years)	A. >6 months	[e] Children's emotional health and problem areas: delinquent behavior, aggression, attention problems, thought disorders, social acceptance problems, anxiety and depression, somatic complaints, and withdrawal behavior.	Third Party: Trained Interviewer	Children with an MS parent displayed higher levels of depression and anxiety than children from the control group. Furthermore, children in the study group reported a greater degree of separation anxiety, compared with the control group	Medium

* Graphic Appraisal Tool for Epidemiology (GATE).
Instruments used to measure the stated outcomes:
a. Rorschach test.[77]
b. Child Behaviour Checklist.[78]
c. Strengths and Difficulties Questionnaire.[79]
d. Achenbach's Child Behaviour Checklist and Youth Self Report.[80]
e. Youth Self Report,[80] and Separation Individuation Test of Adolescence.[81]
f. Draw-A-Person,[82] Semantic Differential[83] and The Body-Cathexis Scale.[84]
g. Youth Activities of Caregiving Scale.[85]
h. Family environment scale.[86]

A broad range of outcomes were considered in the selected studies, including, anxiety, depression, peer relations, caregiving responsibility, family cohesion, body image, parent-child interaction and hopefulness. Some studies used validated, standardized questionnaires such as Child Behavioural Checklist or Youth Self Report [80] and others used study-specific questionnaires to measure the outcome. Outcomes were assessed either by an interviewer who administered the questionnaires or were self-reported by the parents, the children or both. Amongst studies that systematically evaluated this question, 8 found an association between exposure to parental MS and adjustment problems in their offspring. Five studies did not find an association and 5 studies found both positive and negative effects of caring for a parent with MS.

Negative psychosocial aspects

Of the 8 studies with a suitable comparison group, 6 described negative psychosocial outcomes for children who had a parent with MS compared with the children of healthy parents. Of these, two found higher levels of depression and anxiety [74] and greater emotional and behavioural problems [23] in the children with an MS-affected parent. Both studies were of medium quality. Studies measuring the caregiving activities of children with an MS parent showed that such children had more responsibility and obligations (compared with children of healthy parents) and consequently a greater sense of burden, anger and lower levels of life satisfaction.[41,75] One of these studies was of low quality and the other was of medium quality. Furthermore, adolescents with an MS parent exhibited a higher degree of responsibility and experienced more fear and anxiety compared with adolescents with healthy parents.[74] In one study, there was higher conflict, lower cohesion and a general 'lack of togetherness' reported by children with an MS parent (compared with children of non-MS parents)[70] and higher

levels of body concern, hostility constraint, interpersonal relations and a pattern of false maturity in another.[68] Both these studies were of medium quality.

Several studies compared the psychosocial score of children of MS parent's to the population norm.[24,53] One study estimated that 25% (45 of 174) of children with MS parents were classified as being "at risk" for a mental health problem compared with 12% to 20% of children in the population.[53] Furthermore, adolescent's self-reported scoring for internalizing disorders was significantly over the expected normal.[24] Both were rated as low quality studies due to a failure to adjust for important demographic variables (such as socioeconomic status), and sub-optimal data collection.

Of the remaining three quantitative studies with no comparison group, one demonstrated that children of parents with MS were at risk of mental health problems and would benefit from individual psychotherapy.[72] One study suggested that children who had partial information about their parent's condition exhibited significantly more problems as compared with children who had explicit information or no information.[25] In addition, one longitudinal study found that youth with greater caregiving responsibilities reported lower life satisfaction, higher somatization and higher emotional and behavioural difficulties.[46] All three studies were of low methodological quality, with interpretation of findings difficult in the absence of a comparison group.

Three of the four qualitative studies included described both positive and negative experiences related to having a parent with MS.[29,30,73] Higher family tension and extra responsibilities, which limited children's involvement with peers and time spent at play and learning, were

associated with having a parent with MS.[29] Further, all children expressed anxiety about both the immediate and long-term health and well-being of their parents.[29,73] Both studies were high quality. Finally, a medium quality study noted that children's limited knowledge and understanding of the disorder and the related implications of having a parent with MS seemed to be a threat to their achievement of happiness.[30]

Absence of psychosocial effects

In contrast to some of the above-mentioned findings, no statistically significant differences on body image distortion were found in children with an MS parent vs. a healthy parent.[69] Furthermore, no significant differences in mother-daughter interactions during work and play tasks were observed when the mother had MS vs. when the mothers was not affected by MS.[31] One study was of low quality,[31] and the other was of medium quality.[69] In addition, two studies showed that the children of MS parents did not appear to differ from the community norms for overall difficulties and externalizing problems.[24,45] Yet these children were over three times more likely than a community sample of children to be perceived by their affected parents as having psychological problems. This difference may not have been due to the child's actual psychological well-being; rather it could have related to the parents' perception of their own MS and its effect on their children.[24,45] Both studies were of low quality. Finally, a qualitative study (of medium quality) noted that for the most part, children with an MS parent reported a good quality of life.[30]

Positive psychosocial aspects

In one quantitative study, findings indicated that although parental MS was associated with a higher social-emotional burden, and a greater share of domestic household duties, this actually

led to an increase in pro-social behaviour in youth.[46] Furthermore, these youth voiced pride when taking on family responsibilities.[29,30] Children described having higher personal competence and feeling more empathetic to others and more "grown-up," as a consequence to having a parent with MS.[71,73]

2.5 Discussion

In this systematic review I evaluated the association between parental MS and psychosocial adjustment in children and adolescents. Although most studies tended to report that children of MS parents exhibited negative psychosocial behaviour compared with children of healthy parents, some positive aspects in caring for a parents with MS were also highlighted. However, overall the strength of the evidence was rather weak, with only 2 of 18 studies appearing to be of 'high quality', and this precluded firm conclusions.[29,73]

Our findings were broadly consistent with other systematic reviews, which have also reported negative psychosocial effects in children living with a parent with a physical disability or a chronic illness.[7,26,87] A meta-analysis examining studies of children who had a parent with a chronic illness showed that overall such children displayed significantly more internalizing behaviours (such as anxiety, depression, and withdrawal) than children with healthy parents.[7] Furthermore, in a population-based sample of children with a parent dealing with a serious physical illness, there was an elevated risk of psychosocial maladjustment, with internalizing problems being more prevalent than externalizing problems (such as aggression and delinquent behavior).[5]

Our systematic review suggests that children of MS parents have higher rates of depression,

anxiety, somatization, difficulty in relating to others and greater emotional and behavioural problems.[23,41,45,46,53,68,72,75] Children also perceived their families as being less cohesive, with greater tension and isolation, as compared with unaffected families.[70,73] Uncertainty regarding the future, as well as illness exacerbation, was a cause of fear and anxiety in children of parents with MS.[44,75] Caregiving roles and the potential stigma attached to a parent's MS were also sources of stress for children.[46] Among adolescents, greater family responsibilities were linked to fewer social relationships and higher distress.[41,46,74] On the other hand, several studies found no measurable effect (negative or positive) of having a parent with MS,[24,31,45,69] and a few found some positive effects, such as higher personal competence.[71,73]

This pattern of positive and negative outcomes could reflect the costs and benefits associated with caregiving that is also evident in adult caregivers.[88] Some children in our review described pride in their caregiving abilities, as these children had become adept at tasks and acquired skills unknown to their peers.[29] However, circumstances in which children felt coerced into becoming caregivers led to family stress.[26,41] Children were more prone to becoming caregivers in single-parent families, low-income families, families who did not have access to home care support, and families with little social support.[45,89]

Our systematic review showed that limited knowledge and understanding of MS was associated with poor adjustment in children.[25,30] This finding is consistent with those of other studies, which also show that it is important to provide children with information about MS that is tailored to their developmental level. Lack of such information can lead to misconceptions in children with some children believing that their own behaviour or other people's behaviour caused their parent's illness.[90,91] Young children, in particular, appear to

have a need for information that is often not met.[90] Children need better information on the etiology of MS and also need to be reassured that their own risk for developing MS is minimal.[90] Children who are unaware of their parent's illness may display high levels of anxiety and distress as they witness family tension without being aware of its source.[25] It is curious that educated mothers are less likely to provide information regarding their illness to their children.[25] This observation is noteworthy, especially as MS patients who participate in research have a higher socioeconomic status compared with patients with other chronic illnesses, and this could potentially lead to selection and reporting bias.[45,92]

Some studies in our review reported that family dysfunction and lack of social support were associated with a child's externalizing problems, while the mothers' severity of impairment was associated with children's internalizing problems.[23,73] Other studies showed that the level of depression among MS affected mothers (as estimated by depression scores) is negatively correlated with their coping ability and positively correlated with depression scores in their healthy partners. Likewise, the coping ability of the healthy parents appeared to be a strong predictor of whether children successfully cope with the parental disease.[47,93] Nevertheless, no study in our systematic review examined fatigue as a risk factor for family and child coping, even though fatigue has been shown to be one of the most common, yet "hidden," symptoms of MS.[94] Parents with MS identified fatigue as one of the primary problems that interferes with parenting functions, as it leads to difficulties in being involved with day-to-day activities, and to a lack of patience in interactions with children.[46] Furthermore, in a group of patients with different chronic illnesses, including MS, one study demonstrated that maternal fatigue potentially mediates some of the relationship between maternal depression and maladaptive child outcomes.[92] Other factors which emerged as potentially influencing a child's adjustment

to parental illness from the included studies were: gender of the parent and the child,[46,47,93] the child's age and developmental stage,[29,41] level of social support,[29] physical condition or disability caused by the disease,[41] single parenthood and the family environment.[29,41,53,72]

Interpretation of our systematic review is constrained by limitations in the original studies, particularly exposure assessment and potential sources of bias. First, none of the studies included in the present systematic review provided details regarding the validity of the MS diagnosis. Similarly, most studies did not use a teacher-rated standardized tool to measure child psychosocial adjustment. Second, studies failed to provide demographic characteristics of the participants and also failed to account for important confounding factors such as socioeconomic status. Third, many studies did not include a comparison group, which is critical for assessing whether the findings are specific to children who have a parent with an illness. Finally, relying on cross-sectional design meant that the temporal sequence of cause and effect could not be studied. The interaction between progressive MS and child developmental needs longitudinal follow up for ascertaining if MS related stressors preceded potential problems in child development. This is particularly relevant since disability in MS can often be minimal in the early stages of the disease, and the overall lifespan of the parent with MS may not be affected as with other chronic diseases. Ideally, studies seeking to identify if there is an MS specific characteristic that influence's child development also need to investigate the psychosocial wellbeing of children with other chronic diseases and also children of healthy parents.

A population-based longitudinal study with the inclusion of an appropriate comparison group is required in order to overcome the deficiencies of the studies mentioned previously. In

addition, rigorous, objective, and validated measurement tools are needed to assess child development such as the Early Development Instrument,[34] or the Child Behaviour Checklist.[78] Measurement of appropriate confounders, mediators and effect modifiers such as socioeconomic status, gender of the child and the marital status of the parents are also required for providing an unbiased and comprehensive picture of the relationship between parental MS and child development. Ideally, these design and analysis features should be analyzed in the context of information on the clinical characteristics of the affected parents, such as disease duration, level of disability and presence of comorbidity. A large study size is also necessary to ensure adequate study power. Findings from such studies would help in developing and evaluating family centered interventions to improve child and family outcomes.[95]

Our review is affected by some of the limitations that are common across systematic reviews, and these include issues such as publication bias and problems in the study selection process. I sought to mitigate the latter by having two independent reviewers, and by checking reference lists of previously published reviews and articles retrieved in the search for studies that I might have missed. Despite these measures, the selection and qualitative synthesis of eligible studies can be a subjective process. However, by using a standardized form to extract the data, and assessing methodological quality using a validated checklist, I attempted to maximize the objectivity in our search and abstraction strategy. For non-experimental studies, there is currently a lack of consensus regarding the most appropriate methodology for assessing study quality in the context of a systematic review.[96] Although the GATE tool is an excellent tool to critically appraise different types of studies, it does not assign a score to studies and this limits its utility.[97,98]

The current literature does not permit a clear understanding of the relationship between parental MS and child development as the paucity of high quality studies makes it difficult to draw robust conclusions. Larger studies that explore the relationship in a comprehensive manner are required for clarifying the effects of parental MS on children. From the limited available evidence, it appears children exposed to parental MS may be at a higher risk of psychosocial problems compared with children of parents without this chronic disease. Although the few studies examining the impact of parental chronic disease on children's development and health represent important first steps in understanding these relationships, these studies are affected by significant methodological limitations. Study limitations include a lack of clarity with regard to the diagnosis of MS, potential bias due to the lack of a suitable comparison group, and failure to adjust for important confounders such as socioeconomic status. Population based studies with longitudinal follow up, validated diagnoses of MS and objective measures of developmental health are required for providing insight into the relationship between parental MS and child development. Although better research is needed before appropriate recommendations can be made, healthcare professionals, and community partners, such as educators, patient group and policy makers, should be cognizant of the potential impact that chronic parental illness can have on the developing child.

Chapter 3: Impact of parental multiple sclerosis on early childhood development: The Manitoba study[2]

3.1 Synopsis

Objective: Exposure to parental chronic illness may be associated with adverse developmental health in children. I examined the association between parental multiple sclerosis (MS) and child development.

Methods: I conducted a population-based retrospective cohort study in Manitoba, Canada, and contrasted children who had a parent with MS with children of unaffected parents matched on sex, region and year of developmental assessment. Data for the study were obtained from linked provincial health and education databases. The outcome was childhood development at 5 years of age, expressed as vulnerability (absent vs. present) on 5 domains of the Early Development Instrument (EDI). Conditional logistic regression was used to control for matching factors and potential confounders including maternal age, socioeconomic status, number of siblings, age at EDI and parental mental morbidity.

Results: Overall, children with an MS parent (n=153) were similar to children of unaffected parents (n=876) on all EDI domains. However, mental health morbidity among MS parents was associated with children's vulnerability on the social competence (OR, 5.73, 95% confidence interval [CI] 1.11-29.58) and emotional maturity (OR, 3.03, 95% CI 1.03-8.94) domains. The duration of the child's exposure to parental MS (in years) was also associated with vulnerability on the physical health domain (OR, 1.49, 95% CI 1.03-2.15).

---

[2] A version of this chapter has been published as Razaz N, Tremlett H, Boyce WT, Guhn M, Joseph KS, Marrie RA. Impact of parental multiple sclerosis on early childhood development: a retrospective cohort study. *Multiple Sclerosis Journal* 2015;1–12

Conclusion: Parental MS is not associated with adverse early childhood developmental health. However, children of parents with both MS and mental health morbidity, and those with longer duration of exposure to parental MS are at higher risk for developmental vulnerability in early childhood.

3.2 Background and objectives

This Chapter presents the findings of a study on the association between parental MS and child developmental health at kindergarten age in Manitoba, Canada. The analysis of developmental vulnerability among children with parental MS was examined by risk factors of interest, including parental mental health comorbidity and the duration of child's exposure to parental MS.

Studies show that early-life stressors such as parental chronic disease are associated with adverse developmental health, including poor social and emotional functioning.[6,99] Most research in this area has focused on cancer patients, specifically mothers with breast cancer and their adolescent offspring.[5] Information on other chronic illnesses and potential impacts on young children is lacking.

MS affects more women than men and typically manifests between the ages of 20 and 40 years, when parenting can be an important issue.[45] As a result, many children are exposed to a parent coping with a potentially disabling chronic neurological condition.[5,7] Owing to the broad array of potential health effects, including physical and cognitive disability, MS can cause considerable stress and anxiety to individuals and their families, and indirectly affect the developmental health of children.[23,27] The few cross-sectional studies published on this issue

show that children with an MS parent are at risk of adjustment difficulties, particularly internalizing disorders and behavioural problems, which are associated with depressive disorders later in life.[23,28]

The studies that have addressed the issue of psychosocial well-being of children with an MS parent have methodological limitations including cross-sectional design, lack of a comparison group,[73,100] self-reported data,[100] and failure to adjust for relevant confounding variables.[28] I, therefore, carried out a study to investigate the association between parental MS and developmental health in children using a population-based cohort study.

3.3 Methods

I carried out a retrospective matched cohort study in Manitoba, a province of 1.2 million people in the geographic centre of Canada. Children of parents with MS were contrasted with matched children of unaffected parents in terms of child development at kindergarten age. All data for the study were obtained from the Manitoba Population Health Research Data Repository.[65] Due to comprehensive universal health care coverage, virtually all contacts between residents of Manitoba and the health care system are captured for 98% of the population.[65] All data files used in this study were anonymized, and linkage at the individual-level was performed using the scrambled personal health identification number (PHIN) identifying the person who received the service.

The province-wide databases used in this study included the Drug Programs Information Network (capturing outpatient prescription drug dispensations since 1996, including date, drug name, and drug identification number for all Manitoba residents); the Physician Claims

database (including outpatient service date, and three-digit ICD-9-CM diagnosis from April 1, 1984 to March 31, 2012); the Hospital Discharge Abstracts database (containing admission and discharge dates, and up to 16 discharge diagnoses, recorded as five-digit ICD-9-CM codes from April 1, 1984 to March 31, 2004, and from April 1, 2004 to March 31, 2012 using ICD-10-CA codes); and the Manitoba Health Insurance Registry (providing demographic information e.g., sex, age, dates of health coverage, and enabling identification of the family for all individuals registered in Manitoba). Two data sources were used to determine socioeconomic status of the child's family: the provincial Employment and Income Assistance data (identifying individuals requiring social assistance) and Census data (providing mean household income in the area of residence). Finally, Early Development Instrument (EDI)[34] data, which provided information on early childhood development, were accessed through linkage with the Healthy Child Manitoba Office. The reliability and validity of these data sources have been well-documented.[101-104]

Using hospital and physician claims data from April 1, 1984 to March 31, 2012 along with prescription claims from April 1, 1996, I identified all Manitobans with MS using a case definition that was previously validated against medical records.[105] These were individuals with ≥3 records related to MS in any combination of hospital, physician, or prescription claims.[105] Using diagnoses abstracted from medical charts as the gold standard, the case definition of ≥3 medical contacts in administrative data had a positive predictive value of 80.5% and negative predictive value of 75.5%.[105] All persons with MS who had a child born between January 1st, 1999 and December 31st, 2006, with EDI data were included in this index cohort. The birth dates allowed each child to have reached his/her fifth birthday between 2005 and 2011 and to be part of the EDI data collection. Parents whose MS onset occurred after

their child's EDI assessment (ascertained based on the date of the first health care claim for a demyelinating disease, Supplementary Table A.3) were excluded from the study, as were individuals who had a partner who also had MS. Up to 6 children from the population who had EDI data were selected for each case, matched on regional health authority and year of the EDI assessment, to form a reference (comparison) group. Where multiple children were eligible from the same family, one was selected randomly. Children of parents with diagnostic codes for any demyelinating disease were excluded from the matched comparison cohort.

The primary outcome of interest was child development, as measured by the EDI. The EDI has routinely been administered biannually in all 37 public school divisions in Manitoba beginning in 2005/06. All kindergarten students at participating schools are included unless they are withdrawn from participation by their parents. Teachers completed the EDI for each child in their kindergarten class, typically when children were five or close to turning five years of age, mid-way through the school year. The EDI was developed as an assessment of school readiness with the understanding that readiness is a holistic concept involving several developmental areas.[34] The EDI consists of 104 binary and Likert-scale items designed to tap five core areas of early childhood development:[34,106] physical health and well-being; social competence; emotional maturity; language and cognitive development; and communication skills and general knowledge (Supplementary Table A.4).[34] Children were considered vulnerable on a domain if their scores fell below the 10th percentile value[107] based on the national EDI cut-off scores.[108] The EDI has been found to be a psychometrically reliable and valid tool for research.[34,109] Research on the EDI's predictive validity over a 1-year period has demonstrated that kindergarten EDI scores provide as good an assessment of children's achievement in Grade 1 as direct cognitive assessment,[110] and significantly predicted reading

and numeracy achievements during the elementary school years. Further, neighborhood- or community-level EDI scores have been shown to be valid indicators of regional developmental health inequalities and corresponding variability in the qualities of early childhood experiences (i.e., reflecting on the social and emotional domains) until school entry.[111,112] With respect to the reliability of the instrument, the internal consistency of the EDI varies from 0.84 to 0.96, which indicates a high internal consistency. Test-retest reliability correlations are also high (ranges from 0.82 to 0.94).[34]

The main determinant of interest was the presence (vs. absence) of parental MS. Confounding factors considered for adjustment included maternal age at child's birth, socioeconomic status, number of siblings, age at EDI and parental mental and physical morbidity. Socioeconomic status was defined as the mean household income in the child's residential area (identified using the child's residential postal code obtained from the EDI assessment) as documented in the 2006 Canadian Census, and grouped into quintiles.[113] This was complemented by parental receipt of income assistance at any time from the child's birth to the EDI assessment. This information (income quintiles and income assistance) was then combined to create 3 approximately equal sized socioeconomic groups: low (quintile 1 or income assistance recipients); medium (quintiles 2 and 3); and high (quintiles 4 and 5).

As comorbidity is relatively common in MS,[114] our analyses included covariates for morbidity. I included comorbidities affecting ≥5% of the MS population. Parental mental health disorders (either depression or anxiety disorder[115]), diabetes, hypertension, hyperlipidemia, and chronic lung disease (e.g., asthma, bronchitis) were identified using validated algorithms, generated through hospital and physician claims and drug data.[37,116] Case definitions for the above-

mentioned morbidities have been previously validated against medical records (Supplementary Table A.5). Only parental morbidity occurring before the child's EDI assessment was considered.

Demographic and clinical characteristics of the parent-child family unit were compared between the children of MS parents and the children in the matched comparison cohort using paired *t*-tests, and the Wilcoxon signed rank test. Multivariable conditional logistic regression models were used to determine the association between parental MS and each domain of the EDI, adjusted for potential confounders. Confounders were included in the final models based on the literature[107,117] or statistical significance (p value <0.10). The full model included the following covariates: maternal age at child's birth (5 year categories), age of the child at the time of EDI completion (years), number of siblings (1,2, ≥3 vs. 0), and parental mental morbidity (absent vs. present). Parental mental morbidity was the only health condition associated with the outcome or showing evidence of confounding, and this was the only morbidity included in the final model. Further, to test whether the effect of MS on child development was modified by parental mental morbidity, I included an interaction term in the fully adjusted models.

Secondary analyses restricted to the MS cohort were also carried out, including assessment of the effect of parental mental comorbidity (presence vs. absence). I also examined whether a the effect of parental MS was associated (in dose-response fashion) with (i) the child's duration of exposure to parental MS in years (i.e., time from onset of MS or the child's birth, whichever was later, to the child's EDI assessment), and (ii) the duration of parental MS in years (i.e., time from onset of MS to the child's EDI assessment).

Results were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Regression model fit was assessed using the likelihood ratio test. A two-sided p value <0.05 was used to determine statistical significance. Sensitivity analyses were also carried out with EDI considered as a continuous score in multiple linear regression models.

The University of Manitoba Health Research Ethics Board approved the study, and the Manitoba Health Information Privacy Committee approved data access. Analyses were performed using SAS Version 9.2 (SAS Institute Inc., Cary, NC).

3.4 Results

Of 17,009 individuals with any health claim(s) related to a demyelinating disease, 3,116 individuals met the case definition of MS; of these 211 had a child with an available EDI assessment (**Figure 3.1**). This index cohort of MS parents and children were matched to a reference cohort of 1207 children and their parents who did not have MS. Children were excluded from these cohorts for the following reasons: MS onset occurred after the EDI assessment (n=27), no demographic or postal code information (n=3) and multiple eligible reference children (n=35). The final study population contained 153 children with an MS parent and 876 children and their parents in the matched reference cohort.

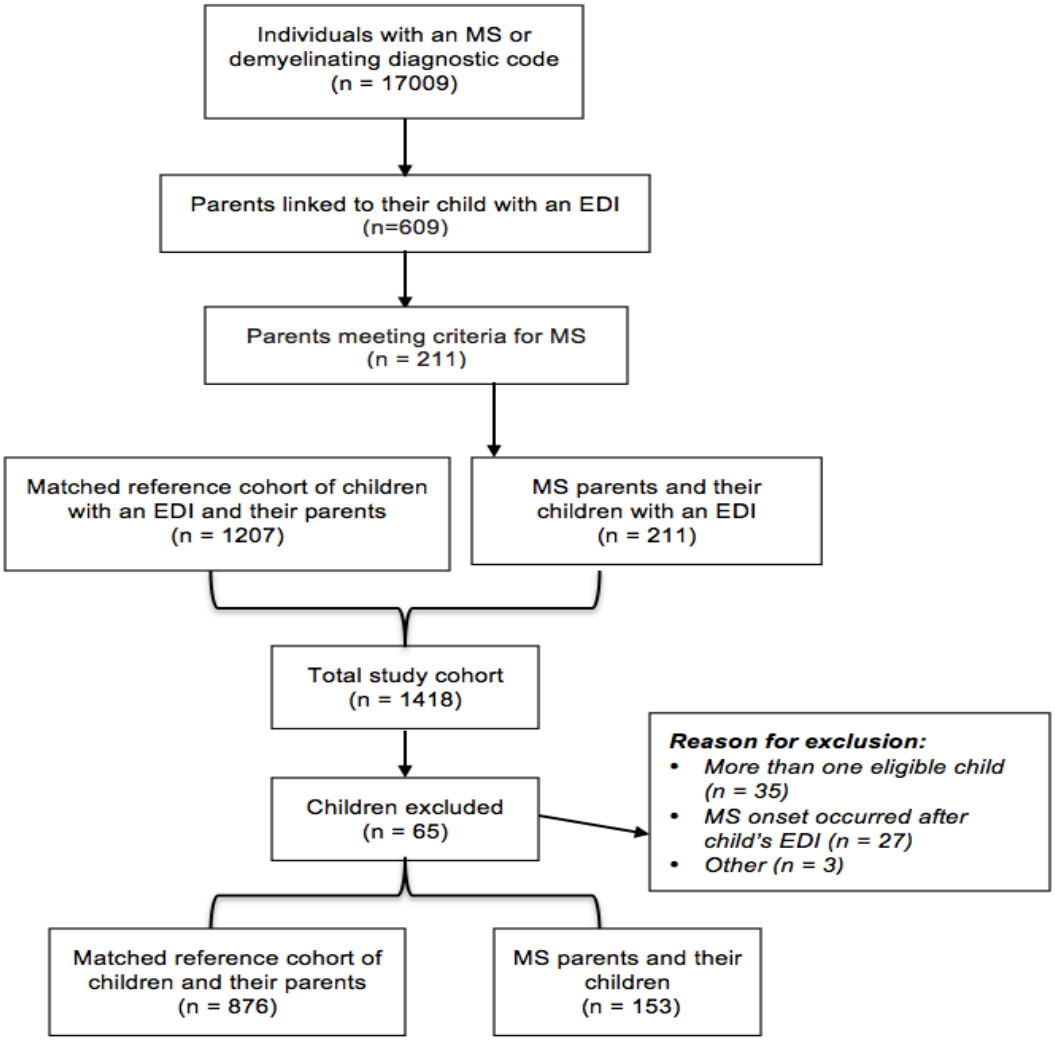


Figure 3.1. Schematic depiction of the process for identifying the study cohorts.
MS denotes Multiple Sclerosis and EDI refers to the Early Development Instrument.
*Please note that the total number of children excluded in the penultimate step (n = 65) does not include the children in the matched reference cohort that were excluded with each corresponding index child.

The MS affected and matched comparison cohorts were similar in terms of age at EDI collection (mean [standard deviation] 5.7 [0.3] years), and marital status (**Table 3.1**). However, MS-affected parents were on average 3 years older at the time of the child's birth, were more likely to be native English speakers, and had a higher socioeconomic status than parents in the comparison group. The frequency of diabetes, hypertension and hyperlipidemia was similar

between parents with MS and those in the matched comparison cohort, but MS parents were more likely to have a mental health comorbidity and chronic lung disease (**Table 3.1**). Differences in mental health morbidity were particularly striking (49.7% vs. 35.3% among MS parents and unaffected parents, respectively).

Table 3.1. Characteristics of multiple sclerosis (MS) affected child-parent dyads and the matched reference group, Manitoba, Canada

Characteristics	Parent with MS (n=153) no. (%)	Parent in matched reference cohort (n=876) no. (%)	p value
Child's age at EDI assessment (years)			
Mean (SD)	5.7 (0.3)	5.7 (0.4)	0.98[a]
Maternal age at the time of birth			
Mean in years (SD)	31.3 (4.9)	28.3 (5.8)	**<.001**[a]
<25 years	16 (10.5)	267 (30.5)	
25-29	41 (26.8)	262 (29.9)	**<.001**[b]
30-34	61 (39.9)	242 (27.6)	
≥35	35 (22.9)	105 (12.0)	
Neighborhood income (SES)			
Highest SES	85 (55.6)	284 (32.4)	
Middle SES	42 (27.5)	253 (28.9)	**<.001**[b]
Lowest SES or income assistance	26 (17.0)	339 (38.7)	
Siblings			
None	20 (13.1)	145 (16.6)	
1 sibling	88 (57.5)	387 (44.2)	**0.03**[b]
2 siblings	30 (19.6)	213 (24.3)	
≥3 siblings	15 (9.8)	131 (15.0)	
Marital status			
Married	92 (60.1)	462 (52.7)	0.09[b]
Not married	61 (39.9)	414 (47.3)	
Child's first language			
English	137 (89.5)	700 (79.9)	**0.01**[b]
Other	16 (10.5)	176 (20.1)	
Parental mental health (depression and/or anxiety)			
Yes	76 (49.7)	309 (35.3)	**<.001**[b]
No	77 (50.3)	567 (64.7)	
Parental diabetes			

Table 3.1. Characteristics of multiple sclerosis (MS) affected child-parent dyads and the matched reference group, Manitoba, Canada

Characteristics	Parent with MS (n=153) no. (%)	Parent in matched reference cohort (n=876) no. (%)	p value
Yes	12 (7.8)	52 (5.9)	0.35[b]
No	141 (92.2)	824 (94.1)	
Parental hypertension			
Yes	33 (21.6)	159 (18.2)	0.29[b]
No	120 (78.4)	717 (81.9)	
Parental hyperlipidemia			
Yes	25 (16.3)	107 (12.2)	0.15[b]
No	128 (83.7)	769 (87.8)	
Parental chronic lung disease			
Yes	45 (29.4)	185 (21.1)	**0.02[b]**
No	108 (70.6)	691 (78.9)	
Child's EDI score			
Physical Health and Well-being			
Mean (SD)	8.7 (1.4)	8.7 (1.3)	0.88[c]
Vulnerable Yes	21 (13.7)	101 (11.5)	0.41[b]
No	132 (86.3)	775 (88.5)	
Social Competence			
Mean (SD)	8.5 (1.7)	8.2 (1.9)	0.07[c]
Vulnerable Yes	11 (7.2)	111 (12.7)	0.06[b]
No	142 (92.8)	765 (87.3)	
Emotional Maturity			
Mean (SD)	7.9 (1.6)	7.8 (1.6)	0.41[c]
Vulnerable Yes	21 (13.7)	116 (13.4)	0.83[b]
No	132 (86.3)	760 (86.8)	
Language and Cognition			
Mean (SD)	8.6 (1.7)	8.1 (2.0)	**<0.001[c]**
Vulnerable Yes	12 (7.8)	102 (11.6)	0.16[b]
No	141 (92.2)	774 (88.4)	
Communication and General Knowledge			
Mean (SD)	8.1 (2.4)	7.4 (2.7)	**0.003[c]**
Vulnerable Yes	13 (8.5)	115 (13.1)	0.11[b]
No	140 (91.5)	761 (86.9)	

[a] Paired t-test

[b] Conditional logistic regression

[c] Wilcoxon Signed Rank Test

SD – Standard deviation

The clinical characteristics of the MS parents are shown in **Table 3.2**. The median age at MS

onset was 29.4 years and 85% of MS parents were women. The median disease duration at the time of EDI completion was 6 years (range, <1 to 25 years), and over half of the parents had received disease-modifying medication.

Table 3.2. Characteristics of the cohort with multiple sclerosis (MS), Manitoba, Canada

Characteristics	MS Parent No. (%)
Sex of the MS parent	
Male	23 (15.0)
Female	130 (85.0)
Ever on MS disease-modifying treatments	
Yes*	78 (51.0)
No	75 (49.0)
Age of parent at MS onset	
<20 years	10 (6.5)
20-29 years	73 (47.7)
30-39 years	65 (42.5)
≥40 years	5 (3.3)
Median [range]	29.4 [10.3 - 43.8]
Parental MS disease duration at the time of the EDI	
<3	37 (24.2)
3 - <6 Years	35 (22.9)
6 - <12 Years	44 (28.8)
≥12 Years	37 (24.2)
Median [range]	6.4 [<1.0 - 24.5]
Child's duration of exposure to MS parent at the time of the EDI	
<3 Years	37 (24.2)
3 - <5 Years	26 (17.0)
≥5 Years	90 (58.8)
Median [range]	5.3 [<1.0 - 6.1]
Parental MS onset after child's birth	
Yes	90 (58.8)
No	63 (41.2)

*n=13 (16.7%) were exposed to glatiramer acetate and n= 65 (83.3%) to a beta-interferon.
EDI refers to the Early Development Instrument

In univariate analyses (**Table 3.1**), significant differences were noted in mean EDI scores for language and cognition and communication and general knowledge, with children of MS parents receiving higher scores. However, there was no statistically significant difference in vulnerability on EDI domains between children in the index group and the matched reference cohort.

Findings from the multivariable conditional logistic regression analyses were similar (**Table 3.3**). Factors significantly associated with vulnerability in children of MS and non-MS parents across three or more domains included: presence of parental mental morbidity (vs. absence), low socioeconomic status (vs. highest socioeconomic status) and three or more siblings (vs. none). In the adjusted model, younger age of the child at completion of the EDI (years) was associated with vulnerability on the social competence domain. Maternal age at the time of birth was not associated with vulnerability on the EDI. Tests for multiplicative interaction between parental MS and mental morbidity were not statistically significant for any of the EDI domains (data not shown). Multiple linear regression analyses with EDI domain scores represented as continuous values revealed similar associations between parental MS and EDI (data not shown).

Analyses within the MS cohort (n=153 children and 153 parents) showed that the duration of the child's exposure to parental MS was associated with vulnerability on the physical health and well-being domain of the EDI (aOR, 1.49, 95% CI 1.03-2.15, p value 0.03, **Table 3.4**). Although the duration of the child's exposure to parental MS was not significantly associated with the other four EDI domains, all these associations showed a non-significant increased risk of vulnerability with each additional year of exposure to parental MS. There was also no

significant association between the parent's absolute disease duration and vulnerability on the EDI. However, children with an MS parent who also had a mental comorbidity had a 3-fold greater odds of vulnerability on the emotional maturity domain compared with MS parents without a mental health condition (aOR 3.03, 95% CI 1.03-8.94) and a 5-fold greater odds of vulnerability on the social competence domain (aOR 5.73, 95% CI 1.11-29.6).

Table 3.3. Unadjusted and adjusted odds ratios (95% confidence intervals) showing the effect of parental multiple sclerosis (MS) and other factors on vulnerability within the five Early Development Instrument (EDI) domains, Manitoba, Canada

Factor	Unadjusted*			Adjusted †		
	OR	(95% CI)	p value	OR	(95% CI)	p value
Presence of parental multiple sclerosis (vs. absence)						
Physical Health and Well-being	1.24	(0.75 - 2.05)	0.41	1.59	(0.89 - 2.83)	0.12
Social Competence	0.53	(0.28 - 1.02)	0.06	0.51	(0.25 - 1.06)	0.06
Emotional Maturity	1.06	(0.63 - 1.76)	0.83	0.96	(0.55 - 1.67)	0.89
Language and Cognition	0.64	(0.34 - 1.20)	0.16	0.91	(0.46 - 1.83)	0.80
Communication and General Knowledge	0.61	(0.34 - 1.12)	0.11	0.69	(0.37 - 1.31)	0.26
Parental mental morbidity (vs. absence of mental morbidity)						
Physical Health and Well-being	2.41	(1.57 - 3.69)	**<.001**	1.93	(1.22 - 3.06)	**0.005**
Social Competence	1.92	(1.25 - 2.95)	**0.003**	1.94	(1.21 - 3.11)	**0.01**
Emotional Maturity	1.94	(1.28 - 2.92)	**0.002**	1.74	(1.13 - 2.66)	**0.01**
Language and Cognition	1.10	(0.70 - 1.72)	0.68	0.90	(0.54 - 1.47)	0.66
Communication and General Knowledge	0.68	(0.44 - 1.06)	0.09	0.60	(0.38 - 0.96)	**0.03**
Socioeconomic Status (SES)						
Lowest SES (vs. Highest SES)						
Physical Health and Well-being	3.17	(1.94 - 5.20)	**<.001**	3.13	(1.73 - 5.69)	**<.001**
Social Competence	2.49	(1.54 - 4.02)	**<.001**	2.40	(1.37 - 4.20)	**0.002**
Emotional Maturity	1.38	(0.87 - 2.17)	0.17	1.35	(0.80 - 2.29)	0.26
Language and Cognition	4.37	(2.58 - 7.42)	**<.001**	3.96	(2.18 - 7.20)	**<.001**
Communication and General Knowledge	1.67	(1.03 - 2.69)	**0.04**	1.68	(0.97 - 2.91)	0.06
Middle SES (vs. Highest SES)						
Physical Health and Well-being	0.64	(0.34 - 1.19)	0.16	0.66	(0.35 - 1.24)	0.19
Social Competence	0.49	(0.25 - 0.95)	**0.03**	0.56	(0.29 - 1.10)	0.09

Table 3.3. Unadjusted and adjusted odds ratios (95% confidence intervals) showing the effect of parental multiple sclerosis (MS) and other factors on vulnerability within the five Early Development Instrument (EDI) domains, Manitoba, Canada

Factor	Unadjusted*			Adjusted †		
	OR	(95% CI)	p value	OR	(95% CI)	p value
Emotional Maturity	0.64	(0.37 - 1.10)	0.10	0.67	(0.38 - 1.16)	0.15
Language and Cognition	0.77	(0.40 - 1.49)	0.44	0.75	(0.39 - 1.47)	0.41
Communication and General Knowledge	0.82	(0.48 - 1.40)	0.46	0.73	(0.42 - 1.27)	0.27
Child's age at EDI completion (years)						
Physical Health and Well-being	0.63	(0.34 - 1.14)	0.12	0.70	(0.37 - 1.32)	0.27
Social Competence	0.48	(0.27 - 0.86)	**0.01**	0.51	(0.28 - 0.93)	**0.03**
Emotional Maturity	1.05	(0.59 - 1.86)	0.87	1.11	(0.62 - 2.00)	0.72
Language and Cognition	0.44	(0.24 - 0.82)	**0.001**	0.53	(0.27 - 1.01)	0.05
Communication and General Knowledge	1.05	(0.60 - 1.85)	0.86	1.16	(0.64 - 2.08)	0.62
Maternal age††						
Physical Health and Well-being	0.97	(0.94 - 1.01)	0.13	1.01	(0.82 - 1.24)	0.95
Social Competence	0.98	(0.94 - 1.02)	0.28	1.10	(0.88 - 1.37)	0.41
Emotional Maturity	1.02	(0.98 - 1.06)	0.33	1.16	(0.95 - 1.42)	0.14
Language and Cognition	0.96	(0.92 - 0.99)	**0.03**	1.00	(0.80 - 1.25)	0.98
Communication and General Knowledge	1.00	(0.97 - 1.04)	0.96	1.12	(0.91 - 1.38)	0.27
Siblings						
One Sibling (vs. none)						
Physical Health and Well-being	0.80	(0.43 - 1.48)	0.47	1.20	(0.61 - 2.37)	0.60
Social Competence	0.99	(0.54 - 1.83)	0.98	1.33	(0.69 - 2.55)	0.40
Emotional Maturity	0.83	(0.46 - 1.48)	0.53	0.90	(0.49 - 1.66)	0.73
Language and Cognition	1.00	(0.53 - 1.91)	0.99	1.44	(0.71 - 2.94)	0.32
Communication and General Knowledge	1.33	(0.68 - 2.57)	0.40	1.50	(0.76 - 2.98)	0.25
Two Siblings (vs. none)						
Physical Health and Well-being	1.43	(0.73 - 2.77)	0.30	1.81	(0.89 - 3.70)	0.10
Social Competence	1.08	(0.55 - 2.11)	0.83	1.14	(0.55 - 2.35)	0.72
Emotional Maturity	0.84	(0.44 - 1.60)	0.60	0.91	(0.47 - 1.76)	0.77
Language and Cognition	0.99	(0.48 - 2.06)	0.98	1.29	(0.59 - 2.84)	0.53
Communication and General Knowledge	1.56	(0.76 - 3.20)	0.23	1.77	(0.85 - 3.68)	0.13
Three or More Siblings (vs. none)						
Physical Health and Well-being	2.39	(1.18 - 4.86)	**0.02**	2.34	(1.10 - 4.96)	**0.03**
Social Competence	2.66	(1.29 - 5.48)	**0.01**	2.50	(1.15 - 5.45)	**0.02**
Emotional Maturity	1.75	(0.87 - 3.51)	0.12	1.64	(0.80 - 3.37)	0.18
Language and Cognition	3.43	(1.64 - 7.17)	**0.001**	3.65	(1.63 - 8.15)	**0.002**

Table 3.3. Unadjusted and adjusted odds ratios (95% confidence intervals) showing the effect of parental multiple sclerosis (MS) and other factors on vulnerability within the five Early Development Instrument (EDI) domains, Manitoba, Canada

Factor	Unadjusted*			Adjusted †		
	OR	(95% CI)	p value	OR	(95% CI)	p value
Communication and General Knowledge	4.17	(1.97 - 8.84)	**<.001**	4.16	(1.95 - 8.86)	**<.001**

*Unadjusted conditional logistic regression models; children in the index and reference groups were matched on, health authority, and year of EDI data collection

†Adjusted conditional logistic regression models based on matching factors plus SES (Lowest, Middle vs. Highest), age at EDI (years), maternal age (per 5 years), parental mental health morbidity (vs. absence), and siblings (1,2,3 or more vs. none).

†† Odds ratios express the change in EDI vulnerability per 5-year increase in maternal age.

Table 3.4. Adjusted odds ratios (95% confidence intervals) showing the effect of parental characteristics on vulnerability in the five Early Development Instrument (EDI) domains, multiple sclerosis (MS) cohort of 153 parents and 153 children, Manitoba, Canada

Factors	Adjusted		
	OR (95% CI)		p value
Number of years the child was exposed to parental MS (years)[a]			
Physical Health and Well-being	1.49	(1.03 - 2.15)	**0.03**
Social Competence	1.22	(0.79 - 1.91)	0.37
Emotional Maturity	1.17	(0.87 - 1.57)	0.31
Language and Cognition	1.25	(0.82 - 1.92)	0.31
Communication Skills and General Knowledge	1.13	(0.81 - 1.59)	0.48
Parental disease duration (years)[b]			
Physical Health and Well-being	1.05	(0.98 - 1.14)	0.17
Social Competence	0.98	(0.88 - 1.09)	0.69
Emotional Maturity	1.00	(0.92 - 1.08)	0.92
Language and Cognition	1.01	(0.91 - 1.11)	0.88
Communication Skills and General Knowledge	1.00	(0.91 - 1.10)	0.99
Parental mental morbidity (vs. absence of mental morbidity) [c]			
Physical Health and Well-being	1.75	(0.60 - 5.09)	0.30
Social Competence	5.73	(1.11 - 29.6)	**0.04**
Emotional Maturity	3.03	(1.03 - 8.94)	**0.04**
Language and Cognition	1.76	(0.49 - 6.30)	0.38
Communication Skills and General Knowledge	1.73	(0.50 - 5.98)	0.39

Logistic regression models adjusted for: child's sex (male vs. female), age of the child at EDI (years), and: **a.** parental mental health morbidity (vs. absence), SES (low, middle vs. high), siblings (1,2,3 or more vs. none); **b**: parental mental health morbidity (vs. absence); **c.** child's exposure to parental MS (years), SES (lowest, middle vs. high), siblings (1,2,3 or more vs. none)

3.5 Discussion

Our population-based investigation of the association between parental MS and early childhood development at the kindergarten stage showed no statistically significant associations between parental MS and child vulnerability on any domain of developmental health, as measured by the EDI. However, there was a significant association between the duration of the child's exposure to parental MS and vulnerability on the physical health and well-being domain of the EDI. Although the relationships between parental MS and the remaining four EDI domains were not statistically significant, all associations showed an increased risk of vulnerability. In addition, the presence of mental health morbidity in the parent adversely influenced children's developmental health. Even though the effect of mental health morbidity on developmental vulnerability in any EDI domain was not different among children of MS parents vs. the children of MS unaffected parents, the substantially higher rate of mental health morbidity among MS parents was striking (49.7% vs. 35.3%). Children whose parent had both MS and a mental health condition (vs. MS, but no mental health comorbidity) were at an increased risk of vulnerability on emotional maturity and social competence domains of the EDI.

Our study findings highlight the complex nature of the relationship between parental MS and childhood developmental health, and may help explain some of the discordant findings in the literature. Previous studies have shown that mother-daughter interactions during work and play tasks were perceived as similar, irrespective of whether the mother did or did not have MS.[31] Similarly, other studies have shown that children with an MS affected parent did not appear to differ from the community norms in terms of behavioural and externalizing

problems.[24,45] However, these studies also showed that parents with MS were more likely to report that their children had psychological problems.[24,45] Reliance on parental perception, and other study limitations including the lack of an appropriate comparison group and failure to adjust for important confounders are other potential explanations for some of the contradictory findings with regard to parental MS and developmental health in children.[26,100]

Our finding that a child's duration of exposure to parental MS was not associated with adverse developmental health, except for the significant association with physical health and well-being, is not consistent with previous studies that have reported negative psychosocial behaviour among children of MS parents.[100] Studies have reported a greater risk of depression, anxiety, somatization, difficulty in relating to others and greater emotional and behavioural problems in children of MS parents.[23,45,46,72,75] It is possible that children of MS parents have relatively normal developmental trajectories in early childhood, but that the stress of parental MS manifests with vulnerability on the physical health dimension first.[68] Furthermore, the physical well-being domain of the EDI also captures children's physical readiness for school, such as being dressed inappropriately, coming to school late, and being hungry, or tired. Consequently, children of parents with longer disease duration, who experience physical constraints in planning and preparing for a school day, are likely to perform poorly on the physical well-being domain of the EDI. Our study was restricted to early childhood development and I cannot rule out effects in later childhood and adolescence.

The negative impact of parental mental health morbidity on childhood development observed in our study is consistent with findings from previous work demonstrating an association between depression in a parent with MS and poor social adjustment in children.[23,72] The

broader literature on the impact of parental mental health on child health suggests that it is these co-occurring daily problems and stressors, such as children's exposure to parental anxiety and depression that are often the determinants of children's subsequent mental health.[99]

The strengths of our study included the ability to access comprehensive health and education-related databases at the population level, and the use of previously validated case definitions for both MS and other morbidity. Together, this allowed for a population-based cohort study, with an MS cohort matched to an appropriate comparison cohort. However, I was only able to identify morbidity among subjects who had contact with the health care system. Also, since it was difficult to distinguish between depression and anxiety disorders within our data sources,[115] the presence of either (or both) diagnoses was considered a 'mental health morbidity.'[115] I also lacked information regarding the severity of parental MS but used disease duration as a proxy for disease severity given the association between increasing disability with increasing disease duration. Other strengths of our study included the use of EDI to assess early childhood development, and the adjustment for potential confounders. The EDI has undergone significant psychometric testing to confirm validity and reliability as a research tool[34,103] and has been shown to be correlate with later literacy achievements,[118] and psychological assessments.[119] Nonetheless, there may be some individual differences in teachers' ability to evaluate developmental health on the EDI.[108] Although I attempted to control for a broad range of confounders, unmeasured and residual confounding may have occurred due to factors not available in our data sources or imprecise measurement of factors such as socioeconomic status.

In summary, our study showed that the presence of parental MS was not independently associated with adverse developmental health in kindergarten-level children. However, children whose parents also suffered from mental health morbidity and those who were exposed to parental MS for a longer period were at higher risk for developmental vulnerability. While other longitudinal studies are needed to confirm our findings, health professionals need to be aware of the effects of mental health morbidity commonly associated with MS, and their impact on early child development. Mental illness such as anxiety and depression among MS parents should suggest the need for appropriate support for children (and their families) who are potentially at risk for poor developmental health.

Chapter 4: Relationship between parental multiple sclerosis and child development: The British Columbia study[3]

4.1 Synopsis

Objective: Exposure to parental chronic illness is associated with adverse developmental health. I examined the association between parental multiple sclerosis (MS) and parental MS-related clinical factors on developmental health in children.

Methods: I carried out a population-based cohort study in British Columbia, Canada, comparing developmental health among children of parents with MS and children of unaffected parents. Parents with MS were identified through hospital, physician and prescription drug claims information in linked health databases. The outcome was childhood development at 5 years of age, expressed as vulnerability on the Early Development Instrument (EDI). Adjusted odds ratios (aOR) and 95% confidence intervals (CI) were estimated using conditional logistic regression (which accounted for the matching by year of birth, parent's sex and school district).

Results: MS affected parents (n=783) were older, more likely to be English speakers and had higher rates of mental health morbidity (39.6% vs. 22.2%, $p<0.001$) than unaffected parents (n=2,988). In the adjusted models, children of mothers with MS (aOR 0.62, 95% CI 0.44-0.87), but not children of the fathers with MS (aOR 1.15, 95% CI 0.75-1.78), had a lower risk of vulnerability on the social development domain of the EDI (p value for interaction 0.01). However, mental health morbidity (aOR 1.62, 95% CI 1.05-2.50) and physical morbidity

[3] A version of this chapter is submitted for publication as Razaz N, Joseph KS, Boyce WT, Guhn M, Forer B, Carruthers R, Marrie RA, Tremlett H. Relationship between parental multiple sclerosis and childhood developmental health.

(aOR 1.67, 95% CI 1.05-2.64) among mothers with MS were associated with vulnerability on the EDI.

Conclusion: Maternal MS, but not paternal MS, is associated with lower rates of developmental vulnerability on the social development domain. Children of MS affected mothers with mental and physical comorbidity had higher rates of developmental vulnerability.

4.2 Background and objectives

Chapter 4 builds on the work in Chapter 3 and replicates the Manitoba study by using a relatively larger study sample in British Columbia to examine the effect of parental MS and other factors on developmental vulnerability. The larger study size provided the opportunity to carry out detailed analyses exploring the effects of several risk factors not examined in the Manitoba study including the level of MS-related parental disability, and gender of the affected parent.

Although the relevant literature is sparse, some studies have suggested that children of parents with MS display higher rates of adjustment difficulties, particularly anxiety disorders and behavioural disturbances.[26,100] Comorbidity is relatively common in MS with over one-third reporting at least one physical comorbidity, and approximately 50% of MS patients suffering from depression and anxiety disorders.[37] Overall, parental mental illness is an important predictor of child adjustment and has been associated with a detrimental effect on children's emotional development.[120,121] As MS disease course changes over time and disability progresses, the family may experience more conflict and less cohesion, with parents sometimes paying less attention to the child's needs.[45]

Few studies have examined the association between parental MS and MS-related clinical characteristics and children's developmental health. I therefore carried out a population-based cohort study to investigate the association between parental MS and MS-related clinical factors (such as the presence of mental and physical comorbidity, disability level and disease duration) on the child's developmental health.

4.3 Methods

I carried out a longitudinal study in British Columbia, Canada, comparing developmental health among children of parents with MS and children of unaffected parents. Information on study subjects was obtained from several population-based linked health and education databases. The publicly funded provincial health care program in British Columbia covers all residents and a lifelong unique personal health care number is assigned to each individual. Health information maintained in various databases can be linked through this unique identification number. Anonymized linked data used for this study included information from the Medical Services Plan[56] database that contained fee-for-service physician billing claims; the Discharge Abstract Database[57] comprised of hospital discharge records; the PharmaNet[59] database, which contained information on prescription drugs; Census GeoData files which provided family level socioeconomic status data expressed as average neighbourhood income quintiles (obtained from Statistics Canada using postal codes); the Consolidation File which provided demographic information on study subjects and confirmed residency in the province; the Vital Statistics birth[60] database, which contained information on all births in the province; and Early Development Instrument (EDI)[34] data, which provided information on early childhood developmental health on the study children, were accessed through linkage with the Human Early Learning Partnership.[61] MS-related clinical information (i.e. disease course and

disability level) was obtained for a sub-set of individuals via linkage with the British Columbia MS database.[122]

Parents with MS were identified using a validated algorithm as those with ≥3 records for a relevant hospital or physician claim between April 1, 1985 and December 31, 2011 or a relevant prescription claim after April 1, 1996 (Supplementary Table A.3).[105] Using the birth registry and the Consolidation File databases, individuals with MS were linked to their offspring. All persons with MS who had a child born between January 1st, 1994 and December 31st, 2006, with EDI data were included in the study cohort. These birth dates allowed each child to have reached his/her fifth birthday between 1999 and 2011 and to have been part of the EDI data collection. The onset date of MS was based on the first date for MS or a demyelinating condition identified in any hospital, physician or prescription claim (Supplementary Table A.3). Up to 4 children with parents who were not known to have MS or any demyelinating condition, selected from the population of British Columbia, matched on year of birth and school district, formed the comparison group. The MS affected parent was also matched by sex to a parent in the reference cohort. Matches for parental sex could not be obtained in 4% of instances and the next available parent in the database was selected in such cases. Children, both of whose parents had MS, were excluded from the study.

The primary outcome of interest was childhood development, as measured by the EDI. The EDI has been routinely administered province-wide every one to three years since the 1999/2000 school year, achieving at least 85% participation of kindergarten children from each school district in the province. Teachers completed the EDI for each child in their kindergarten class (age range 5-7 years) in February. The EDI consists of 104 binary and

three-category items designed to tap five core areas of early childhood development:[34,106] physical health and well-being; social competence; emotional maturity; language and cognitive development; and communication skills and general knowledge (Supplementary Table A.4).[34] The EDI domain scores of children are highly skewed and are not amenable to simple transformation. Hence, children's scores on each of the EDI were categorised as 'developmentally vulnerable' if their scores fell below the 10th percentile value[107] based on the national EDI cut-off scores for each of the five domains.[108] Developmentally vulnerability on any domain of the EDI should be interpreted to imply that the child demonstrated a lower than a normative ability (<10th centile) in the competencies measured in that domain.[123]

The main determinant of interest was the presence (vs. absence) of parental MS. Other variables of interest included the child's sex, child's first language at home (English vs. other), age of the child at the time of the EDI assessment (in years), and socioeconomic status. Parental characteristics of interest were parental age at the time of child's birth, sex and comorbidity. I studied all comorbidities affecting ≥5% of the overall MS population.[114,124] Parental comorbid conditions examined included mental health disorders (either depression or anxiety disorder)[37] and physical morbidity (i.e., presence of diabetes mellitus, hypertension, hyperlipidemia or chronic lung disease)[116] before the EDI data collection. All comorbidities were identified using previously validated algorithms based on hospital, physician visit and prescription information (Supplementary Table A.5).[37,116]

Conditional logistic regression was used to compare the characteristics of the parent-child dyads in the MS and matched reference cohorts. Multivariable conditional logistic regression models were used to determine the association between parental MS and vulnerability on one

or more domains as well as on each domain of the EDI separately, adjusted for potential confounders. Generalised estimating equations, with an assumed unstructured correlation framework, were used to adjust the variance as some parents had more than one child in the cohort. Confounders were included in the final models based on the literature[107,117] or statistical significance (p value <0.1). The full model included age of the child at the time of EDI completion (continuous), child's sex (female vs. male), and average neighbourhood income quintiles as proxy for family-level socioeconomic status (expressed as quintiles), parental age (continuous), parental mental morbidity (present vs. absent), parental physical morbidity (present vs. absent) and parental sex (male vs. female). Interactions between parental MS and confounders were examined and stratified results were presented when an interaction was present.

The association between MS-related clinical factors on the child's developmental health was examined within the MS cohort. Analyses restricted to the MS cohort included an assessment of the impact of parental mental comorbidity (present vs. absent); parental physical morbidity (present vs. absent); the duration of parental MS (i.e. time from onset of MS to the child's EDI assessment); and disability level (as measured by the Expanded Disability Status Scale [EDSS] score)[76] at the time of EDI data collection (±3 years). MS disease duration was categorised as: <5, 5 to <10 and ≥10 years. MS disability was dichotomized <4.0 vs. ≥4.0 on the EDSS (an EDSS of ≥4 signifies moderate or severe disability).

Results were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Regression model fit was assessed using the likelihood ratio test, and a two-sided p value <0.05 was used to determine statistical significance. Analyses were performed using SAS Version 9.2 (SAS

Institute Inc., Cary, NC). The University of British Columbia's Clinical Research Ethics Board approved the study.

4.4 Results

After applying the exclusion criteria, the final study population consisted of 783 children with an MS parent and 2,988 parent-child dyad in the matched reference cohort (**Figure 4.1).** The children of parents with and without MS were similar in terms of sex, age and socioeconomic status at the time of EDI data collection (**Table 4.1**). Parents affected by MS were on average 1.5 years older, and were more likely to be English speakers. The frequency of physical morbidity was similar among parents with and without MS, although mental health morbidity affected considerably more parents with MS compared with non-MS parents (39.6% vs 22.2%, p value<0.001).

The disease characteristics of the MS parents are shown in **Table 4.2**. The median age at onset of MS was 31 years and 35% of the parents were ever on MS disease-modifying medication. The median disease duration at the time of EDI completion was 5.4 years (range, <1 to 26 years). Of the 280 (36%) MS parents for whom an EDSS score was available, most (81%) had minor neurological findings, while 19% had moderate or severe disability.

The presence of vulnerability within each of the EDI domains by parental MS is shown in **Figure 4.2**. Overall 29% (1086/3771) of children were vulnerable on one or more domains of the EDI, with physical and social domains having the highest rates of vulnerability at 15% (547/3771) and 12% (452/3771), respectively. The rates of vulnerability were lower for

children of parents with MS on all domains of the EDI compared with the matched reference cohort although these differences were not statistically significant.

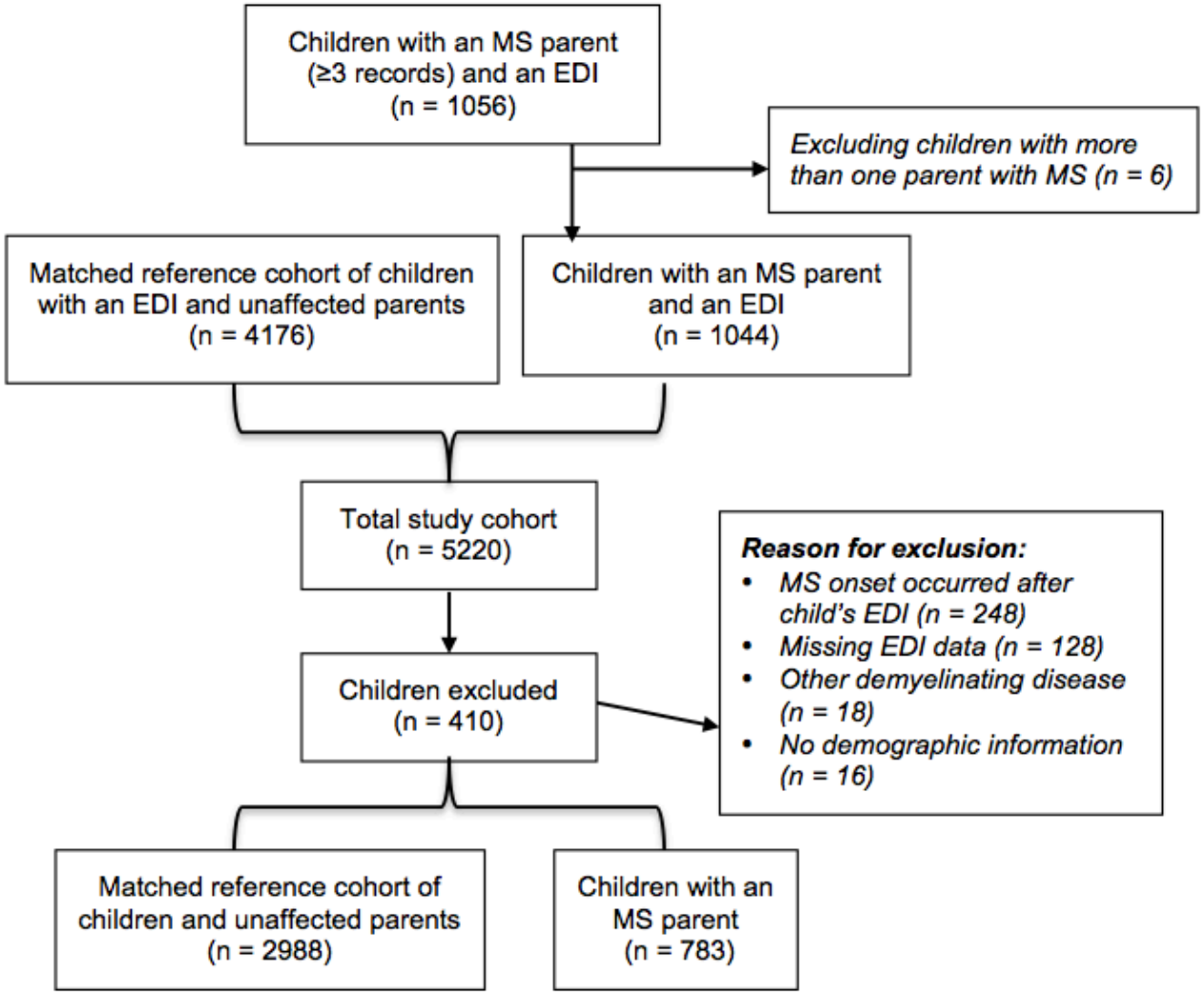


Figure 4.1. Schematic depiction of the cohort selection process

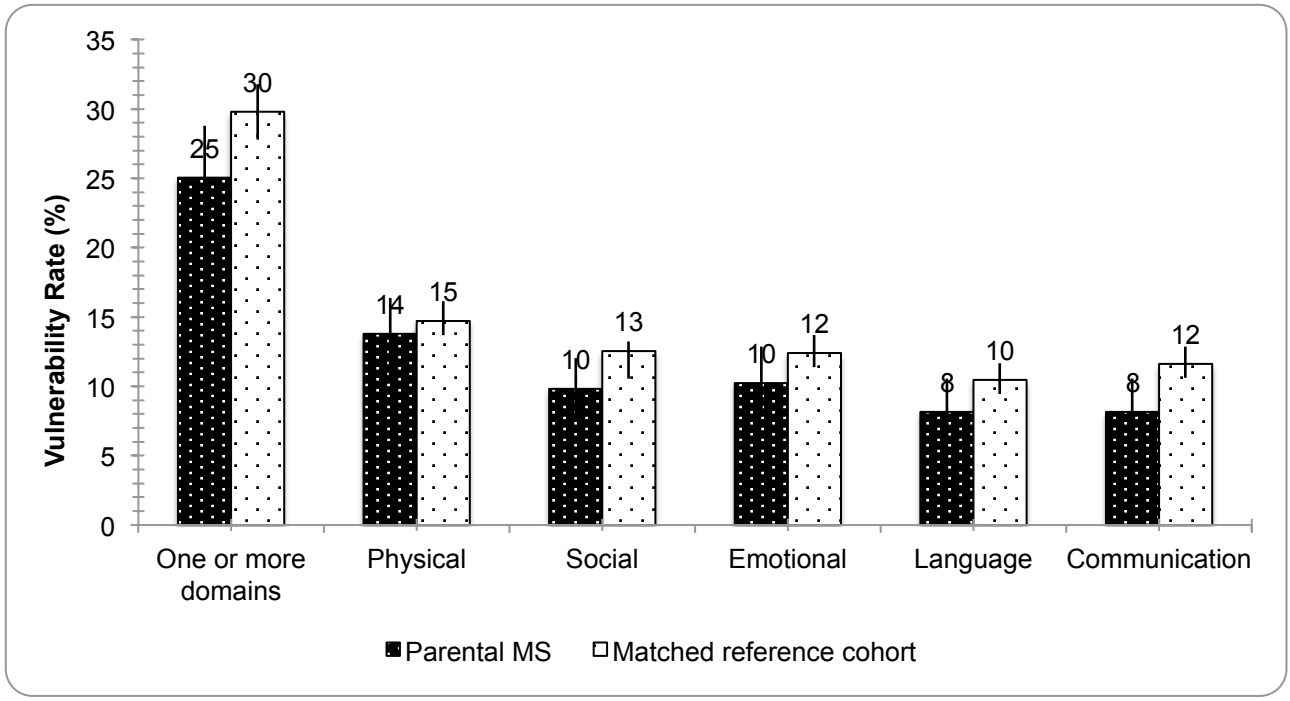


Figure 4.2. Rates of children's vulnerability (%) within each Early Development Instrument (EDI) domain by parental multiple sclerosis (MS) status, British Columbia, Canada.
Error bars represent 95% confidence intervals

The unadjusted analysis (**Table 4.3**) showed that children of parents with MS had lower odds of vulnerability on one or more domains of the EDI compared with children in the matched reference cohort (OR 0.79, 95% CI 0.66-0.95). Greater odds of vulnerability on one or more domains of the EDI was observed among boys, children who were younger at completion of the EDI, children who were in the lower income quintiles (vs. highest), and those whose parents had a mental or physical morbidity (**Table 4.3**).

In the adjusted model (**Table 4.3**), parental sex modified the relationship between parental MS and vulnerability on the EDI (p value for interaction 0.05). In analyses stratified by parental sex, the odds of vulnerability on one or more domains of the EDI was significantly lower among children of mothers with MS compared with the children of mothers without MS

(adjusted odds ratio [aOR] 0.75, 95% CI 0.60-0.95). Paternal MS did not show this association (aOR 1.07, 95% CI 0.77−1.48).

Analyses examining the association between parental MS and each domain of the EDI demonstrated that parental MS was associated with significantly lower odds of vulnerability on the social competence domain of the EDI (**Table 4.3**). Parental MS was not significantly associated with vulnerability on any of the other four EDI domains (**Table 4.4**). Parental sex modified the relationship between parental MS and vulnerability on the social domain (p value for interaction 0.01). The odds of vulnerability on the social competence domain was 38% lower among children of mothers with MS compared with the children of mothers without MS (aOR 0.62, 95% CI 0.44-0.87; Table 4.3). Paternal MS did not show the same association (aOR 1.15, 95% CI 0.75−1.78).

Table 4.1. Characteristics of the children of parents with and without multiple sclerosis (MS), British Columbia, Canada

Characteristics	**Parent with multiple sclerosis (n =783)**		**Matched reference cohort (n = 2,988)**		**p value***
	No.	% /(SD)	No.	% /(SD)	
Sex of the child: Female	403	51.5	1450	48.53	0.13
Male	380	48.5	1538	51.47	
Child's age at EDI collection in years Mean (SD)	5.6	0.3	5.7	0.3	0.17
Child's first language: English	711	90.8	2386	79.9	**<0.001**
Other	72	9.2	602	20.2	
Sex of the parent: Female	543	69.4	2211	74.0	**<0.001**
Male	240	30.7	777	26.0	
Parental age at the time of birth Mean (SD)	32.3	5.5	30.8	6.0	
<25 years	61	7.8	499	16.7	
25-29	204	26.1	822	27.5	**<0.001**
30-34	280	35.8	961	32.2	
≥35	238	30.4	706	23.6	
Socioeconomic status					
5th quintile [Highest]	154	19.7	610	20.4	0.13
4th quintile	180	23.0	656	22.0	

Table 4.1. Characteristics of the children of parents with and without multiple sclerosis (MS), British Columbia, Canada

Characteristics	Parent with multiple sclerosis (n =783)		Matched reference cohort (n = 2,988)		p value*
	No.	% /(SD)	No.	% /(SD)	
3rd quintile	182	23.2	604	20.2	
2nd quintile	151	19.3	575	19.3	
1st quintile [Lowest]	116	14.8	543	18.2	
Parental mental health morbidity: No	473	60.4	2326	77.8	**<0.001**
Parental mental health morbidity: Yes	310	39.6	662	22.2	
Depressive disorders †	230	29.4	646	15.5	
Anxiety disorders †	159	20.3	356	11.9	
Parental physical morbidity: No	573	73.2	2234	74.8	
Parental physical morbidity: Yes	210	26.8	754	25.2	0.35
Chronic lung disease †	132	16.9	464	15.5	
Hypertension †	63	8.1	187	6.3	
Hyperlipidemia †	27	3.5	105	3.5	
Diabetes mellitus †	23	2.9	128	4.3	

* From conditional logistic regression that accounted for matching at the design stage.
† Denominator is all individuals within each cohort
SD denotes standard deviation

Table 4.2. Characteristics of the cohort with multiple sclerosis (MS; n=783 parents), British Columbia, Canada

Characteristics	MS Parent No. (%)
Ever on MS disease-modifying treatments	
Yes*	272 (34.7)
No	511 (65.3)
Age of parent at MS onset	
<20 years	23 (3.0)
20-29 years	314 (40.1)
30-39 years	384 (49.0)
≥40 years	62 (7.9)
Median [range]	31.1 [11.7 - 54.1]
Parental MS disease duration at the time of the EDI assessment	
<5 years	358 (45.7)
5-9 years	224 (28.6)
≥10 years	201 (25.7)
Median [range]	5.4 [<1.0 - 25.6]
Child Exposure to MS parent at the time of the EDI assessment	
0- <2 years (Infancy)	150 (19.2)
2-4 years (Toddlerhood)	208 (26.5)

Table 4.2. Characteristics of the cohort with multiple sclerosis (MS; n=783 parents), British Columbia, Canada

Characteristics	MS Parent No. (%)
≥5 years (Preschooler)	425 (54.3)
Median [range]	5.2 [<1.0 - 6.4]
Parental MS onset occurred after the child was born	
Yes	406 (51.8)
No	377 (48.2)
Disease course	
No. †	403
Relapsing-remitting	381 (94.5)
Primary progressive	22 (5.5)
EDSS Score	
No. †	280
≤3.5	228 (81.4)
≥4	52 (18.5)
Median [range]	2.0 [0 - 9.5]

*n=64 (23.5%) were exposed to glatiramer acetate and n= 208 (76.5%) to a beta-interferon

† EDSS denotes Expanded Disability Status Scale. EDSS data was available on a subset of MS parents

Table 4.3. Unadjusted and adjusted odds ratios and 95% confidence intervals showing the association between parental multiple sclerosis (MS) and the child's vulnerability on the Early Development Instrument (EDI), British Columbia, Canada

	Vulnerability on one or more domains of the EDI			
	Odds Ratio (95% Confidence Interval)			
Factors	**Unadjusted §**	**Adjusted †**	**Mothers †**	**Fathers †**
Parental multiple sclerosis (vs. absence)	0.79 (0.66−0.95)*	0.75 (0.60−0.94)*	0.75 (0.60−0.95)*	1.07 (0.77−1.48)
Sex of the child: female (vs. male)	0.44 (0.38−0.50)*	0.42 (0.36−0.49)*	0.43 (0.36−0.51)*	0.40 (0.3−0.53)*
Child's age at EDI completion (years)	0.57 (0.44−0.74)*	0.57 (0.44−0.74)*	0.56 (0.42−0.76)*	0.58 (0.35−0.97)*
Socioeconomic Status (vs. 5th quintile)	1.00 (-)	1.00 (-)	1.00 (-)	1.00 (-)
4th	1.36 (1.08−1.72)*	1.31 (1.03−1.67)*	1.17 (0.88−1.55)	1.81 (1.13−2.89)*
3rd	1.67 (1.33−2.11)*	1.57 (1.23−2.00)*	1.53 (1.15−2.04)*	1.72 (1.07−2.76)*
2nd	1.76 (1.39−2.23)*	1.57 (1.22−2.01)*	1.57 (1.18−2.10)*	1.59 (0.97−2.58)
1st [most disadvantaged]	2.39 (1.89−3.03)*	2.11 (1.65−2.70)*	2.09 (1.57−2.79)*	2.20 (1.37−3.54)*
Child's first language (English vs. other)	0.59 (0.49−0.70)*	0.63 (0.52−0.75)*	0.61 (0.49−0.76)*	0.68 (0.48−0.96)*
Sex of the parent: father (vs. mother)	1.00 (0.85−1.17)	1.04 (0.86−1.27)		
Parental age at the time of child's birth (years)	0.97 (0.96−0.98)*	0.97 (0.96−0.98)*	0.97 (0.96−0.99)*	0.97 (0.95−0.99)*
Parental mental morbidity (vs. absence)	1.18 (1.01−1.38)*	1.24 (1.05−1.47)*	1.28 (1.05−1.55)*	1.15 (0.78−1.68)
Parental physical morbidity (vs. absence)	1.27 (1.09−1.49)*	1.27 (1.07−1.50)*	1.27 (1.04−1.54)*	1.27 (0.91−1.75)
Parental MS x Sex of parent		1.44 (0.97−2.14)		

	Social Competence Domain			
Factors	**Unadjusted §**	**Adjusted †**	**Mothers †**	**Fathers †**
Parental multiple sclerosis (vs. absence)	0.76 (0.59−0.98)*	0.61 (0.43−0.86)*	0.62 (0.44−0.87)*	1.15 (0.75−1.78)
Sex of the child: female (vs. male)	0.37 (0.30−0.45)*	0.36 (0.29−0.45)*	0.30 (0.24−0.40)*	0.54 (0.36−0.79)*
Child's age at EDI completion (years)	0.89 (0.63−1.26)	0.86 (0.61−1.23)	0.86 (0.58−1.30)	0.77 (0.37−1.60)
Socioeconomic Status (vs. 5th quintile)	1.00 (-)	1.00 (-)	1.00 (-)	1.00 (-)
4th [most advantage]	1.41 (1.00−1.98)*	1.38 (0.98−1.94)	1.28 (0.84−1.95)	1.64 (0.89−3.02)
3rd	1.63 (1.61−2.28)*	1.63 (1.15−2.30)*	1.80 (1.20−2.71)*	1.27 (0.66−2.45)
2nd	1.55 (1.10−2.19)*	1.50 (1.05−2.14)*	1.78 (1.17−2.69)*	0.89 (0.43−1.81)
1st [most disadvantage]	2.48 (1.79−3.45)*	2.37 (1.69−3.33)*	2.41 (1.61−3.61)*	2.29 (1.24−4.26)*
Child's first language (English vs. other)	0.93 (0.72−1.20)	1.02 (0.78−1.32)	0.86 (0.63−1.17)	1.65 (0.93−2.93)
Sex of the parent: father (vs. mother)	0.99 (0.79−1.23)	0.96 (0.74−1.25)		
Parental age at the time of child's birth (years)	0.97 (0.95−0.99)*	0.98 (0.96−1.00)	0.98 (0.95−1.00)	0.98 (0.95−1.02)
Parental mental morbidity (vs. absence)	1.28 (1.03−1.59)*	1.30 (1.03−1.63)*	1.39 (1.08−1.80)*	1.05 (0.64−1.73)
Parental physical morbidity (vs. absence)	1.19 (0.95−1.48)	1.18 (0.94−1.48)	1.29 (0.99−1.67)	0.86 (0.54−1.37)
Parental MS Sex of parent		1.99 (1.14−3.46)*		

* p value < 0.05

§ Unadjusted model: children in the multiple sclerosis and reference cohorts were matched on child's year of birth, school district and sex of the parent.

† Model adjusted for matching factors plus the variables listed in the table.

Within the MS cohort (n=783), children with an MS mother who also had mental health comorbidity had 62% greater odds of vulnerability on one or more domains of the EDI (aOR 1.62, 95% CI, 1.05-2.50; **Table 4.5)** compared with MS mothers without mental health comorbidity. This effect was significant for two domains: language and cognitive development, and physical health. Paternal MS with mental health comorbidity was associated with higher odds of vulnerability on the emotional domain of the EDI (aOR 2.52, 95% CI 1.01-6.26) compared with paternal MS without mental health comorbidity. Presence of physical comorbidity in mothers with MS put children at significantly higher odds of vulnerability on one or more domains of the EDI (aOR 1.67, 95% CI 1.05-2.64). The odds ratio was similar for children of fathers with physical comorbidity but not statistically significant.

Table 4.4. Adjusted odds ratios and 95% confidence intervals showing the association between parental multiple sclerosis (MS) and vulnerability on Early Development Instrument (EDI) domains by parental sex, British Columbia, Canada

	Odds Ratio (95% Confidence Interval) †			
	Physical Domain		Emotional Domain	
Factors	**Mothers**	**Fathers**	**Mothers**	**Fathers**
Parental multiple sclerosis (vs. absence)	0.75 (0.56−1.02)	1.22 (0.82−1.83)	0.75 (0.55−1.03)	0.83 (0.52−1.33)
Sex of the child: female vs. (male)	0.52 (0.42−0.65)*	0.41 (0.29−0.58)*	0.32 (0.25−0.42)*	0.38 (0.25−0.59)*
Child's age at EDI completion (years)	0.52 (0.34−0.78)*	0.83 (0.45−1.52)	0.92 (0.61−1.39)	0.94 (0.45−1.97)
Socioeconomic Status (vs. 5th quintile)				
4th [most advantage]	0.92 (0.62−1.36)	1.70 (0.94−3.05)	1.02 (0.67−1.54)	1.84 (0.96−3.50)
3rd	1.63 (1.12−2.36)*	1.88 (1.04−3.40)*	1.62 (1.08−2.41)*	1.16 (0.55−2.23)
2nd	1.82 (1.25−2.64)*	1.97 (1.07−3.61)*	1.92 (1.30−2.85)*	1.28 (0.65−2.55)
1st [most disadvantage]	2.29 (1.58−3.32)*	1.97 (1.07−3.63)*	2.30 (1.54−3.41)*	1.87 (0.96−3.66)
Child's first language (English vs. others)	1.16 (0.87−1.57)	1.31 (0.82−2.07)	1.27 (0.92−1.75)	1.51 (0.86−2.68)
Parental age at the time of birth (years)	0.98 (0.96−1.00)	0.98 (0.96−1.01)	1.00 (0.97−1.02)	0.96 (0.93−1.00)
Parental mental morbidity (vs. absence)	1.50 (1.19−1.91)*	1.25 (0.79−1.97)	1.40 (1.09−1.80)*	1.27 (0.76−2.13)
Parental physical morbidity (vs. absence)	1.42 (1.12−1.80)*	1.04 (0.69−1.56)	1.29 (1.00−1.66)*	0.76 (0.46−1.25)

Table 4.4. Adjusted odds ratios and 95% confidence intervals showing the association between parental multiple sclerosis (MS) and vulnerability on Early Development Instrument (EDI) domains by parental sex, British Columbia, Canada

	Odds Ratio (95% Confidence Interval) †			
	Language Domain		Communication Domain	
Factors	**Mothers**	**Fathers**	**Mothers**	**Fathers**
Parental multiple sclerosis (vs. absence)	0.75 (0.52−1.08)	1.01 (0.61−1.67)	0.67 (0.45−1.00)	1.41 (0.85−2.32)
Sex of the child: female vs. (male)	0.47 (0.36−0.62)*	0.41 (0.27−0.61)*	0.52 (0.38−0.69)*	0.46 (0.30−0.70)*
Child's age at EDI completion (years)	0.28 (0.17−0.46)*	0.39 (0.17−0.88)*	0.70 (0.43−1.14)	0.33 (0.14−0.75)*
Socioeconomic Status (vs. 5th quintile)				
4th [most advantage]	2.01 (1.21−3.35)*	1.17 (0.63−2.16)	1.20 (0.78−1.84)	1.98 (0.94−4.15)
3rd	2.78 (1.67−4.63)*	0.73 (0.38−1.42)	1.32 (0.80−2.18)	1.4 (0.66−3.03)
2nd	2.40 (1.43−4.02)*	0.82 (0.42−1.61)	1.36 (0.87−2.14)	1.47 (0.69−3.13)
1st [most disadvantage]	3.07 (1.85−5.09)*	1.27 (0.66−2.43)	1.79 (1.16−2.76)*	3.60 (1.77−7.32)*
Child's first language (English vs. Other)	0.54 (0.40−0.72)*	0.98 (0.58−1.65)	0.27 (0.20−0.35)*	0.27 (0.18−0.42)*
Parental age at the time of birth (years)	0.97 (0.95−1.00)	0.99 (0.94−1.01)	0.97 (0.95−1.00)	0.99 (0.96−1.03)
Parental mental morbidity (vs. absence)	1.28 (0.97−1.70)	0.80 (0.45−1.42)	1.06 (0.76−1.48)	0.96 (0.55−1.69)
Parental physical morbidity (vs. absence)	1.11 (0.82−1.51)	1.53 (0.97−2.42)	1.13 (0.83−1.54)	1.23 (0.77−1.95)

* p value < 0.05

Children in the MS and reference groups were matched on child's year of birth, school district and sex of the parent.

† Adjusted model with variables listed in the table

Table 4.5. Associations between parental characteristics and the child's vulnerability on the Early Development Instrument (EDI) domains stratified by parental sex among parents with multiple sclerosis (MS), British Columbia, Canada (n=783 children)

Factors	Odds Ratio (95% Confidence Interval) †	
Parental Mental Morbidity (present vs. absent)	**Mothers with MS**	**Fathers with MS**
One or more domains	1.62 (1.05−2.50)*	1.04 (0.53−2.05)
Physical Health and Well-being	2.15 (1.24−3.72)*	0.98 (0.42−2.26)
Social Competence	1.27 (0.67−2.42)	1.66 (0.73−3.74)
Emotional Maturity	1.49 (0.82−2.69)	2.52 (1.01−6.26)*
Language and Cognition	2.78 (1.36−5.71)*	1.14 (0.43−3.03)
Communication Skills	1.13 (0.55−2.36)	0.37 (0.12−1.20)
Parental Physical Morbidity (present vs. absent)		
One or more domains	1.67 (1.05−2.64)*	1.52 (0.77−2.99)
Physical Health and Well-being	1.69 (0.98−2.93)	0.94 (0.41−2.16)
Social Competence	1.87 (0.96−3.64)	0.59 (0.23−1.54)
Emotional Maturity	1.49 (0.80−2.74)	1.25 (0.42−3.73)
Language and Cognition	1.46 (0.67−3.17)	2.35 (0.95−5.81)
Communication Skills	2.10 (0.90−4.89)	1.17 (0.42−3.25)
Parental MS disease duration		
5-10 years (vs. <5 years)		
One or more domains	1.13 (0.66−1.92)	1.17 (0.59−2.32)
Physical Health and Well-being	1.10 (0.55−2.17)	0.85 (0.39−1.86)
Social Competence	0.94 (0.42−2.10)	0.80 (0.34−1.88)
Emotional Maturity	1.64 (0.82−3.31)	0.79 (0.32−1.96)
Language and Cognition	0.79 (0.34−1.80)	0.49 (0.17−1.42)
Communication Skills	1.51 (0.69−3.30)	0.57 (0.22−1.46)
≥10 years (vs. <5 years)		
One or more domains	1.21 (0.72−2.03)	0.77 (0.34−1.76)
Physical Health and Well-being	1.49 (0.76−2.94)	0.53 (0.18−1.55)
Social Competence	1.03 (0.48−2.18)	0.85 (0.29−2.48)
Emotional Maturity	1.43 (0.72−2.86)	0.29 (0.06−1.48)
Language and Cognition	1.37 (0.60−3.14)	0.44 (0.12−1.63)
Communication Skills	1.42 (0.61−3.31)	0.45 (0.13−1.59)

* p value <0.05

† Model adjusted for parental mental morbidity, parental physical morbidity, parental disease duration, child's sex, age of the child at EDI, socioeconomic status, and child's first language

Table 4.6. Adjusted odds ratios (95% confidence intervals) showing the association between parental disability measured using the Expanded Disability Status Scale and the child's vulnerability on the five Early Development Instrument (EDI) domains, within a subset of the multiple sclerosis (MS) cohort (n=280 children), British Columbia, Canada

EDSS Score (≥ 4 vs. <4)	Odds Ratio (95% Confidence Interval) †
One or more domains	1.79 (0.84−3.79)
Physical Health and Well-being	2.58 (1.10−6.05)*
Social Competence	1.65 (0.57−4.74)
Emotional Maturity	1.95 (0.75−5.05)
Language and Cognition	5.02 (1.67−15.1)*
Communication Skills	2.37 (0.92−6.11)

* p value <0.05
† Model adjusted for disease duration, child's sex, age of the child at EDI, socioeconomic status, and child's first language

There was a 2-fold greater odds of vulnerability on the physical health domain (aOR 2.58, 95%CI 1.10-6.05) and 5-fold greater odds of vulnerability on language and cognitive development (aOR 5.02, 95% CI 1.67-15.1) domain of the EDI, among children of parents with moderate to severe disability compared with those with less severe disability (**Table 4.6**). Although disease duration was not significantly associated with vulnerability on any of the EDI domains, children of mothers with a disease duration ≥10 years had non-significantly higher odds of vulnerability on all domains of the EDI compared with mothers with a disease duration of <5 years (**Table 4.5).**

4.5 Discussion

In this large population-based study, I showed that children of parents who had MS had a lower risk of developmental vulnerability at 5 years of age, as measured by the EDI. However, this relationship was modified by the sex of the affected parent. Children of mothers with MS had lower risk of vulnerability on the social development domain of the EDI compared with

the matched children of mothers without MS. This association was not observed for fathers. The presence of mental health morbidity and physical health morbidity in mothers with MS was associated with higher rates of developmental vulnerability on the language and cognitive, and the physical health and well-being domains compared with mothers who had MS but no mental health comorbidity. On the other hand, children of fathers with MS who had a coexisting mental health condition were at an elevated risk of vulnerability on the emotional maturity domain. Finally, children whose MS parent had moderate to severe disability had a higher risk of vulnerability on the physical health, and language and cognition development domains of the EDI compared with children whose MS affected parent had less severe disability.

The lower risk of developmental vulnerability in children with parental MS in our study extends previous work by our group based on a smaller cohort from Manitoba (which showed a borderline non-significant lower risk of developmental vulnerability on the social domain among children of MS affected parents; OR 0.51, 95% CI 0.25-1.06; p value 0.06).[121] The relatively small size of the MS cohort in the Manitoba study (n=153 MS parent-child dyads vs. n=783 in the current study) likely limited the ability to detect differences.[121] Other qualitative and cross-sectional studies have also shown that parental MS imposes a greater burden of domestic/household duties on children and this results in an increase in pro-social behavior in many children.[29,30,46] Children from such families describe having higher personal competence, feeling more empathetic to others and more 'grown-up,' as the result of having a parent with MS.[71,73] Even though these latter studies were focused on older children, such findings are consistent with the hypothesis that mild, intermittent stressors (positive stress), in a child's life may have beneficial effects and are likely helpful for child development.[125,126]

However, it is possible that some children are adversely affected by parental MS, with stage of childhood and adolescence, degree of family stress, and magnitude of the parental disability being potential determinants of the end result.[100]

In our study, children of mothers with MS (but not those of fathers with MS) had lower rates of overall vulnerability on the EDI and specifically on the social domain of the EDI. To the best of our knowledge, there are no similar studies on the issue of the parental sex, MS and child development. Nevertheless, the broader literature does suggests that children who have a mother with a chronic condition, such as MS, do not experience serious academic difficulties unless the burden of illness and associated stress reaches an extreme level.[127] Although, I was able to demonstrate a difference between the effects of paternal MS on developmental vulnerability, our study was likely underpowered to examine the possible association(s) between paternal MS and early childhood development.

The negative association between mental and physical comorbidity and vulnerability on the EDI is consistent with findings from previous work demonstrating that children whose parent had both MS and a mental health condition (vs. MS, but no mental health comorbidity) were at an increased risk of vulnerability on emotional maturity and social competence domains of development.[23,121] Further, in our subgroup of MS parents with information on disability (as measured by the EDSS), a greater level of MS-related disability in the parent was associated with an increased risk of developmental vulnerability among children. The literature suggests that disability in parents may disrupt parenting and constrain them from accessing timely care for their children.[42,43] Indeed, studies with older children show that parental MS-related disability has adverse effects on youth adjustment and family functioning through the higher

caregiving demands on the youth and the potential stigma related to the parent's disability.[52]

The strengths of our study include the large study size, the comprehensive and longitudinal population-based nature of our cohort and the use of previously validated case definitions for both MS and other morbidity. The EDI assessment by teachers avoided reliance on parental or self-report of the child's developmental health. Although the EDI has undergone significant psychometric testing to confirm validity and reliability as a research tool,[34,103] there may be some individual differences in teachers' ability to evaluate developmental health.[123] The relatively small number of MS-affected fathers limited our ability to draw robust conclusions about the association between paternal MS and developmental health in children. Also, I was only able to identify morbidity among subjects whose condition was recognized by the health care system. Finally, I did not have family-specific information on socioeconomic status, and used neighborhood-level median income as a proxy for families' socioeconomic status.

In summary our population-based study demonstrates that maternal MS is associated with lower rates of developmental vulnerability, specifically vulnerability on the social development domain, in children at 5 years of age. However, presence of mental and physical comorbidity, and greater disability in the MS-affected mothers are associated with a higher risk of vulnerability in children, as was mental health comorbidity in fathers with MS. The provision of appropriate support strategies and services to parents affected by MS and mental and physical morbidity may help mitigate adverse developmental effects on their children.

Chapter 5: Incidence of mood or anxiety disorders in children of parents with multiple sclerosis[4]

5.1 Synopsis

Objective: Although parental multiple sclerosis (MS) may put children at increased risk for mental health disorders such as anxiety and depression, the incidence and determinants of such disorders have not been examined.

Methods: I carried out a retrospective cohort study in British Columbia, Canada, among children of parents with MS and age-matched children of unaffected parents. Cox regression was used to estimate the association between parental MS and mood or anxiety disorders in children.

Results: The study included 1,028 children of MS parents, 4,010 children of unaffected parents, and 25,464 child-years of follow up. Mental health morbidity was more common among MS parents vs. unaffected parents (50.4% vs. 33.1%, P<0.001) and among MS affected mothers vs. unaffected mothers (54.6% vs. 38.0%, P <0.001). The incidence of child mood or anxiety disorders was 8.3 and 6.3 per 1000 child-years among children of parents with and without MS, respectively. Sex of the MS affected parent modified the relationship between parental MS and mood or anxiety disorders in children (P=0.04). Compared with children of unaffected mothers, children of mothers affected by MS had higher rates of mood or anxiety disorders (hazard ratio 1.65, 95% confidence interval 1.14-2.39), whereas children of MS-

[4] A version of this chapter is submitted for publication as Razaz N, Tremlett H, Boyce WT, Guhn M, Marrie RA, Joseph KS. Incidence and determinants of mental health disorders in children of parents with multiple sclerosis.

affected fathers did not (Hazar Ratio 0.51, 95% confidence interval 0.15-1.74). Adjustment for mental health morbidity in mothers diminished the association between maternal MS and child mood or anxiety disorders.

Conclusion: Maternal MS is associated with a higher rate of mood or anxiety disorders in children and this association is mediated by maternal mental health morbidity.

5.2 Background and objectives

Chapters 3 and 4 provided detailed analyses of risk factors for developmental vulnerability among 5-year old children of parents with MS. This chapter explores the impact of parental MS on mental health morbidity among children beyond the kindergarten stage and up to eighteen years of age. The goal of this study was to examine the relationship between parental MS, mental health comorbidity (identified as a risk factor for developmental vulnerability in Chapters 3 and 4) and child mood or anxiety disorders.

As previously mentioned, early exposure to perceived daily stressors, such as chronic illness in parents, is an important risk factor for a child's current and future mental health problems.[1-5] MS, is the prototypical chronic disease that can affect parents and substantially increase daily stress in a child's life. The disease course of MS is unpredictable and the uncertainty over future disability constitutes a potential threat to the affected individual's mental health.[22]

Depression and anxiety disorders affect individuals with MS at more than twice the frequency observed among people without MS.[37,39] Chronic exposure to maternal depressive symptoms has been consistently shown to have an adverse effect on children's mental health.[120,121] Given the high prevalence of mental health co-morbidity among people with MS, it is likely that

parental mental health mediates the relationship between parental MS and mental health outcomes in their children.

The incidence and patterns of mood or anxiety disorders among children with parental MS have not been documented. Furthermore, there are no population-based studies evaluating the association between parental MS and mental health comorbidity, and child mental health outcomes.[100] I, therefore, carried out a study to quantify the incidence of mood or anxiety disorders in children with parental MS, and to identify risk factors associated with the development of mood or anxiety disorder in such children.

5.3 Methods

As previously discussed, this study was part of a wider program of research examining the association between parental MS and child development. The study included children in British Columbia, Canada, born between 1993 and 2006, who had a parent with a diagnosis of MS, and a matched cohort of children without parental MS. All children were routinely assessed for developmental status in kindergarten.

Information was obtained from several population-based linked health and demographic databases in British Columbia. The anonymized linked data included information from the Medical Services Plan database[56] containing fee-for-service physical billing claims; the Discharge Abstract Database[57] containing hospital admission and discharge records; the PharmaNet database[59] containing prescription drugs dispensed at out-patient pharmacies regardless of the payment source; Census GeoData, which provided demographic information including average neighbourhood income, used as an indicator of area-level socioeconomic

status (SES) based on postal code of residence; and the Vital Statistics birth database,[60] containing information on all births in British Columbia. In addition, the Consolidation File[58] for all British Columbia residents enrolled in the universal health care plan was used to confirm residency/emigration over the course of the study.

Parents with MS were identified using a validated algorithm as those with ≥3 records for a relevant hospital or physician claim between April 1, 1985 and December 31, 2011 or a relevant prescription claim after April 1, 1996 (Supplementary Table A.3).[105] Using the birth registry and the Consolidation File databases, individuals with MS were linked to their offspring. All persons with MS who had a child born between January 1, 1993 and December 31, 2006 were included in the study cohort. The onset date of MS was based on the first date for MS or a demyelinating disease in any of the records (Supplementary Table A.3). Up to 4 children with parents who were not known to have MS or another demyelinating condition were randomly selected from the population after matching on year of birth and school district to form the reference group. The affected parent with MS was also matched by sex to a parent in the reference cohort. Exact matching for parental sex could not be done in 2% of instances and the available parent in the database was selected in such instances. Children, both of whose parents had MS, were excluded from the study. Children were followed for a minimum of 4 years and up to eighteen years between 1993 and 2011.

The primary outcome of interest was mood or anxiety disorders in children and ranged from poor adjustment reactions and anxiety state to phobic disorders, obsessive–compulsive disorders, affective psychoses, and neurotic depression.[128,129] These conditions are often difficult to distinguish in administrative data because of variations in clinical presentations,

coding practices, and comorbidity.[115] In this study, mood or anxiety disorders in children were identified through a combination of hospital, physician and prescription drug claims using a previously validated algorithm (Supplementary Table A.6).[128,130] Such algorithms are widely used for research and population surveillance of mental health morbidity,[128,131,132] and validation studies show that they have a modest sensitivity and a high specificity for diagnosing mental health morbidity such as depression, high distress, chronic distress and contact with a health professional for mental health problems.[130] The date associated with the first record of a mood or anxiety disorder was considered the date of onset of the outcome. Diagnosis of a mood or anxiety disorder in children was restricted to the period after the child's fourth birthday to increase the validity of such diagnoses.[128,133]

The date of cohort entry (index date) for a child whose parent had MS was defined as (the month of) the child's fourth birthday. If the onset of parental MS occurred after the child reached 4 years of age, the onset date of MS was considered the index date. The same index dates were assigned to the age-matched children in the reference cohort. Children were followed from the index date until the first diagnosis of a mood or anxiety disorder, emigration from British Columbia or 31 December 2011. Children whose mood or anxiety disorder was diagnosed before the index date were excluded from the study.

The main determinant of interest was the presence (vs. absence) of parental MS. Other variables of interest included the child's sex, the child's age at cohort entry, the child's first language at home (English vs. other) and socioeconomic status. Parental characteristics modeled were: parental age, sex and comorbidity. I included specific comorbidity that affected ≥5% of the overall MS population. Parental comorbid conditions included mental health

disorders in the 5 years prior to the index date (using the same conditions as those used for children [Supplementary Table A.6.])[128,129] and physical morbidity (i.e., presence of diabetes mellitus, hypertension, hyperlipidemia or chronic lung disease). All comorbidity was identified using a previously validated algorithm based on hospital, physician visit or prescription information (Supplementary Table A.5).[37,116]

Conditional logistic regression was used to compare the characteristics of the parent-child dyads in the index and matched reference cohorts. The incidence of mood or anxiety disorders in children was quantified by dividing the number of children with mood or anxiety disorders by the total follow-up time in child-years. Incidence patterns of mood or anxiety disorders in children were examined using Kaplan Meier curves and Cox proportional hazards regression. In the Cox models, standard errors were adjusted for within-family clustering[134] as some parents had more than one child in the cohort. Confounders were included in the final model based on the literature[107,117] or statistical significance, and the proportionality (of hazards) assumption was checked for each variable in the model.[135] The full model included socioeconomic status (expressed as quintiles), parental mental morbidity (present vs. absent), parental physical morbidity (present vs. absent) and parental sex (male vs. female).

Modification of the association between parental MS and mood or anxiety disorders in children and other determinants was explored and potential mediation of the relationship between parental MS and child mood or anxiety disorder by parental mental health morbidity was tested.[136] The latter testing included demonstrating that 1) parental MS was associated with parental mental health comorbidity and with mood or anxiety disorders in children, 2) parental mental health morbidity was associated with child mood or anxiety disorders, and 3)

the relation between the parental MS and mood or anxiety disorders in children was attenuated after controlling for parental mental health morbidity. Additionally, the Sobel test was used to assess the degree of mediation, and the explained variance accounted for by mental health morbidity in parents was calculated.[136,137]

Results were expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). Regression model fit was assessed using the likelihood ratio test, and a two-sided p value <0.05 was used to determine statistical significance. Analyses were performed using SAS Version 9.2 (SAS Institute Inc., Cary, NC). The University of British Columbia's Clinical Research Ethics Board approved the study.

5.4 Results

The source population included 1,044 children who had a parent with MS and a matched reference cohort of 4,176 children and their parents who were not known to have MS (**Figure 5.1**). After applying the exclusion criteria, the study cohort included 1,028 children with a parent who had MS and 4,010 parent-child dyads in the reference group.

The children of parents with and without MS were similar in terms of sex, age and socioeconomic status at cohort entry (**Table 5.1**). Parents affected by MS were significantly older (albeit by one year on average), more likely to be English speakers and more likely to have a physical comorbidity. Mental health morbidity affected considerably more parents with MS compared with unaffected parents (50.4% vs. 33.1%, P<0.001). Mothers affected by MS had higher rates of mental health morbidity compared with mothers in the reference cohort without MS (54.6% vs. 38.0%; p value <0.001). Similarly, fathers with MS also had higher

rates of mental health morbidity compared with fathers without MS (40.2% vs. 20.2%; p value <0.001). Further details of the MS cohort are shown in **Table 5.2**. The median age at onset of MS was 33 years and the median disease duration at the index date was 2 years. Approximately 32% of the MS parents had received disease-modifying medication.

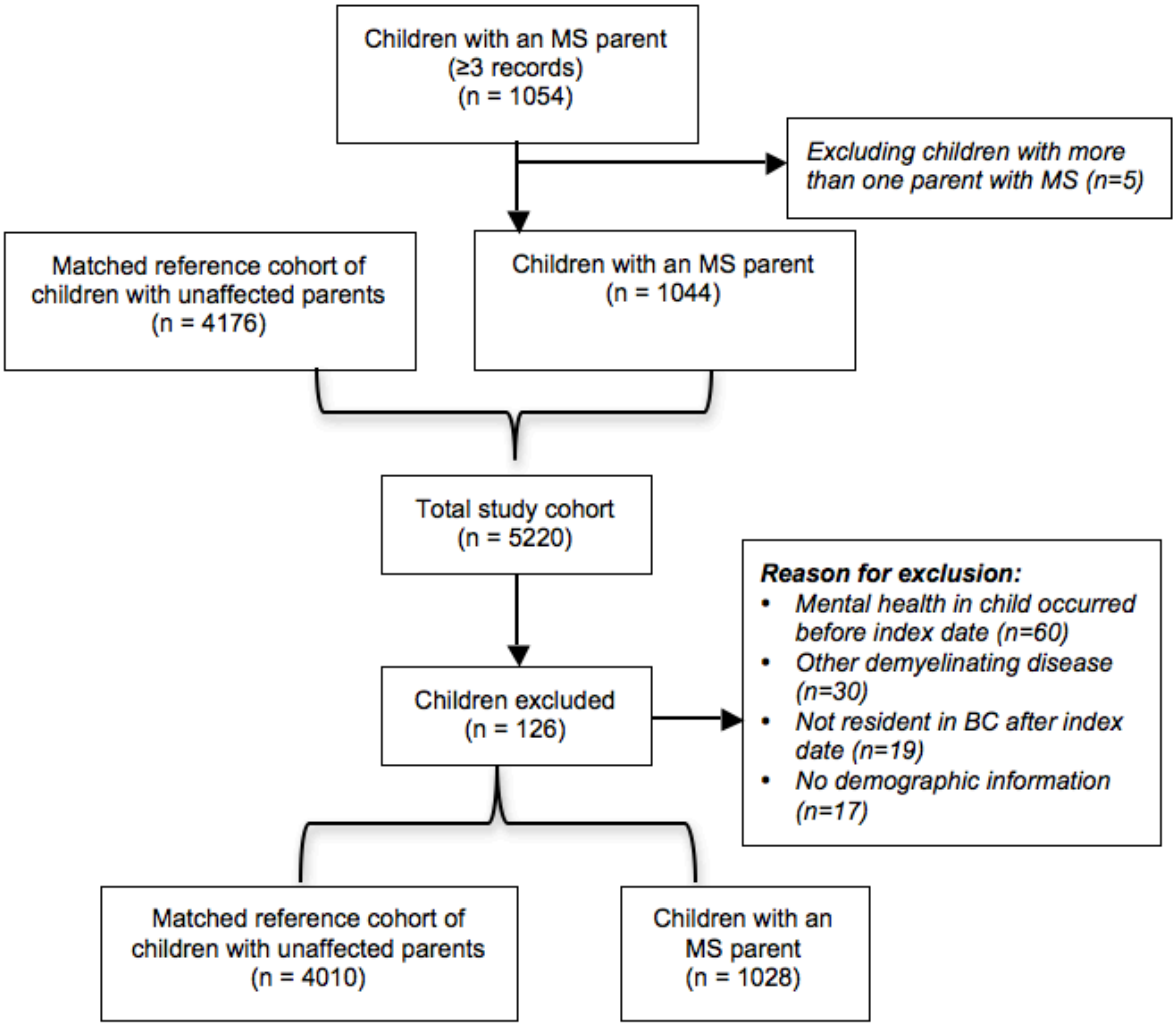


Figure 5.1. Schematic depiction of the cohort selection process
*Please note that the total number of children excluded (n = 126) does not include the sum of children in the matched reference cohort that were excluded with each corresponding index child.

Overall, the 5,038 parent-child dyad contributed 25,464 years of follow-up with a median follow-up of 4 years for both the MS affected and matched reference cohorts; for purposes of the Kaplan-Meier analysis, 4,713 (93.5%) children were followed until the end of the study period, 170 (3.5%) until the diagnosis of mood or anxiety disorder and 155 (3.0%) until emigration from the province. The association between parental MS and mood or anxiety disorders in children was modified by the sex of the affected parent, with maternal MS being associated with an increased rate of mood or anxiety disorders and paternal MS showing no significant association (**Figure 5.2**).

The incidence of mood or anxiety disorders was 8.3 per 1000 child-years among children of parents with MS and 6.3 per 1000 child-years among those without parents affected by MS (**Table 5.3**). The incidence of mood or anxiety disorders in children was higher among older children, children in the lowest income quintile and those whose parents suffered from mental and physical morbidity (**Table 5.3**).

The unadjusted Cox model showed that parental MS was not significantly associated with mood or anxiety disorders in children (HR 1.30, 95% CI 0.96-1.76; **Table 5.4**). The first adjusted model, which did not include parental mental health morbidity, showed that parental MS was a risk factor for mood or anxiety disorders in children (HR 1.58, 95% CI 1.11-2.27). The second adjusted model, which controlled for parental mental health morbidity, also showed that parental MS was significantly associated with mood or anxiety disorders in children (HR 1.46, 95% CI 1.02-2.09; **Table 5.4**)

Table 5.1. Characteristics of the children of parents with and without multiple sclerosis (MS), British Columbia, Canada

Characteristics	Parent with multiple sclerosis (n =1,028)		Matched comparison cohort (n = 4,010)		p value*
	No.	%	No.	%	
Sex of the child: Female	517	50.3	1928	48.0	0.21
Male	511	49.7	2082	52.0	
Child's age at cohort entry: Median (yrs) [Range]	4.0	[4 - 16.0]	4.0	[4 - 16.3]	0.99
4-5 years	796	77.4	3139	78.3	
6-10 years	185	18.0	688	17.2	0.31
≥11 years	47	4.6	183	4.5	
Child's first language at home: English	932	90.7	3192	79.6	**<0.001**
Other	96	9.3	818	20.4	
Child mood or anxiety disorder †: No	985	95.8	3883	96.8	0.11
Child mood or anxiety disorder: Yes	43	4.2	127	3.2	
Depressive Disorder	18	1.8	63	1.6	
Anxiety Disorders	25	2.4	64	1.6	
Child's age at first diagnosis of mood or anxiety disorder					
Median in years [Range]	10.7	[4.5 - 17.6]	10.2	[4.1 - 17.1]	0.66
4-10 years	23	53.5	72	56.7	0.57
≥11 years	20	46.5	55	43.3	
Sex of the parent: Female	727	70.7	2916	72.7	**0.03**
Male	301	29.3	1094	27.3	
Parental age at cohort entry: Mean in years (SD)	37.1	5.8	36.0	6.4	**<0.001**
<30 years	95	9.2	706	17.6	
30-34 years	276	26.9	1044	26.0	**<0.001**
35-39 years	349	34.0	1210	30.2	
≥40 years	308	30.0	1050	26.2	
Socioeconomic status at cohort entry					
5th quintile [highest]	193	18.8	792	19.8	
4th quintile	250	24.3	904	22.5	
3rd quintile	223	21.7	846	21.1	0.62
2nd quintile	192	18.7	749	18.7	
1st quintile [lowest]	170	16.5	719	17.9	
Parental mental morbidity §: No	510	49.6	2681	66.9	**<0.001**
Parental mental morbidity: Yes	518	50.4	1329	33.1	
Affective psychoses	25	2.4	66	1.7	
Depressive disorders	292	28.4	733	18.3	
Anxiety disorders	181	17.6	459	11.5	
Adjustment reaction	20	2.0	71	1.8	
Parental physical morbidity ¶ : No	657	63.9	2706	67.5	
Parental physical morbidity (lifetime): Yes	371	36.1	1304	32.5	**0.03**
Chronic lung disease	239	23.3	779	19.4	
Hypertension	109	10.6	395	9.9	
Hyperlipidemia	63	6.1	268	6.7	

Table 5.1. Characteristics of the children of parents with and without multiple sclerosis (MS), British Columbia, Canada

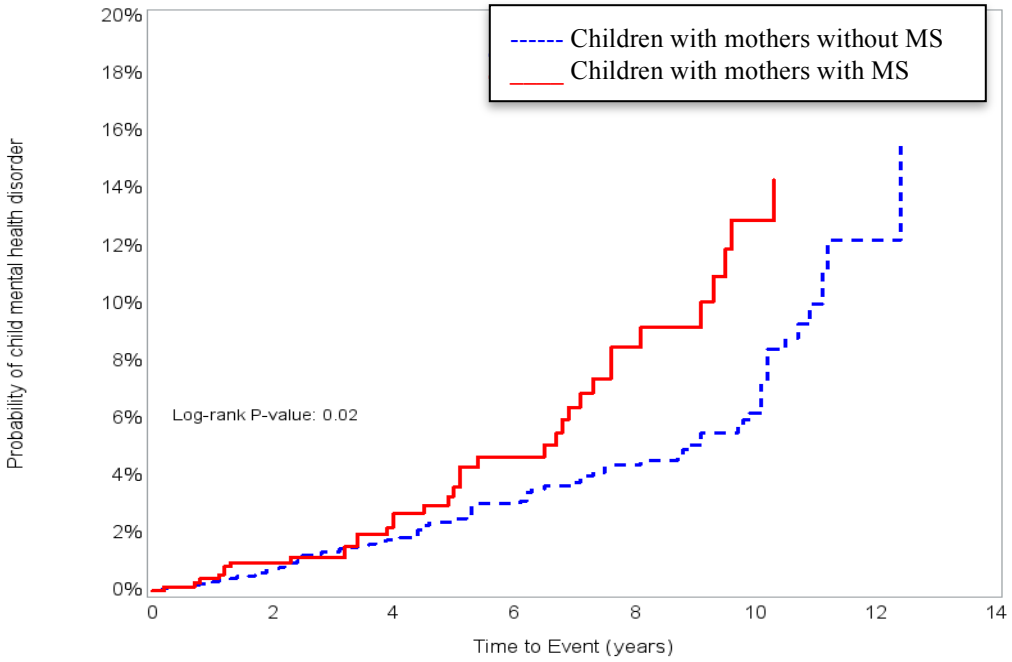
Characteristics	Parent with multiple sclerosis (n =1,028)		Matched comparison cohort (n = 4,010)		p value*
	No.	%	No.	%	
Diabetes mellitus	50	4.9	242	6.0	
Follow-up times (years): Median [IQR]	4.3	[2.5 - 7.4]	4.3	[2.6 - 7.4]	0.46

* From conditional logistic regression that accounted for matching at the design stage.
† Children with mood or anxiety disorders diagnosed between index date and study end date;
§ Parents with mental morbidity prior to child's onset of mood or anxiety disorder;
¶ Parents with physical morbidity prior to study end date, not including multiple sclerosis.
SD denotes standard deviation and IQR refers to the inter-quartile range.

Table 5.2. Additional characteristics of the cohort with multiple sclerosis (MS; n=1028), British Columbia, Canada

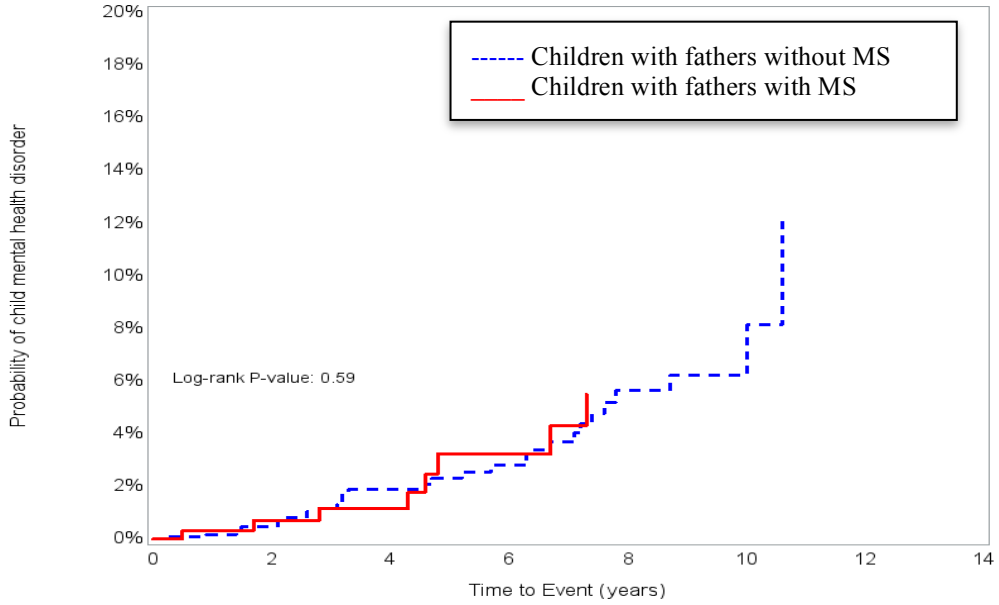
Characteristics	No. (%)
Ever on MS disease-modifying treatments	
Yes	332 (32.3)
No	696 (67.7)
Age of parent at MS onset	
<20 years	23 (2.2)
20-29 years	332 (32.3)
30-39 years	502 (48.8)
≥40 years	171 (16.6)
Median [range]	33.0 [11.7 - 63.4]
Parental disease duration at index date (years)	
0 (i.e. MS onset coincided with index year)	369 (35.9)
>0-2 years	207 (20.1)
3-5 years	159 (15.6)
≥6 years	293 (28.5)
Median [range]	2.1 [0 months-24.1 years]

n=80 (24%) were exposed to glatiramer acetate or natalizumab (<2%) and n= 252 (76%) to a beta-interferon



Children at risk of developing mood or anxiety disorder at selected time points:

Time (years)	**0**	**2**	**4**	**6**	**8**	**10**
Children with mother with MS	727	616	407	252	144	76
Children with mother without MS	2916	2482	1645	997	621	372



Children at risk of developing mood or anxiety disorders at selected time points:

Time (years)	**0**	**2**	**4**	**6**	**8**	**10**
Children with father with MS	301	258	173	104	63	38
Children with father without MS	1094	935	572	358	198	99

Figure 5.2. Kaplan-Meier curves showing the time from index date to onset of a mood or anxiety disorder among children with and without a parent with multiple sclerosis (MS) by parental sex, British Columbia, Canada

Table 5.3. Numbers and incidence rates of mood or anxiety disorders in children by parental sex, British Columbia, Canada

Factors	Mood or anxiety disorders in children								
	All			Mothers			Fathers		
	No.	Follow up (years)	Rate /1000 child-years	No.	Follow up (years)	Rate /1000 child-years	No.	Follow up (years)	Rate /1000 child-years
Parental multiple sclerosis									
Yes	43	5,198	8.3	35	3,660	9.6	8	1,538	5.2
No	127	20,266	6.3	94	14,947	6.3	33	5,319	6.2
Sex of the child									
Female	76	12,295	6.2	58	8,989	6.5	18	3,306	5.4
Male	94	13,169	7.1	71	9,618	7.4	23	3,551	6.5
Child's age at cohort entry (years)									
4-5 years	133	21,524	6.2	106	15,914	6.7	27	5,609	4.8
6-10 years	25	3,475	7.2	15	2,364	6.3	10	1,111	9
≥11 years	12	466	25.8	*	*	24.3	*	*	29.2
Child's first language									
English	143	20,929	6.8	110	15,445	7.1	33	5,484	6
Other	27	4,535	6	19	3,162	6	8	1,373	5.8
Sex of the parent									
Female	129	18,607	6.9						
Male	41	6,857	6						
Parental age at cohort entry (years)									
<30 years	34	4,410	7.7	28	3,555	7.9	6	855	7
30-34 years	39	7,085	5.5	31	5,600	5.5	8	1,485	5.4
35-39 years	47	8,038	5.8	37	5,832	6.3	10	2,206	4.5
≥40 years	50	5,931	8.4	33	3,620	9.1	17	2,311	7.4
Socioeconomic status at cohort entry									
5th quintile [highest]	19	4,918	3.9	14	3,605	3.9	5	1,313	3.8
4th quintile	44	6,015	7.3	33	4,337	7.6	11	1,677	6.6
3rd quintile	37	5,273	7	29	3,843	7.5	8	1,431	5.6
2nd quintile	33	4,824	6.8	27	3,636	7.4	6	1,188	5.1
1st quintile [lowest]	37	4,435	8.3	26	3,186	8.2	11	1,249	8.8
Parental mental morbidity									
No	73	14,985	4.9	46	10,084	4.6	27	4,902	5.5
Yes	97	10,479	9.3	83	8,523	9.7	14	1,956	7.2
Depressive disorders	54	6,406	8.4	43	5,112	8.4	11	1,294	8.5
Anxiety disorders	43	4,073	10.6	*	*	11.7	*	*	4.5
Parental physical morbidity									
No	91	16,670	5.5	69	12,172	5.7	22	4,498	4.9
Yes	79	8,794	9	60	6,435	9.3	19	2,396	7.9

Table 5.3. Numbers and incidence rates of mood or anxiety disorders in children by parental sex, British Columbia, Canada

Factors	Mood or anxiety disorders in children								
	All			Mothers			Fathers		
	No.	Follow up (years)	Rate /1000 child-years	No.	Follow up (years)	Rate /1000 child-years	No.	Follow up (years)	Rate /1000 child-years
Chronic lung disease	50	5,281	9.5	41	4,209	9.7	9	1,072	8.4
Hypertension	24	2,697	8.9	17	1,828	9.3	7	869	8.1

*****Suppressed due to small cell size (≤5).

No. column refers to the number of cases of mood and anxiety disorders in children

Table 5.4. Results from Cox regression models showing the association between parental multiple sclerosis and mood or anxiety disorders in children

	Hazard Ratio (95% confidence interval)		
	Unadjusted *	**Adjusted model ****	**Adjusted model §**
Parental multiple sclerosis (vs. absence)	1.30 (0.96−1.76)	**1.58 (1.11−2.27)**	**1.46 (1.02−2.09)**
Socioeconomic Status (vs. 5th quintile)			
4th	**2.06 (1.23−3.47)**	**1.91 (1.14−2.16)**	**1.79 (1.07−2.99)**
3rd	**1.98 (1.16−3.39)**	**1.82 (1.10−3.11)**	1.64 (0.97−2.79)
2nd	**1.85 (1.07−3.19)**	1.69 (0.98−2.92)	1.55 (0.90−2.68)
1st [lowest]	**2.35 (1.34−4.12)**	**2.15 (1.21−3.83)**	**1.98 (1.10−3.55)**
Parental mental morbidity (vs. absence)	**1.91 (1.40−2.62)**	–	**1.79 (1.26−2.54)**
Parental physical morbidity (vs. absence)	**1.61 (1.18−2.20)**	**1.57 (1.14−2.16)**	**1.51 (1.10−2.08)**
Male parental sex (vs. female)	1.02 (0.57−1.80)	1.62 (0.71−3.67)	1.92 (0.76−4.83)
Parental MS*male parental sex		0.38 (0.14−1.03)	**0.33 (0.11−0.98)**

Children in the index and reference groups were matched on child's year of birth, school district and sex of the parent.

***** Unadjusted model

****** Adjusted model included variables listed in the table (except parental mental morbidity)

§ Adjusted model included variables listed in the table.

Table 5.5. Results from Cox regression models showing the association between parental multiple sclerosis and mood or anxiety disorders in children by parental sex

Characteristics	Hazard Ratio (95% Confidence Interval)			
	Mothers		Fathers	
	Model 1 *	Model 2 †	Model 3 *	Model 4 †
Parental multiple sclerosis (vs. absence)	**1.65 (1.14−2.39)**	1.43 (0.98−2.1)	0.51 (0.15−1.74)	0.46 (0.13−1.57)
Socioeconomic Status (vs. 5th quintile)				
4th	**2.59 (1.37−4.92)**	**2.53 (1.35−4.77)**	0.95 (0.25−3.63)	0.91 (0.24−3.52)
3rd	**2.36 (1.23−4.53)**	**2.19 (1.16−4.12)**	1.04 (0.30−3.58)	1.01 (0.29−3.45)
2nd	**2.05 (1.08−3.90)**	**1.92 (1.00−3.67)**	1.70 (0.47−6.13)	1.63 (0.46−5.82)
1st [lowest]	**2.83 (1.39−4.92)**	**2.77 (1.35−5.69)**	2.40 (0.72−8.02)	2.46 (0.74−8.24)
Parental mental morbidity (vs. absence)	−	**2.43 (1.62−3.66)**	−	1.50 (0.68−3.31)
Parental physical morbidity (vs. absence)	**1.48 (1.02−2.15)**	1.43 (0.98−2.07)	1.95 (0.84−4.52)	1.85 (0.78−4.38)

Children in the index and reference groups were matched on child's year of birth, school district and sex of the parent.
* Models 1 & 3 adjusted for socioeconomic status and parental physical morbidity.
† Models 2 & 4 adjusted for socioeconomic status, parental physical morbidity and parental mental morbidity.

Analyses stratified by parental sex showed that rates of mood or anxiety disorders were significantly higher among children of mothers with MS compared with the children of mothers without MS (HR 1.65, 95% CI 1.14-2.39; **Table 5.5**, model 1 not adjusted for parental mental morbidity). Adjustment for maternal mental health morbidity diminished this association (HR 1.43, 95% CI 0.98-2.1; **Table 5.5**, model 2). The Sobel test revealed that there was a significant indirect effect of maternal MS on mood and anxiety disorder in children through maternal mental health morbidity (P <0.001) and accounted for 90% of the explained variance in mood or anxiety disorders in children. Paternal MS and paternal mental health morbidity were not associated with child mood or anxiety disorders (**Table 5.5**)

5.5 Discussion

Our longitudinal study provides evidence of an association between maternal MS and mood or

anxiety disorders in children and adolescents. Children of mothers affected by MS, but not those of the fathers affected by MS, had an increased risk for mood or anxiety disorders as compared with matched children of parents unaffected by MS. Parents with MS had higher levels of mental health morbidity compared with parents without MS and such mental health comorbidity among mothers with MS mediated the observed increase in rates of mood or anxiety disorders among children. Other risk factors for mood or anxiety disorders in children included physical morbidity in parents and low socioeconomic status.

To the best of our knowledge, there are no similar studies on this issue. Nevertheless, our finding of an association between parental MS and adverse child outcomes is consistent with earlier, smaller studies, describing negative psychosocial outcomes in children of chronically ill parents in general,[6] and parents with MS in particular.[23,53,74] Higher levels of depression and anxiety, and emotional and behavioural problems have been reported in children of parents affected by MS as compared with the children of healthy parents.[23,53,74] On the other hand, some studies have concluded that older children and youth of parents with MS did not differ from community norms with respect to adjustment problems.[138]

The absence of adverse effects of parental MS in previous studies may reflect methodological limitations including use of cross-sectional designs, lack of a comparison group or use of self-reported data. Alternatively, the lack of association between parental MS and adverse mental health outcome in children may be a consequence of the remedial effects of supports and services for the older children of parents with MS in some jurisdictions.[138] Methodological differences and shortcomings of the above-mentioned studies notwithstanding, the overall picture highlights the need for support services directed at families with MS, especially when

the mother is affected, the family is socioeconomically deprived and the parent has a physical or mental health comorbidity.

The modifying effect of parental MS on mood or anxiety disorders among children is intriguing. Our finding that maternal but not paternal MS increased the rate of mood or anxiety disorders in children could be related to the smaller number of MS-affected fathers in our study. On the other hand, it could also be attributable to gender roles and differences since fathers are reported as being less involved with childcare, especially if affected by a chronic condition.[24] A few previous studies have examined the association between parent's gender and child mental health and concluded that children whose mothers had MS were more likely to suffer emotional problems and have poor coping abilities as compared with children of healthy parents.[23,47]

Our study suggests that maternal MS is associated with an increased rate of mood or anxiety disorders in children because MS increases the rate of maternal mental health comorbidity. Mental health comorbidity in the parent with MS, specifically mothers, represents the most unfavorable context for psychopathology and poor developmental health in children.[23,139] Psychiatric comorbidity in MS has been associated with patients experiencing high stress, low social support and stigmatization, lower quality of life, suicidal ideation and a negative disease course.[39] Furthermore, parents with MS identify emotional and personality changes and mood swings as key challenges to successful parenting.[140] The impact of MS on family members includes some children feeling anxious and depressed as a result of trying to help their parents manage their sorrow and grief, while others are happier and better adjusted when they believe that the parent is actively coping with MS.[46] Health professionals working with MS patients

need to be aware of the effects of mental health morbidity commonly associated with MS, and its impact on patients and children.[25,141]

The strengths of our study include a comprehensive population-based data source with longitudinal follow up and the use of previously validated case definitions for both MS and other morbidity. Limitations of our study include our inability to assess severity of mental health disorders that could differ between mothers and fathers. Mood or anxiety disorders in children were identified through a combination of hospital, physician and prescription drug claims.[128,130] Validation studies have shown that such algorithms for diagnosing chronic disease (e.g., asthma, diabetes and hypertension) and mental health disorders have good accuracy.[142,143] Studies validating algorithms for identifying mental health problems such as depression, high distress, chronic distress and contact with a health professional for mental health problems show that hospital, physician and prescription drug claims data have modest sensitivity and high specificity for such diagnoses (see Supplementary Table A7).[130] This is expected since the validation was carried out against a gold standard which classified respondents according to their risk of major depression in the preceding 12 months based on the Composite International Diagnostic Interview Short Form.[132] The mostly non-differential misclassification of the outcome (due to a relatively high false negative rate and a low false positive rate) would have resulted in a bias toward the null in the estimated association between parental MS and mood and anxiety disorders in children. Also, I was only able to identify morbidity among subjects whose condition was recognized by the health care system. Further, I did not have information on the marital or relationship/support status of the parents at the time of cohort entry. Finally, I did not have a family-specific variable to assess socio-

economic status, but used neighborhood-level median income as a proxy for the family's socio-economic status.

In conclusion, maternal MS appears to lead to higher rates of mood or anxiety disorders in children and adolescents. Children of mothers affected by MS, but not those of the fathers affected by MS, have an increased risk for mood or anxiety disorders as compared with matched children of parents unaffected by MS. Parents with MS have higher levels of mental health morbidity compared with parents without MS and such mental health comorbidity among mothers with MS mediates the observed increase in rates of mood or anxiety disorders among children. Other risk factors for mood or anxiety disorders in children included physical morbidity in parents and low socioeconomic status. Preventive efforts aimed at mitigating the impact of parental MS on mood or anxiety disorders in children should address the psychological needs of MS parents and their children.

Chapter 6: Peripartum depression in parents with multiple sclerosis and psychiatric disorders in children[5]

6.1 Synopsis

Background: Peripartum depression is the most common morbidity of pregnancy. Although mental health comorbidity affects individuals with multiple sclerosis (MS) at twice the frequency observed among people without MS, the frequency of peripartum depression in individuals with MS and its potential association with children's psychiatric disorders has not been determined.

Method: I conducted a retrospective cohort study in British Columbia, of parents with MS and age-matched unaffected parent-child dyads and determined the frequency of psychiatric disorders among the children in each group. The diagnosis of peripartum depression and MS were based on information from hospital admission, physician visit and drug prescription claims. Conditional logistic regression was used to quantify the association between parental MS and peripartum depression, and Cox regression was used to estimate the association between parental MS and psychiatric disorders in children.

Results: The study included 360 parents with MS and their children and 1,207 unaffected parent-child dyads. Peripartum depression was significantly more common among MS parents vs. unaffected parents (25.8% vs. 18.5%, p value 0.02) and among MS affected fathers vs. unaffected fathers (25.7% vs. 10.2%, p value <0.006). The incidence of psychiatric disorders in children was 3.3 and 2.7 per 100 child-years among children with and without an MS

[5] A version of this chapter is submitted for publication as Razaz N, Tremlett H, Marrie RA, Joseph KS. Peripartum depression in parents with multiple sclerosis and psychiatric disorders in children.

parent, respectively. The rate of psychiatric disorders was significantly higher in children with an MS parent (vs. without, adjusted hazard ratio [aHR] 1.37, 95% confidence interval [CI] 1.05-1.78) and among parents with peripartum depression (aHR 2.05, 95% CI 1.48-2.82). Children whose parents had both MS and peripartum depression had a 3.5 fold increased risk of developing psychiatric disorders as compared with children whose parents did not have MS or peripartum depression.

Conclusion: Parental MS is associated with a higher risk of peripartum depression and increases the risk of psychiatric disorders in children.

6.2 Background and objectives

This chapter builds on the findings of studies reported in previous chapters and explores the effect of peripartum depression on children. The role of peripartum depression has been increasingly recognized in the recent literature as an important influence on maternal and child health. However, no studies have examined the frequency of peripartum depression and its potential effect on psychiatric disorders among children exposed to parental MS since birth.

Postpartum depression is the most frequent form of maternal morbidity and affects 15%-20% of mothers in the first year following delivery; 10% of fathers are also affected.[144-146] Postpartum depression is under-recognized and adherence to treatment is poor. In addition, approximately 18% of women exhibit depressive symptoms antenatally.[147] Consequently, in 2013, the American Psychiatric Association amended the nomenclature for this condition to peripartum depression and stipulated that the onset of peripartum depression can occur in pregnancy or after childbirth.[148] Peripartum depression affects the individual's quality of life, and its impact extends to the partner and family, and influences mother-child attachment.[149-151]

Depression and anxiety affect individuals with MS at twice the frequency observed among people without MS.[37,39] Although many individuals with MS will experience depression, there is a dearth of information on the frequency of peripartum depression among parents with MS.

Parental depression has been found to adversely affect children's emotional and behavioural development.[79,120] Thus it is important to quantify the frequency of peripartum depression in parents with MS and to assess its potential impact on their children's mental health. This study builds on previous work (examining the effects of parental multiple sclerosis on depression and child mental health)[152] by examining the timing of parental depression, specifically the frequency of peripartum depression, and its potential association with psychiatric disorders among children exposed to parental MS since birth.

6.3 Methods

This study was part of a broader program of research examining the association between parental MS and child development. All children in British Columbia, Canada, born between 1993 and 2006, and who had a parent with MS, as well as a matched cohort of children who did not have a parent with MS were part of the study. Children born between 1993 and 2006 participated in routinely administered developmental assessments in all school districts in British Columbia at kindergarten entry (approximately 5 years of age).

Information on study parent-child dyads was obtained from several population-based linked health and demographic databases in British Columbia. The publicly funded provincial health care program in British Columbia covers all residents; a lifelong unique personal health care number is assigned to each resident and available in all health databases. The anonymized

linked health data files used in this study included: the Discharge Abstract Database (with hospital admission dates and diagnosis codes),[57] the Medical Services Plan Billing database (providing information on physician visits and diagnosis codes),[56] the PharmaNet database (with information on dispensed prescriptions),[59] and Vital Statistics birth files (with records of all births in the province).[60] The Consolidation File[58] provided dates of entry and exit from the provincial health care plan (which confirmed residency in British Columbia), and socioeconomic status (SES) was based on average neighbourhood income (obtained through postal codes and national census data),[62] expressed as quintiles. Diagnoses in these databases were coded using the International Classification of Diseases codes (ICD-9 or ICD-10-CA), and prescription medications were coded using Drug Identification Numbers and the Anatomical Therapeutic Chemical (ATC) classification system.

MS in parents was identified using a validated algorithm, as those with ≥3 records related to MS in hospital admission or physician visit claims between April 1, 1985 and December 31, 2011 or in prescription claims after April 1, 1996 (Supplementary Table A.3).[105] Parents with MS were linked to their offspring using the birth registry and the Consolidation file database. All persons with MS who had a child born in British Columbia between January 1, 1994 and December 31, 2006 were included in the study cohort. The MS cohort was restricted to individuals whose MS onset occurred before their child's birth, based on the first date for MS or a demyelinating condition identified in any of the hospital, physician or prescription claims (Supplementary Table A.3). A matched reference cohort (of up to 4 children with parents who were not known to have MS or a demyelinating condition) was selected from the population of British Columbia. Children in the reference cohort were matched to the index cohort on the year of birth and school district. The parent with MS was also matched by sex to a parent in

the reference cohort. In instances where exact matching for parental sex could not be carried out (i.e. in 4% of cases), the available parent in the database was selected. Children for whom both parents had MS were excluded. All children in the study were followed for a minimum of 4 years and up to eighteen years between 1994 and 2011.

Peripartum depression was defined as a mood or anxiety disorder since these conditions have a shared psychopathology, are highly comorbid and are often difficult to distinguish in primary care.[133,153,154] Parents in the study were classified as having peripartum depression if they had one or more records related to mood disorders or anxiety in hospital, physician or prescription drug claims in the last 4 weeks before delivery and up to 12 months (13 month window) after the child's birth. Individuals with mood or anxiety disorders were defined as those with at least one physician visit, hospital admission or drug prescription with one of the following codes: mood disorders (ICD-9: 296.0–296.9 and 311.0; ICD-10: F30-F39), anxiety disorders (ICD-9: 300.0-300.9; ICD-10: F40-F48 and F93), or one or more prescription for an antidepressant, anxiolytic or mood stabilizer (ATC codes N03AB02, N03AB52, N03AF01, N05AN01, N05BA, N06A). In British Columbia, an individual with either depression or anxiety can be coded with a single '50B' code and this code was also included in our case definition. The time of onset of peripartum depression was defined as the date of the first record for a mood and/or anxiety disorder during the 13-month peripartum window. History of depression was defined as the presence of a depression or anxiety code in the 2 years prior to the defined peripartum period.

Psychiatric disorders in children were defined as one or more records for internalizing (mood or anxiety) psychiatric disorders or externalizing (ADHD or conduct) psychiatric disorders in

physician or hospital claims. Diagnosis codes included those for anxiety disorders (ICD-9: 300.0-300.9; ICD-10: F40-F48 and F93), depressive disorders (ICD-9: 296.0–296.9 and 311.0; ICD-10: F30-F39), Attention-Deficit Hyperactivity Disorder (ICD-9: 314; ICD-10: F90), conduct disorder (ICD-9: 312, 313, 347; ICD-10: F91-F94, F98), physician claim for anxiety/depression (50B), or prescription for an antidepressant, anxiolytic, mood stabilizer, or psychostimulant (ATC codes N03AB02, N03AB52, N03AF01, N05AN01, N05BA, N06A, N06BA).[155,156] The date associated with the first record of such psychiatric disorder was considered the date of onset for the outcome. Diagnosis of a psychiatric disorder in children was restricted to the period after the child's fourth birthday in order to increase the validity of such a diagnosis.[128,133] Although recent studies[155,156] have used a similar approach to identifying mental health disorders, I also identified mental health disorders in children and parents using a previously validated algorithm.[128,132] The latter diagnoses were used in a sensitivity analysis to assess if results comparing children of parents with and without MS were affected by potential changes in diagnostic accuracy.

The date of cohort entry (index date) for all children was defined as the month of the child's fourth birthday. Children were followed from the index date until the first diagnosis of a psychiatric disorder, emigration from British Columbia or the study end date, which was 31 December 2011. The child's characteristics examined included sex, the child's first language at home (English vs. other), presence of an older sibling (yes vs. no), and socioeconomic status at index date (expressed as quintiles). Parental characteristics studied included parental sex, parental age (continuous) and marital status at the time of the child's birth.

Conditional logistic regression was used to compare the characteristics of the parent-child

dyads in the MS and matched reference cohorts. The frequency of peripartum depression among parents with and without MS was estimated using cumulative rates and 95% confidence intervals (CI). Multivariable conditional logistic regression models were used to determine the association between parental MS and peripartum depression, after adjusting for potential confounders including parental marital status, age at the time of the child's birth, parental sex, and socioeconomic status.

The incidence (density) of psychiatric disorders in children of parents with and without MS was quantified by dividing the number of children with psychiatric disorders by the total follow-up time in child-years in each category. Incidence patterns of psychiatric disorders in children were examined using Kaplan Meier curves and Cox proportional hazard regression. In the Cox models, standard errors were adjusted for within-family clustering[134] to account for the sequential births to the same parent in the cohort. Confounders were included in the final model based on the literature[107,117] or statistical significance (p value < 0.1), and the proportionality assumption in the Cox model was checked for each variable in the model.[135] The full Cox model included the child's sex (female vs. male), socioeconomic status (expressed as quintiles), peripartum depression (present vs. absent), parental marital status (not married vs. married) and parental sex (male vs. female). Modification of the effect of parental MS by other factors was examined using interaction terms, and stratified analyses were presented to illustrate potential effect modification.

Results were expressed as odds ratios (ORs) and hazard ratios (HRs) with 95% confidence intervals (CI). Regression model fit was assessed using the likelihood ratio test, and a 2-sided p value <0.05 was used to determine statistical significance. Analyses were performed using

SAS Version 9.2 (SAS Institute Inc., Cary, NC). The University of British Columbia's Clinical Research Ethics Board approved the study.

6.4 Results

The study cohort included 360 children with an MS parent and 1,207 parent-child dyads in the matched reference cohort (**Figure 6.1**). The characteristics of children with a parent with MS and those with unaffected parents were similar in terms of sex, birth order, and socioeconomic status at cohort entry (**Table 6.1**). Parents affected by MS were on average older, more likely to be English speakers and to be married at the time of the child's birth. The median age at onset of MS was 28 years and the median disease duration at the index date was 8.5 years. Approximately 32% of the parents affected by MS had received disease-modifying medication by the index date (**Table 6.2**).

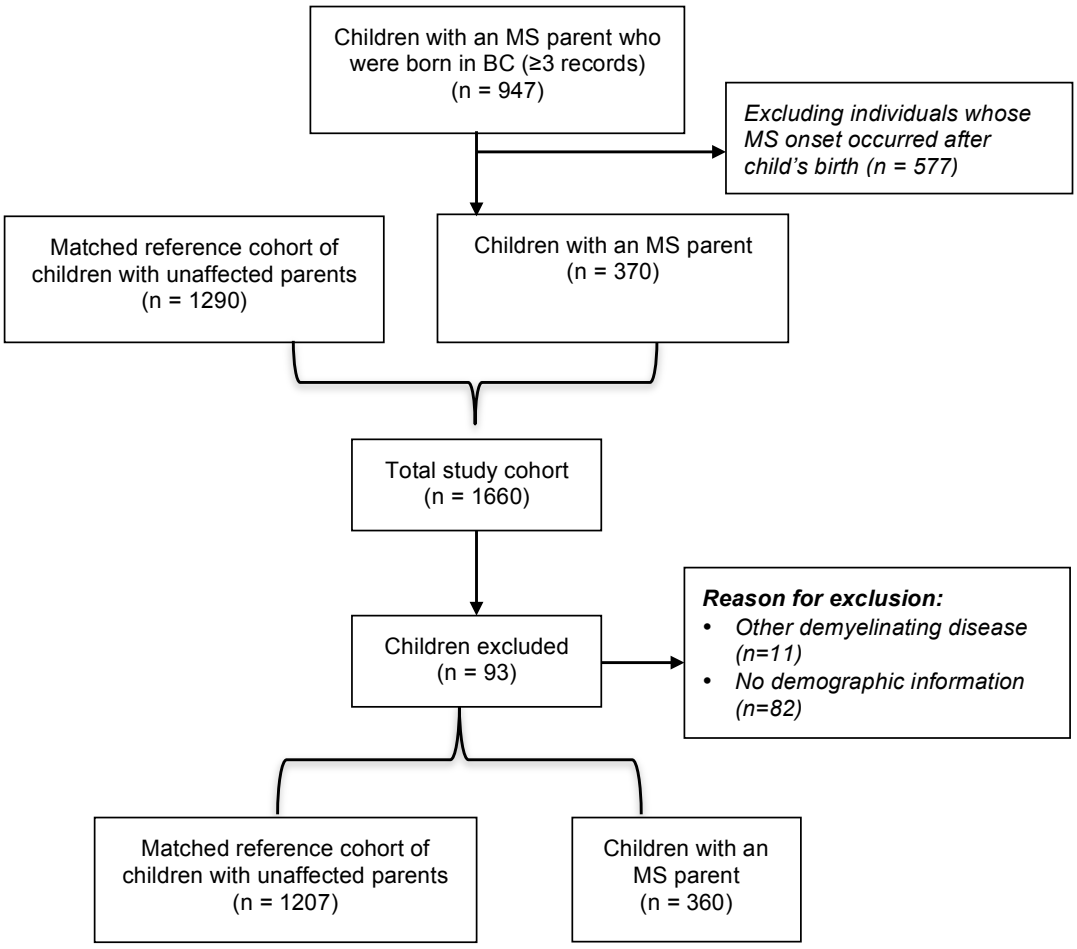


Figure 6.1. Schematic depiction of the cohort selection process

A total of 316 (20%) parents were diagnosed with peripartum depression. Parents affected by MS had higher rates of peripartum depression compared with parents in the reference cohort (25.8% vs. 18.5%, p value 0.004; **Table 6.1**). Among individuals with peripartum depression, 34% of parents with MS and 27% of unaffected parents had a prior history of depression (**Table 6.3**). The association between parental MS and peripartum depression appeared to be modified by the sex of the affected parent; fathers who had MS had considerably higher rates of peripartum depression compared with unaffected fathers (25.7% vs. 10.2%, p value <0.006;

Figure 6.2), while maternal MS showed no such difference (25.9% vs. 21.2%, p value 0.34). Adjusted analyses also showed that parental sex modified the effect of parental MS on peripartum depression (**Table 6.4**; p value for interaction term 0.006). Adjusted analyses stratified by parental sex showed that the odds of peripartum depression were 3-fold higher among fathers with MS as compared with fathers without MS (OR 3.08, 95% CI 1.35-7.01), while the odds of peripartum depression were not elevated among mothers with MS (OR 1.15, 95% CI 0.79-1.67). In stratified analyses restricted to mothers, women who were not married had higher odds of peripartum depression compared with mothers who were married (OR 1.52, 95% CI 1.05-2.22). However, marital status was not a risk factor for peripartum depression among fathers (OR 1.42, 95% CI 0.59-3.40; **Table 6.4**).

Table 6.1. Characteristics of parents with and without multiple sclerosis (MS) and their children, British Columbia, Canada

Characteristics	**Parents with multiple sclerosis (n =360)**		**Matched reference cohort (n = 1,207)**		**p value***
	No.	%	No.	%	
Sex of the child: Female	190	52.8	586	48.5	0.15
Male	170	47.2	621	51.5	
Child's first language: English	328	91.1	1006	83.4	**<0.001**
Other	32	8.9	201	16.7	
Child with psychiatric disorder: No	300	83.3	1041	86.2	0.09
Child with psychiatric disorder: Yes	60	16.7	166	13.8	
Mood or anxiety disorders †	39	65.0	96	57.8	
Conduct disorders†	19	31.7	65	39.2	
ADHD †	23	38.3	67	40.4	
Child's age at first psychiatric disorder					
Mean (SD)	7.8	3.1	7.1	2.5	
4-10 years	46	76.7	148	89.2	0.22
≥11 years	14	23.3	18	10.8	
Older sibling: Yes	196	54.4	688	57.0	0.59
No	164	45.6	519	43.0	
Sex of the parent: Female	255	70.8	904	74.9	**0.02**
Male	105	29.2	303	25.1	
Peripartum depression: Yes	93	25.8	223	18.5	**0.004**
No	267	74.2	984	81.5	

Table 6.1. Characteristics of parents with and without multiple sclerosis (MS) and their children, British Columbia, Canada

Characteristics	Parents with multiple sclerosis (n =360)		Matched reference cohort (n = 1,207)		p value*
	No.	%	No.	%	
Parental age at cohort entry: Mean (SD)	37.3	5.2	34.7	6.0	
<30 years	22	6.1	266	22.0	
30-34 years	101	28.1	357	29.6	**<0.001**
35-39 years	132	36.7	348	28.8	
≥40 years	105	29.2	236	19.6	
Socioeconomic status					
5th quintile [Highest]	61	16.9	226	18.7	
4th quintile	61	16.9	216	17.9	
3rd quintile	76	21.1	255	21.1	0.62
2nd quintile	103	28.6	282	23.4	
1st quintile [Lowest]	59	16.4	228	18.9	
Marital status at time of child birth: Married	272	75.6	821	68.0	**0.007**
Not married	88	24.4	386	32.0	
Follow-up times (years): Median [IQR]	4.3	[0 - 13.6]	4.3	[0 - 13.4]	0.46

* From conditional logistic regression which accounted for matching at the design stage.

† Proportion of all children with psychiatric disorders (several children had more than 1 diagnosis)

SD denotes standard deviation and IQR refers to inter-quartile range.

During the follow-up period from January 1994 through December 2011, 226 children (14%) were diagnosed with a psychiatric disorder (**Table 6.1**). Among children with psychiatric disorders, mood or anxiety disorders were more common than ADHD and conduct disorders. In the Kaplan-Meier analysis, 1,309 (83.5%) children were followed until the end of the study period, 226 (14.4%) until the diagnosis of a psychiatric disorder and 32 (2.1%) until emigration from the province. The incidence of psychiatric disorders (per 100 child-years) was 3.3 among children of parents with MS and 2.7 among those with parents not affected by MS (crude HR 1.19, 95% CI 0.93-1.54; **Table 6.5**). The incidence rate of psychiatric disorders in children was higher among boys, children whose parents had peripartum depression, and children whose parents were not married (**Table 6.5**).

Table 6.2. Additional characteristics of the cohort of parents with multiple sclerosis (MS), British Columbia, Canada

Characteristics	No. (%) (n=360)
Ever on MS disease-modifying treatments at index date*	
Yes	115 (31.9)
No	245 (68.1)
Age of parent at MS onset	
<20 years	23 (6.4)
20-29 years	215 (59.7)
30-39 years	114 (31.7)
≥40 years	8 (2.2)
Median [range]	28.0 [11.7 - 48.7 years]
Parental disease duration at index date (years)	
>0-4 years	31 (8.6)
5-9 years	210 (58.3)
≥10 years	119 (33.1)
Median [range]	8.5 [4.1 - 24.1 years]

*n=30 (26%) were ever exposed to glatiramer acetate and n= 85 (74%) to a beta-interferon

The adjusted Cox model showed that children with parental MS had a 37% higher risk of psychiatric disorders compared with children without parental MS (adjusted HR 1.37, 95% CI 1.05-1.78, **Table 6.6**, model 1). The rate of psychiatric disorders was also higher among children whose parents had peripartum depression compared with children whose parents did not have peripartum depression (adjusted HR 2.05, 95% CI 1.48-2.82). Peripartum depression did not modify the effect of parental MS on psychiatric disorders in children (interaction term HR 1.57, 95% CI 0.75-3.25, p value 0.25; **Table 6.6**, model 2). Model 3 shows the decomposed interaction term and the effects associated with each combination of parental MS and peripartum depression. Children whose parents had both MS and peripartum depression had a 3.5-fold higher rate of psychiatric disorders as compared with children whose parents did not have MS or peripartum depression (adjusted HR 3.54, 95% CI 2.02-6.21). Sensitivity analyses based on mental health disorders identified using a previously validated algorithm

yielded similar results (data not shown).

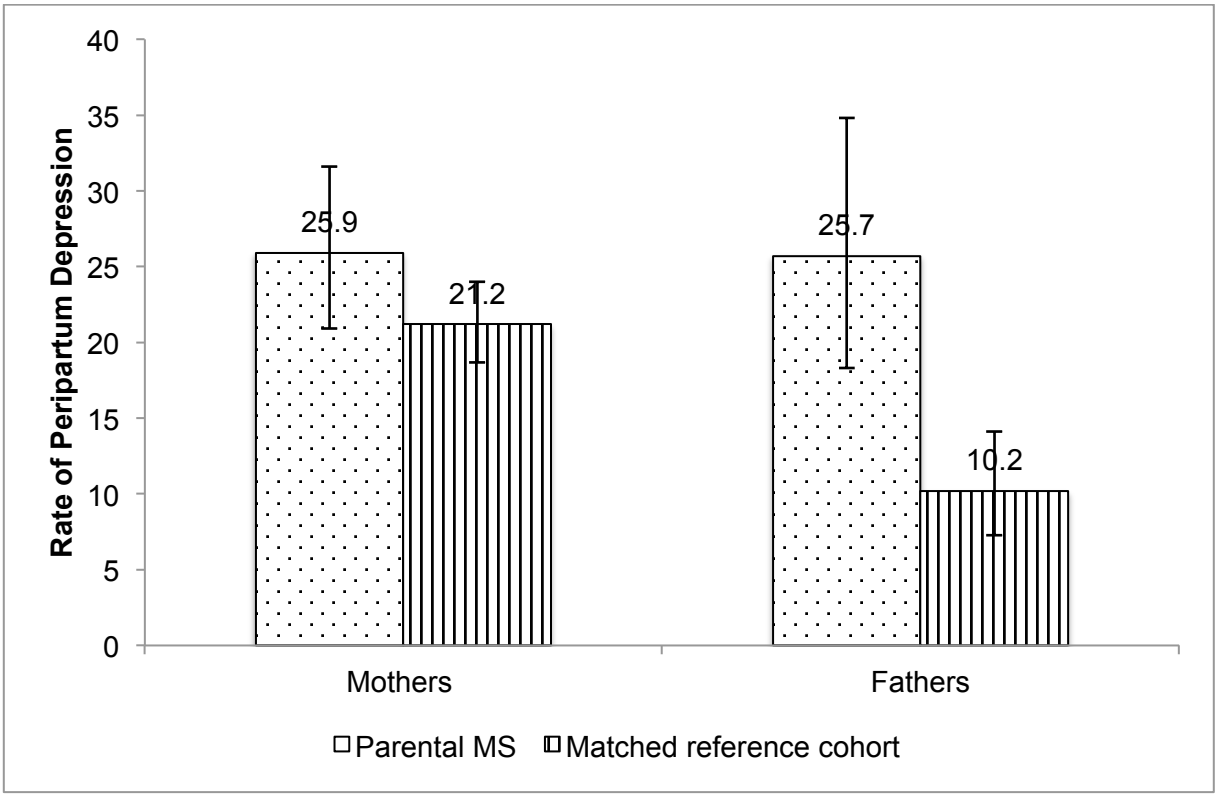


Figure 6.2. Peripartum depression (%) by parental multiple sclerosis (MS) status and parental sex, British Columbia, Canada
Error bars represent 95% confidence intervals

Table 6.3. History of depression (in the 2 years prior to the peripartum period) among parents who had peripartum depression, by parental multiple sclerosis (MS) status and sex, British Columbia, Canada

Peripartum depression	Parent with multiple sclerosis No. (%)	Matched reference cohort No. (%)
History of depression or anxiety	76 (34.2%)	184 (27.0%)
Mothers	54 (33.1%)	163 (28.4%)
Fathers	22 (37.3%)	21 (19.1%)
No history of depression or anxiety	17 (12.3%)	39 (7.4%)
Mothers	12 (13.4%)	29 (8.8%)
Fathers	5 (10.9%)	10 (5.1%)

Table 6.4. Unadjusted and adjusted odds ratios and 95% confidence intervals from conditional logistic regression showing the association between parental multiple sclerosis (MS) and peripartum depression, British Columbia, Canada

	Odds Ratio (95% Confidence Interval)			
	All		Mothers	Fathers
Characteristics	**Unadjusted †**	**Adjusted model §**	**Adjusted model §**	**Adjusted model §**
Parental multiple sclerosis (vs. absence)	1.52 (1.14-2.02)*	1.42 (1.19-1.70)*	1.15 (0.79−1.67)	3.08 (1.35−7.01)*
Socioeconomic Status (vs. 5th quintile)				
1st quintile [lowest]	1.36 (0.84-2.20)	1.19 (0.73−1.94)	1.16 (0.65−2.06)	0.91 (0.23−3.57)
2nd quintile	1.06 (0.64-1.76)	0.97 (0.58−1.63)	1.03 (0.57−1.87)	1.32 (0.33−5.25)
3rd quintile	1.36 (0.84-2.19)	1.26 (0.77−2.05)	1.12 (0.62−2.02)	1.70 (0.53−5.50)
4th quintile	1.47 (0.93-2.31)	1.36 (0.86−2.16)	1.61 (0.93−2.81)	1.67 (0.53−5.23)
Marital status (not married vs. married)	1.49 (1.10-2.02)*	1.56 (1.13−2.17)*	1.52 (1.05−2.22)*	1.42 (0.59−3.40)
Parental age at time of child's birth (years)	1.00 (0.98-1.03)	1.01 (0.98−1.03)	1.01 (0.98−1.05)	1.00 (0.93−1.08)
Male parental sex (vs. female)	0.64 (0.37-1.12)	0.84 (0.64-1.10)		
Parental MS*male parental sex		1.32 (1.08-1.60)*		

* p value <0.05

† Unadjusted model with matching factors only (child's year of birth, school district and sex of the parent)

§ Adjusted model with matching factors (child's year of birth, school district and sex of the parent) plus variables listed in the table

Table 6.5. Incidence of psychiatric disorders in children of parents with and without multiple sclerosis (MS), British Columbia, Canada

Factors	Psychiatric disorders in children			
	No.	Child-years at Risk	Rate per 100/child-years	Hazard Ratio (95% Confidence Interval)
Parental multiple sclerosis				
Yes	60	1,825	3.3	1.19 (0.93-1.54)
No	166	6,046	2.7	Ref
Peripartum depression or anxiety				
Yes	63	1,479	4.3	1.89 (1.39-2.57)*
No	163	6,393	2.5	Ref
Sex of the child				
Female	82	3,909	2.1	0.62 (0.50-0.82)*
Male	144	3,692	3.9	Ref
Child's first language				
English	199	6,734	3.0	Ref
Other	27	1,137	2.4	0.80 (0.50-1.26)
Older sibling				
Yes	112	4,461	2.5	0.79 (0.60-1.04)
No	114	3,410	3.3	Ref
Sex of the parent				
Female	171	5,971	2.9	1.06 (0.65-1.73)
Male	55	1,900	2.9	Ref
Marital status at time of child birth				
Married	144	5,747	2.5	Ref
Not married	82	2,124	3.9	1.77 (1.33-2.38)*
Parental age at cohort entry (years)				
<30 years	52	1,480	3.5	0.95 (0.64-1.40)
30-34 years	65	2,372	2.7	0.74 (0.51-1.09)
35-39 years	56	2,458	2.3	0.56 (0.39-0.84)*
≥40 years	53	1,561	3.4	Ref
Socioeconomic status at cohort entry				
1st quintile [lowest]	41	1,332	3.1	1.47 (0.92-2.34)
2nd quintile	41	1,374	3.0	1.19 (0.76-1.87)
3rd quintile	53	1,539	3.4	1.50 (0.98-2.28)
4th quintile	53	2,166	2.4	0.93 (0.62-1.40)
5th quintile [highest]	38	1,460	2.6	Ref

* p value <0.05 (from Cox regression that accounted for matching at the design stage)

Table 6.6. Adjusted hazard ratios and 95% confidence intervals from Cox regression showing the association between parental multiple sclerosis (MS) and psychiatric disorders in children, British Columbia, Canada

	Hazard Ratio (95% Confidence Interval)		
Characteristics	**Model 1 ****	**Model 2 †**	**Model 3 §**
Parental multiple sclerosis (vs. absence)	**1.37 (1.05−1.78)***	1.23 (0.88−1.71)	
Male child sex (vs. female)	**1.76 (1.31−2.35)***	**1.75 (1.31−2.35)***	**1.75 (1.31−2.35)***
Socioeconomic Status (vs. 5th quintile)			
1st quintile [lowest]	1.29 (0.81−2.03)	1.29 (0.81−2.04)	1.29 (0.81−2.04)
2nd quintile	0.93 (0.58−1.50)	0.95 (0.59−1.55)	0.95 (0.59−1.55)
3rd quintile	1.34 (0.87−2.08)	1.37 (0.88−2.13)	1.37 (0.88−2.13)
4th quintile	0.79 (0.52−1.21)	0.81 (0.53−1.25)	0.81 (0.53−1.25)
Peripartum depression (vs. absence)	**2.05 (1.48−2.82)***	**1.84 (1.26−2.68)***	
Marital status (not married vs. married)	**1.89 (1.38−2.59)***	**1.90 (1.39−2.61)***	**1.90 (1.37-2.61)***
Male parental sex (vs. female)	0.95 (0.59−1.53)	0.94 (0.58−1.52)	0.94 (0.58−1.52)
Paternal MS*Peripartum depression		1.57 (0.75−3.25)	
Parental MS absent, Peripartum depression present			**1.84 (1.26−2.68)***
Parental MS present, Peripartum depression absent			1.23 (0.88−1.71)
Parental MS present, Peripartum depression present			**3.54 (2.02−6.21)***
Parental MS absent, Peripartum depression absent			1.00

* p value < 0.05

** Model 1: Model adjusted for matching factors (child's year of birth, school district and sex of the parent) plus the variables listed in the table

† Model 2: Model 1 plus interaction term

§ Model 3: Model 2 with decomposed interaction term

6.5 Discussion

Our study provides evidence of an association between parental MS and peripartum depression. Fathers with MS had an increased risk of peripartum depression as compared with fathers unaffected by MS. Furthermore, children of parents with MS had a higher risk of developing psychiatric disorders compared with the children of parents without MS, and children whose parents had peripartum depression had a higher risk of developing psychiatric disorders compared with children of parents without peripartum depression. Higher rates of

psychiatric disorders in children were also observed among boys, and children whose parents were not married.

To the best of our knowledge there have been no previous reports that have quantified the frequency of depression or anxiety in the peripartum period among parents with MS. Studies in women with epilepsy show that approximately 25% to 29% of such women screen positive for depression.[157,158] In our study, approximately 26% of parents with MS were identified as having peripartum depression or anxiety, compared with a lower 19% rate of peripartum depression or anxiety in parents without MS. Depression is frequently missed among patients with MS and even when detected is often inadequately managed.[159] Maternal depression is particularly concerning because it is often a risk factor for a poor quality of life, paternal depression, and adverse emotional, intellectual and cognitive development in children.[160] Peripartum depression in people with MS could also adversely impact an individual's adherence to treatment and this can have important consequences on their disease course.[161] However, increasing the level of social support for mothers with MS during the postpartum period has been shown to mitigate some of the observed adverse affects by enhancing everyday functioning, and lowering depressive symptoms.[162,163]

In our study, fathers with MS had substantially higher rates of peripartum depression and/or anxiety (26%) compared with fathers without MS (10%). The latter rate is consistent with studies which show that peripartum depression is not uncommon among fathers and has a 12-month post-partum prevalence of 4% to 10%.[146] The higher risk of peripartum depression in men with MS could be triggered by their new role as fathers, which may require them to confront their physical or cognitive impairments and ability to address their family's

emotional and financial needs.[164] Further, MS-related fatigue and physical disability, and the unpredictable nature of MS symptoms can affect their ability to play an active role in caring for their young children and threaten their self-expectations of fatherhood (compared with fathers without MS). On the other hand, the peripartum experience of new mothers with MS may be comparable with that of mothers without MS, as women with MS who have chosen to become pregnant may have less active disease with less severe symptoms. The less severe disease would have given them the opportunity to discontinue their disease modifying treatment when trying to conceive, and also through gestation and while breastfeeding.

The association between parental MS and psychiatric disorders in children is consistent with previous work demonstrating that maternal MS is associated with a higher rate of mood or anxiety disorders in children; this association appears to be mediated through maternal mental health morbidity.[152] The limited research on this issue supports the notion that children of parents with MS are at greater risk of psychiatric outcomes including higher levels of depression and anxiety as compared with the children of healthy parents.[23,53,74] Our study shows that children whose parents have both MS and peripartum depression have a 3.5-fold increased risk of developing psychiatric disorders as compared with children whose parents do not have MS or peripartum depression. Studies examining the role of parental depression on child mental health suggest that the rates of psychiatric disorders among children of depressed parents are two to five times above normal and that the risk associated with maternal depressive symptoms may be comparable with that of paternal depressive symptoms.[160] Timely and appropriate interventions are key for such families; intervention studies targeted towards treatment for parental depression have shown significant improvement in children's functioning and psychiatric symptoms within one year after initiation of treatment.[166]

The strengths of our study include use of a comprehensive provincial data source and the use of previously validated case definitions for MS. The robustness of our analyses was also confirmed by the sensitivity analyses in which psychiatric disorders were identified using a previously validated algorithm. I also accounted for the clustered nature of the data arising from sequential births to the same parent during the study period. Certain limitations should also be considered in interpreting the findings of our study. First, I was not able to assess severity of peripartum depression and this could have differed between mothers and fathers. Second, our study sample was restricted to children born between 1993 and 2006, who had childhood developmental data, and represented a selected sample of parents with MS and their children. However, given that the assessment of child development has been routinely administered province-wide, the generalizability of our findings to the wider population of parents with MS was likely unaffected. Finally, I did not have a family-specific variable to assess socio-economic status, but used neighborhood-level income as a proxy for socio-economic status.

Our study demonstrated that parental MS, specifically paternal MS, is associated with a higher risk of peripartum depression. Furthermore, parental MS and parental peripartum depression independently increased the risk of psychiatric disorders in children. Given that depression and other psychiatric disorders are believed to be under-diagnosed and under-treated in persons with MS, parents with MS require special attention from health care professionals to ensure that their mental health and their children's mental health are optimized.

Chapter 7: Discussion

7.1 Summary of findings

Although having a parent with MS is often reported to have negative psychosocial effects on children and adolescents, there is a lack of consensus on this issue and some studies have demonstrated positive effects associated with parental MS. However, the literature on this topic is based mostly on cross-sectional studies, studies without comparison groups and studies with outcomes assessed through self-reports or parental reports of child and adolescent behaviour. The lack of good quality longitudinal studies with reasonably objective measures of child development makes it difficult to draw robust conclusions on the effects of parental MS (Chapter 2).

Studies presented in chapters 3 and 4 show no statistical significant association between having a parent with MS and developmental vulnerability in children at 5 years of age. In fact, children of parents with MS were less likely to be vulnerable on overall development as measured by vulnerability on any domain of the Early Development Instrument compared with children of parents without MS. Analyses by Early Development Instrument domain and by the parental sex showed that this difference was primarily due to a maternal effect on social development: children of mothers with MS were less likely to be vulnerable on the social competence domain compared with children of mothers without MS. However, various other factors, such as presence of mental and physical comorbidity in parents, socioeconomic status, greater disability in the MS-affected parents and longer disease duration, also adversely influenced children's developmental health (Chapter 4).

The longitudinal study reported in chapter 5 showed that mental health morbidity was significantly more frequent among parents with MS; both mothers with MS and fathers with MS had higher rates of mental health morbidity compared with mothers without MS and fathers without MS respectively. Further, survival analysis showed that the sex of the MS affected parent modified the relationship between parental MS and mood or anxiety disorders in children. Compared with children of unaffected mothers, children of mothers with MS had higher rates of mood or anxiety disorders, whereas children of fathers with MS were not at increased risk of mood and anxiety disorders compared with children of fathers without MS. The maternal effect of parental MS on child mood and anxiety disorders was mediated by mental health morbidity in mothers with MS i.e., MS increased rates of mental health morbidity in mothers and this appeared to be responsible for the higher rates of mood and anxiety disorders in children. Other risk factors for mood or anxiety disorders in children included physical morbidity in parents and low socioeconomic status (Chapter 5).

The study presented in Chapter 6 showed that parents with MS have a higher risk of developing peripartum depression compared with parents without MS. This excess risk of peripartum depression was restricted to fathers with MS; mothers with MS did not exhibit significantly increased rates of peripartum depression than would be expected in mothers without MS. However, mothers, but not the fathers, who were not married at the time of child's birth had higher risk of peripartum depression compared with mothers who were married. Furthermore, parental MS and parental peripartum depression were both important risk factors for psychiatric disorders in children and adolescents who were exposed to these parental conditions since birth. Overall, in both MS and the matched reference cohort, higher rates of mental health disorders were also observed among boys, children whose parents were

not married, older children, and children in the lowest income quintile (Chapter 6).

7.2 Causal inference

Inferring causation is a complex task and involves some subjectivity. In simplest epidemiologic terms causation requires an association between an exposure and an outcome without confounding or bias. Austin Bradford Hill developed a set of guidelines or criteria required to establish a causal relationship between an exposure and an outcome.[167] These criteria are not absolute requirement (except perhaps for temporality). Failure to satisfy any or even most of these guidelines does not necessarily imply that an association is not casual. The results of the studies in this dissertation satisfied several requirements for inferring causality in connection with parental MS and child outcomes such as developmental health at kindergarten age and mental health morbidity in childhood and adolescence. Causal criteria met in these studies included a) temporality: The longitudinal study design, ensured that parental MS onset preceded child outcomes; b) dose-response: A monotonic relationship was seen between increasing duration of exposure to parental MS and child psychiatric outcomes; c) strength of the association: A modestly strong, statistically significant association was observed between parental MS and child mental health morbidity; d) biological plausibility: It is clinically reasonable to postulate that parental MS, specifically depression and anxiety in parents with MS, puts children at a higher risk of developing emotional difficulties; and e) consistency: Replicating the study in two different settings, Manitoba and British Columbia, demonstrated that parental MS independently is not associated with adverse developmental health in children. On the other hand, the studies conducted in this dissertation were not experimental and the inability to rule out confounding and other bias with certainty potentially weakens the argument for a casual association. Furthermore, it is difficult to establish temporality in

regards to parental MS and mental health disorders, as MS has long subclinical phase and insidious onset, where diagnosis may occur long after the subclinical onset of the disease. In summary, the results of this dissertation offer modest evidence for a causal relationship between parental MS and mental health morbidity in children and adolescents.

7.3 Proposed conceptual framework and future directions

No single theoretical perspective is likely sufficient to encompass the complexity of parental MS and child developmental health especially given the paucity of studies on this topic. Nevertheless, based on the findings of this thesis, I have proposed below a conceptual framework to describe pathways and mechanisms through which parental MS could affect child development and mental health. The theoretical origins of my framework (**Figure 7.1**) lie in the Falkov Family Model,[168] which contends that parent and child relationships are reciprocal in nature - parents and children are influenced by each other through multiple interactions. This model includes vulnerability and protective factors associated with parental MS as well as the relationship of the family with their neighbourhoods and the community. It posits that several related mechanisms link parental MS to a child's mental and developmental health.

The schematic diagram (**Figure 7.1**) shows the various mechanisms that might influence child development when a parent has MS. Parental MS can lead to both positive and negative effects on developmental health in children (1 ➔ 2). The study in chapter 4 showed that parental MS is associated with lower vulnerability on the social competence domain of child development at 5 years of age. However, the longer a child has been exposed to the parent's MS and the older the child, the greater the risk of a mental health disorder in the child (chapter

6). The study reported in Chapter 5 suggests that the relationship between parental MS and mental health disorders in children is mainly mediated through the parent's mental health morbidity (1 ➔ 3 ➔ 2). Although both mothers and fathers affected by MS have higher rates of mental health comorbidity, the influence of parental MS on the child's risk for mood and anxiety disorders appears to act through maternal mental health comorbidity i.e., mothers with MS are more likely to have a mental health comorbidity that leads to higher rates of mood and anxiety disorders in children. On the other hand, peripartum depression which may also increases the risk of mental health disorders in children, appears to manifest more strongly in fathers with MS and less strongly in mothers with MS (relative to fathers and mothers without MS). In summary, MS is associated with substantially higher levels of mental health morbidity and peripartum depression in the affected parent (1 ➔ 3), this adversely influences parenting and family functioning (3 ➔ 4), and leads to a negative impact on children's adjustment and psychopathology (4 ➔ 2).

An additional aspect of family interactions arises because children, particularly those with emotional and behavioural difficulties, can exacerbate mental illness in their parents (2 ➔ 3). The dynamic interplay between familial adversity, such as parental MS or mental health, and the developing child's personality may play an important role in the development of subsequent negative outcomes. Such hypothesized relationships were not examined in this thesis and future studies should investigate the role of child developmental difficulties on the mental health of their MS-affected parent.

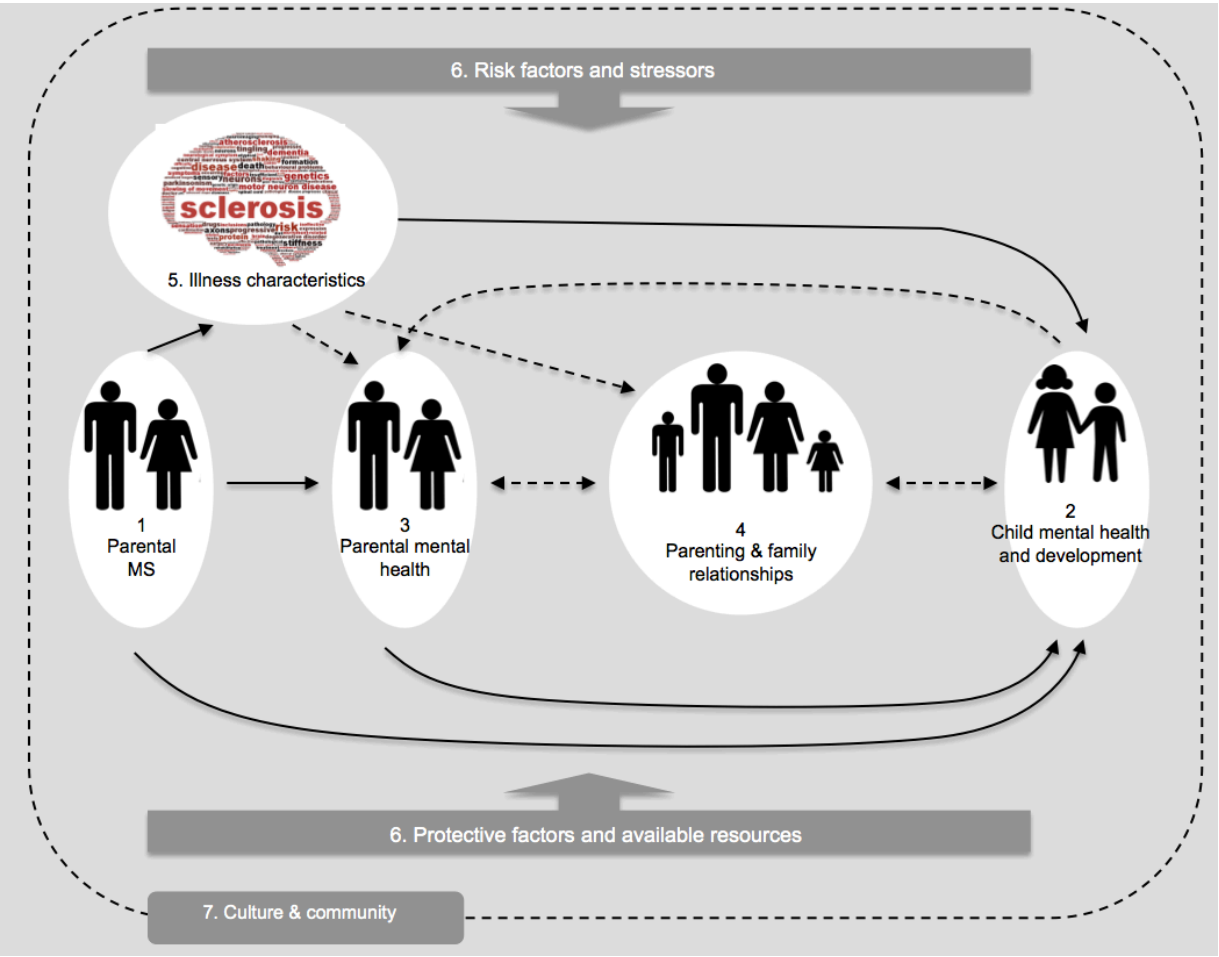


Figure 7.1. Schematic depiction of a conceptual framework describing pathways and mechanisms through which parental multiple sclerosis affects child and adolescent development (derived from the Falkov Family Model). Variables and hypothesized directions of associations studied are illustrated with solid lines while other potential directions of relationships considered important but not studied are illustrated in dashed lines.

_____ Relationships examined in this thesis
--------- Hypothesized relationships not studied in this thesis

The finding that parental MS is associated with less vulnerability on the social competence domain in children at 5 years of age (1 ➔ 2) illustrates the protective factors, such as consistent and sensitive caregiving, that may outweigh the negative effects of parental MS on child development (6 ➔ 1, 2, 3, 4, 5).[169] Such parenting practices can support resilience, enhance children's learning and help them develop adaptive capacities that promote healthy child development and behaviour.[170] While caring for an ill parent might be a risk factor with

regard to children's anxiety and depression, the opportunity to care might also provide children with a learning opportunity to develop their social competences, pro-social behaviors, and empathy. Mutual support within the family during times of stress can strengthen the parent-child bond and give children a sense of pride in their caregiving abilities.[29] The coping ability of parents appears to be a key protective factor for a child's psychological adjustment and could potentially buffer the impact of the parent's illness and mental health on the child.[47,93] Alternatively, if a healthy parent (i.e., without MS) suffers from a mental illness, this increases the child's risk of developmental vulnerability (6 ➔ 1, 2, 3, 4). Future studies should consider the role of the other parent, i.e. the "healthy" partner on the child's mental health status. Another issue of importance is the role of the child's age in relation to stressors associated with parental MS.

Parental factors such as MS disease duration or level of disablity or factors commonly associated with MS, such as presence of physical comorbidity may additionally influence childrens' and adolescents' mental health outcomes (5 ➔ 2). As the MS disease course changes over time and disability progresses, the family may experience more conflict and less cohesion, with parents paying less attention to the growing child's needs.[45] Other common MS-related symptoms or comorbidity, such as fatigue,[94] could also impact child mental health through exacerbation of parental mental health morbidity (5 ➔ 3) or directly by compromising parental competence (5 ➔ 4). These proposed pathways should be examined in future research. Other important factors or stressors that might influence children's adjustment to parental illness would include the gender of the parent and the child, intensity and duration of child's care-giving responsibility, a child's age-related developmental needs, family

structure (i.e. one or two parent families), socioeconomic status of the family, and the level of social support (6 ➔ 1, 2, 3, 4, 5).

The gender of the parent affected by MS can have an important bearing on the child's developmental health. Families with the primary caregiver for the children (typically the mother) diagnosed with MS might restructure household and childcare tasks and alter the homemaker (mother)-child attachment and interaction. Families where the income earner (mother or father) is affected by MS may experience stress due to socioeconomic adversity. Child factors, such as the child's gender, special needs, temperament and cognitive and social skills, and factors external to the child tend to become intertwined through cascading effects that may influence a child's relationship with their parent. Overall, single psychosocial risks may have negligible effects;[171,172] the cumulative effect of multiple risk factors, such as low socioeconomic status, single parenthood, a dysfunction family environment, and low levels of social support could increase the likelihood of parental MS having a negative impact on developmental health outcomes of children.[100] Last, the broader societal and economic framework in which families live and the potential stigma associated with disability or mental illness, are other pathways that could affect the family dynamics (7 ➔ 1, 2, 3, 4, 5, 6).

7.4 Strengths and limitations

The methodological strengths of these studies included the longitudinal design and validated data sources. Access to comprehensive health and education-related databases at the population level in both Manitoba and British Columbia yielded two relatively large studies despite the rarity of parental MS. I used objective and previously validated case definitions for ascertaining MS and mental and physical morbidity and this increased the validity of our

findings. In addition, recall bias (potentially a problem in previous studies which used parental and self-assessments) was minimized in our studies because the data used were based on physician claims, hospital admissions and prescription drug information. These data were collected without *a priori* knowledge of a specific research question, effectively avoiding surveillance and reporting bias. Other strengths of our studies included the use of the Early Development Instrument to assess child development (Chapters 3 and 4). The EDI assessment by teachers avoided reliance on parental or self-report of developmental outcomes. The EDI has undergone significant psychometric testing to confirm validity and reliability as a research tool[34,103] and has been shown to be correlated with later literacy achievements,[118] and psychological assessments.[119] Nonetheless, there may be some individual differences in teachers' ability to evaluate developmental health on the EDI.[108] Finally, in all our analyses I accounted for the clustered nature of the data arising from sequential births to the same parent during the study period.

Several limitations should be noted. A small degree of miscoding and misclassification is inevitable in large health databases. However, several studies have validated the use of such databases as suitable sources for research.[173] In particular, both the Manitoba and British Columbia's linked health administrative databases have been shown to have good validity and reliability compared with population surveys and chart reviews.[101-104] Other limitations included an inability to assess the severity of mental health disorders in our cohorts. Also, I was only able to identify morbidity among subjects whose condition was recognized by the health care system i.e., those who sought medical attention and were diagnosed. In addition, I did not attempt to distinguish between depression and anxiety disorders;[115] the presence of either (or both) diagnoses was considered a mental health morbidity.[115] I was also unable to

differentiate between children who were adopted vs. living with a biological parent. However, since the object of study was an environmental influence (i.e., exposure to MS), rather than a genetic influence, this appears unlikely to have impacted our findings. Also, the relatively small number of MS-affected fathers limited our ability to draw robust conclusions about the association between paternal MS and developmental health in children.

In the study examining peripartum depression in parents with MS, I capitalized on already available data, such that our study sample was restricted to children with developmental information (the EDI) who had been born between 1993 and 2006. , These study subjects represented a selected sample of parents with MS whose disease onset preceded the child's birth. Since the assessment of child developmental health has been routinely administered province-wide, the generalizability of our findings to the wider population of parents with MS was likely unaffected. To our knowledge, this was the first study to investigate the frequency of peripartum depression in individuals with MS. Although I attempted to control for a broad range of confounders, residual confounding may have biased our results. This could have occurred due to information on factors not available in our data source (e.g., parental education) or imprecise measurement of factors such as socioeconomic status as I used neighborhood-level income as a proxy for the family's socioeconomic status.

7.5 Significance and implications of thesis research

Canada, which has a very high prevalence of MS[174] has much to gain from insights into the consequences of MS. Currently some 100,000 people in Canada are affected by MS, with three additional people diagnosed every day.[174] This results in thousands of Canadian children for whom typical childhood challenges may become far more daunting because their parent

has MS. Health Canada and the MS Society have recognized that children exposed to parental MS are a population 'at risk',[8] and hence it is essential to monitor the effects of parental MS on children. Findings from this research could lead to a better understanding of factors influencing child development, a critical step for improving the long-term health status of this potentially at-risk population.

The childhood period is particularly sensitive to environmental influences.[175] A key requisite for optimal child development is secure attachment to a trusted caregiver, with consistent caring, support and affection early in life. Families constitute the first environments within which children interact and are critically important for stimulating, supporting and nurturing children.[176] Adverse environmental experiences, such as those due to parental depression, which are prolonged and intense can be more detrimental to a child's health and well-being than unfavourable experiences that are brief and less traumatic.[169] The optimal approach to reducing developmental risk likely involves early intervention aimed at the child's proximal environment to prevent the consequences of adversity on the developing brain and personality.[169]

The early identification of emerging mental health problems is important since approximately half of adults with a psychiatric disorder have had a diagnosable mental health disorder in childhood.[177] Children from families in which parents experience chronic and severe depression represent a high-risk group for dysfunction and adverse developmental health, and [160] timely and appropriate interventions are required to support such families. Intervention studies targeted towards treatment for parental depression have shown significant improvement in children's psychiatric symptoms within one year after initiation of

treatment.[166] More work needs to be done to identify appropriate interventions that could help mitigate the chronic stresses within families where a parent has MS.

The results of this dissertation are also directly useful for health care professionals, and families affected by MS. The studies provide much needed information on the issues surrounding MS and parenting; parental MS itself does not affect child development but the stress of parental MS can lead to increased mental health morbidity among parents and this in turn can lead to higher rates of adverse developmental and mental health outcomes among children. While other longitudinal studies are needed to confirm our findings, health professionals need to be aware of the effects of mental health morbidity commonly associated with MS, and its impact on childhood development. In addition to interventions specifically directed at the child, there is a need for family-centered support that focuses on parenting difficulties due to MS in the family. In so doing, both the mother's and father's mental health needs should be considered in order to ensure the optimal developmental health of children.[55] Studies show that providing strong social support for parents with MS enhances everyday functioning, and lowers depressive symptomatology.[162,163] Our results may also have implications for other patient groups such as families affected by cancer and other chronic diseases. There is a need to study the effects and costs of implementing intervention programs that support families affected by chronic illnesses so that the impact of disease on these individuals and their children can be minimized.

7.6 Conclusions

The work presented in this dissertation represents a first step in the epidemiologic investigation of the effects of parental MS and related factors on child and adolescent

development. The systematic review revealed a dearth of methodologically robust studies in this area. The subsequent longitudinal studies were carried out in two Canadian provinces and used objective measures of childhood development in a population-based setting. The results suggested that the presence of parental MS was not independently associated with adverse developmental health in kindergarten-level children. Nevertheless, MS is associated with substantially higher levels of mental health morbidity and peripartum depression in parents, and such mental health impairments adversely affect children and adolescent's adjustment and mental health. Prevention efforts aimed at alleviating the impact of parental MS on mental health disorders in children should address the psychological needs of MS parents and their children.

References

1. Irwin LG, Siddiqi A, Hertzman C. Early child development: A powerful equalizer: Final report. Geneva: World Health Organization, 2007.

2. Hertzman C, Power C, Matthews S, Manor O. Child development as a determinant of health across the life course. Curr Pediatr 2004;14:438-443.

3. Hertzman C. Population health and human development. In: Daniel P, Hertzman, C., ed. Developmental health and the wealth of nations: Social, biological, and educational dynamics New York, NY, US: Guilford Press, 1999: 21-40.

4. Mash EJ, Barkely RA. Child Psychopathology, Second ed. New York: The Guilford Press, 2003.

5. Barkmann C, Romer G, Watson M, Schulte-Markwort M. Parental physical illness as a risk for psychosocial maladjustment in children and adolescents: epidemiological findings from a national survey in Germany. Psychosomatics 2007;48:476-481.

6. Sieh DS, Visser-Meily JM, Meijer AM. Differential outcomes of adolescents with chronically ill and healthy parents. J Child Fam Stud 2013;22:209-218.

7. Sieh DS, Meijer AM, Oort FJ, Visser-Meily JM, Van der Leij DA. Problem behavior in children of chronically ill parents: a meta-analysis. Clin Child Fam Psychol Rev 2010;13:384-397.

8. Growing Up Strong: Supporting the Children of Parents with MS; Multiple Sclerosis Society of Canada. 2002. Available at: mssociety.ca/en/pdf/GrowingUpStrongLiteratureReview.pdf. Accessed 26-Jun-2015.

9. Sieh DS, Visser-Meily JM, Oort FJ, Meijer AM. Risk factors for problem behavior in adolescents of parents with a chronic medical condition. Eur Child Adolesc Psychiatry 2012;21:459-471.

10. Leary SM, Porter B, Thompson AJ. Multiple sclerosis: diagnosis and the management of acute relapses. Postgrad Med J 2005;81:302-308.

11. Compston A, Confavreux C, Lassmann H, Miller D, Smith K, Wekerle H, Confavreux C. McAlpine's multiple sclerosis, Fourth Edition ed. London; Edinburgh; New York: Churchill Livingstone Elsevier, 2006

12. Poser CM, Paty DW, Scheinberg L, McDonald WI, Davis FA, Ebers GC, Johnson KP, Sibley WA, Silberberg DH, Tourtellotte WW. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. Ann Neurol 1983;13:227-231.

13. McDonald WI, Compston A, Edan G, Goodkin D, Hartung H-P, Lublin FD, McFarland HF, Paty DW, Polman CH, Reingold SC, Sandberg-Wollheim M, Sibley W, Thompson A, Van Den Noort S, Weinshenker BY, Wolinsky JS. Recommended diagnostic criteria for multiple

sclerosis: Guidelines from the international panel on the diagnosis of multiple sclerosis. Ann Neurol 2001;50:121-127.

14. Hassan-Smith G, Douglas MR. Epidemiology and diagnosis of multiple sclerosis. Br J Hosp Med (Lond) 2011;72:M146-151.

15. Hawker K. Progressive multiple sclerosis: characteristics and management. Neurol Clin 2011;29:423-434.

16. Coles A. Multiple sclerosis. Pract Neurol 2009;9:118-126.

17. Atlas of MS Background [online] 2013; Multiple Sclerosis International Federation Available at: http://www.msif.org/about-us/advocacy/atlas-of-ms/ Accessed June 19, 2015.

18. Tremlett H, Paty D, Devonshire V. Disability progression in multiple sclerosis is slower than previously reported. Neurology 2006;66:172-177.

19. British Columbia Perinatal Database Registry Annual Report 2008; Perinatal Services British Columbia Available at: http://www.perinatalservicesbc.ca/sites/bcrcp/files/AnnualReport/annual_report_2008/TOC_2008.pdf. Accessed 26-Jun-2011.

20. Perinatal Health Report 2008-09 to 2012-13. Vancouver, Canada: Perinatal Services British Columbia 2014.

21. McKay KA, Kwan V, Duggan T, Tremlett H. Risk Factors Associated with the Onset of Relapsing-Remitting and Primary Progressive Multiple Sclerosis: A Systematic Review. BioMed Res Int 2015;2015:11.

22. Murray TJ. The psychosocial aspects of multiple sclerosis. Neurol Clin 1995;13:197-223.

23. Diareme S, Tsiantis J, Kolaitis G, Ferentinos S, Tsalamanios E, Paliokosta E, Anasontzi S, Lympinaki E, Anagnostopoulos DC, Voumvourakis C, Romer G. Emotional and behavioural difficulties in children of parents with multiple sclerosis: a controlled study in Greece. Eur Child Adolesc Psychiatry 2006;15:309-318.

24. Steck B, Amsler F, Grether A, Dillier AS, Baldus C, Haagen M, Diareme L, Tsiantis J, Kappos L, Burgin D, Romer G. Mental health problems in children of somatically ill parents, e.g. multiple sclerosis. Eur Child Adolesc Psychiatry 2007;16:199-207.

25. Paliokosta E, Diareme S, Kolaitis G, Tsalamanios E, Ferentinos S, Anasontzi S, Lympinaki E, Tsiantis A, Tsiantis J, Karageorgiou C, Romer G. Breaking Bad News: Communication Around Parental Multiple Sclerosis With Children. Fam Syst Health 2009;27:64-76.

26. Bogosian A, Moss-Morris R, Hadwin J. Psychosocial adjustment in children and adolescents with a parent with multiple sclerosis: a systematic review. Clin Rehabil 2010;24:789-801.

27. Kouzoupis AB, Paparrigopoulos T, Soldatos M, Papadimitriou GN. The family of the multiple sclerosis patient: a psychosocial perspective. Int Rev Psychiatry 2010;22:83-89.

28. Crick NR, Zahn-Waxler C. The development of psychopathology in females and males: current progress and future challenges. Dev Psychopathol 2003;15:719-742.

29. Turpin M, Leech C, Hackenberg L. Living with parental multiple sclerosis: children's experiences and clinical implications. Can J Occup Ther 2008;75:149-156.

30. Kikuchi JF. The reported quality of life of children and adolescents of parents with multiple sclerosis. Recent Adv Nurs 1987:163-191.

31. Crist P. Contingent Interaction During Work and Play Tasks for Mothers with Multiple Sclerosis and Their Daughters. Am J Occup Ther 1993;47:121-131.

32. Buhse M. Assessment of caregiver burden in families of persons with multiple sclerosis. J Neurosci Nurs 2008;40:25-31.

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

34. Janus M, Offord DR. Development and psychometric properties of the early development instrument (EDI): A measure of children's school readiness. Can J Behav Sci 2007;39:1-22.

35. Marrie RA, Cohen J, Stuve O, Trojano M, Sorensen PS, Reingold S, Cutter G, Reider N. A systematic review of the incidence and prevalence of comorbidity in multiple sclerosis: overview. Mult Scler 2015;21:263-281.

36. Marrie RA, Elliott L, Marriott J, Cossoy M, Blanchard J, Leung S, Yu N. Effect of comorbidity on mortality in multiple sclerosis. Neurology 2015;85:240-247.

37. Marrie RA, Fisk J, Yu BN, Leung S, Elliott L, Caetano P, Warren S, Evans C, Wolfson C, Svenson LW, Tremlett H, Blanchard J, Patten SB, Epidemiology ftCTit, Sclerosis IoCoM. Mental comorbidity and multiple sclerosis: validating administrative data to support population-based surveillance. BMC Neurol 2013;13:16.

38. Marrie RA, Bernstein CN, Peschken CA, Hitchon CA, Chen H, Fransoo R, Garland A. Health care utilization before and after intensive care unit admission in multiple sclerosis. Mult Scler Relat Disord 2015;4:296-303.

39. Viner R, Fiest KM, Bulloch AG, Williams JV, Lavorato DH, Berzins S, Jetté N, Metz LM, Patten SB. Point prevalence and correlates of depression in a national community sample with multiple sclerosis. Gen Hosp Psychiatry 2014;36:352-354.

40. Ramchandani P, Stein A, Evans J, O'Connor TG. Paternal depression in the postnatal period and child development: a prospective population study. Lancet 2005;365:2201-2205.

41. Pakenham KI, Bursnall S. Relations between social support, appraisal and coping and both positive and negative outcomes for children of a parent with multiple sclerosis and comparisons with children of healthy parents. Clin Rehabil 2006;20:709-723.

42. Hyatt RR, Jr., Allen SM. Disability as a "family affair": parental disability and childhood immunization. Med Care 2005;43:600-606.

43. Armistead L, Klein K, Forehand R. Parental physical illness and child functioning. Clin Psychol Rev 1995;15:409-422.

44. Deatrick JA, Brennan D, Cameron ME. Mothers with multiple sclerosis and their children: effects of fatigue and exacerbations on maternal support. Nurs Res 1998;47:205-210.

45. De Judicibus MA, McCabe MP. The impact of parental multiple sclerosis on the adjustment of children and adolescents. Adolescence 2004;39:551-569.

46. Pakenham KI, Cox S. The nature of caregiving in children of a parent with multiple sclerosis from multiple sources and the associations between caregiving activities and youth adjustment overtime. Psychol Health 2012;27:324-346.

47. Steck B, Amsler F, Kappos L, Burgin D. Gender-specific differences in the process of coping in families with a parent affected by a chronic somatic disease (e.g. multiple sclerosis). Psychopathology 2001;34:236-244.

48. Worsham N, Compass B, Ey S. Children's coping with parental illness. In: Wolchik S, Sandler I, eds. Handbook of Children's Coping: Linking Theory and Intervention. New York, NY: Plenum Press, 1997: 195-213.

49. Miller A, Dishon S. Health-related quality of life in multiple sclerosis: The impact of disability, gender and employment status. Qual Life Res 2006;15:259-271.

50. Fernandez O, Baumstarck-Barrau K, Simeoni M-C, Auquier P. Patient characteristics and determinants of quality of life in an international population with multiple sclerosis: Assessment using the MusiQoL and SF-36 questionnaires. Mult Scler 2011;17:1238-1249.

51. Lazarus RS, Folkman S. Stress, appraisal, and coping. New York: Springer, 1984.

52. Pakenham KI, Cox S. Test of a model of the effects of parental illness on youth and family functioning. Health Psychol 2012;31:580.

53. Brandt P, Weinert C. Children's mental health in families experiencing multiple sclerosis. J Fam Nurs 1998;4:41-64.

54. Razaz N, Joseph KS, Marrie RA, Tremlett H. Reproductive issues in multiple sclerosis: Parental MS and child outcomes; the research perspective. In: Houtchens MK, Sadovnick D, eds. Health Issues in Women with Multiple Sclerosis. Toronto, Canada Springer, (Under review).

55. Early childhood development: Adverse experiences and developmental health. Ottawa, ON: Royal Society of Canada-Canadian Academy of Health Sciences Expert Panel (with Ronald Barr, Thomas Boyce, Alison Fleming, Harriet MacMillan, Candice Odgers, Marla Sokolowski, & Nico Trocmé), 2012.

56. British Columbia Ministry of Health [creator] [2012]: Medical Services Plan (MSP) Payment Information File Population Data BC [publisher];Data Extract. MOH (2012).

57. British Columbia Ministry of Health [creator] [2012]: Discharge Abstract Database (Hospital Separations). Population Data BC [publisher];Data Extract. MOH (2012).

58. British Columbia Ministry of Health [creator] [2012]: Consolidation File (MSP Registration & Premium Billing). Population Data BC [publisher];Data Extract. MOH (2012).

59. British Columbia Ministry of Health [creator] (2012): PharmaNet. BC Ministry of Health [Publisher];Data Extract. Data Stewardship Committee (2012).

60. British Columbia Vital Statistics Agency [creator] (2012): Vital Statistics Births. Population Data BC [publisher];Data Extract BC Vital Statistics Agenency (2012).

61. Human Early Learning Partnership [creator] (2012): Early Development Instrument. Population Data BC [publisher];Data Extract. Human Early Learning Partnership. Vancouver, BC: University of British Columbia, School of Population and Public Health (2012).

62. Statistics Canada: Annual Income Estimates for Census Families and Individuals (T1 Family File) Ottawa; Statistics Canada Available at: http://www23.statcan.gc.ca/imdb/p2SV.pl?Function=getSurvey&SDDS=4105&lang=en&db=IMDB&dbg=f&adm=8&dis=2. Accessed 4 July 2015.

63. Stephenson A, Hux J, Tullis E, Austin PC, Corey M, Ray J. Socioeconomic status and risk of hospitalization among individuals with cystic fibrosis in Ontario, Canada. Pediatr Pulmonol 2011;46:376-384.

64. Sweeney VP, Sadovnick AD, Brandejs V. Prevalence of multiple sclerosis in British Columbia. Can J Neurol Sci 1986;13:47-51.

65. Health Information Management Branch, Population Report. Winnipeg, Manitoba: Manitoba Health and Healthy Living, 2008.

66. Smeltzer SC. Reproductive decision making in women with multiple sclerosis. J Neurosci Nurs 2002;34:145-157.

67. Jackson R, Ameratunga S, Broad J, Connor J, Lethaby A, Robb G, Wells S, Glasziou P, Heneghan C. The GATE frame: critical appraisal with pictures. Evid Based Med 2006;11:35-38.

68. Arnaud SH. Some psychological characteristics of children of multiple sclerotics. Psychosom Med 1959;21:8-22.

69. Olgas M. The relationship between parents' health status and body image of their children. Nurs Res 1974;23:319-324.

70. Peters LC, Esses LM. Family environment as perceived by children with a chronically ill parent. J Chronic Dis 1985;38:301-308.

71. Blackford KA. A child's growing up with a parent who has multiple sclerosis: theories and experiences. Disabil Soc 1999;14:673-685.

72. Steck B, Amsler F, Dillier AS, Grether A, Kappos L, Bürgin D. Indication for Psychotherapy in Offspring of a Parent Affected by a Chronic Somatic Disease (e.g. Multiple Sclerosis). Psychopathology 2005;38:38-48.

73. Bogosian A, Moss-Morris R, Bishop FL, Hadwin J. How do adolescents adjust to their parent's multiple sclerosis? An interview study. Br J Health Psychol 2011;16:430-444.

74. Yahav R, Vosburgh J, Miller A. Emotional responses of children and adolescents to parents with multiple sclerosis. Mult Scler 2005;11:464-468.

75. Yahav R, Vosburgh J, Miller A. Separation-individuation processes of adolescent children of parents with multiple sclerosis. Mult Scler 2007;13:87-94.

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

77. Beck SJ. Rorschach Test. I. Basic Processes. Acad Med 1961;36:846.

78. Achenbach TM. Child behavior checklist/4-18. Burlington: University of Vermont 1991.

79. Goodman SH, Rouse MH, Connell AM, Broth MR, Hall CM, Heyward D. Maternal depression and child psychopathology: a meta-analytic review. Clin Child Fam Psychol Rev 2011;14:1-27.

80. Achenbach TM. Integrative guide for the 1991 CBCL/4-18, YSR, and TRF profiles. Vernon: Department of Psychiatry, University of Vermont Burlington, 1991.

81. Levine JB, Green CJ, Millon T. The separation-individuation test of adolescence. J Pers Assess 1986;50:123-139.

82. Koppitz EM. Psychological evaluation of children's human figure drawings: Grune & Stratton New York, 1968.

83. Osgood CE. The measurement of meaning. Urbana: University of Illinois Press, 1957.

84. Secord PF, Jourard SM. The appraisal of body-cathexis: body-cathexis and the self. J Consult Psychol 1953;17:343.

85. Ireland MJ, Pakenham KI. The nature of youth care tasks in families experiencing chronic illness/disability: Development of the Youth Activities of Caregiving Scale (YACS). Psychol Health 2010;25:713-731.

86. Moos RH, Moos BS. Family environment scale manual. Palo Alto, CA: Consulting Psychologists Press, 1994.

87. Kelley SDM, Sikka A, Venkatesan S. A review of research on parental disability: Implications for research and counseling practice. Rehabil Couns Bull 1997;41:105 - 121.

88. Pakenham KI. The positive impact of multiple sclerosis (MS) on carers: associations between carer benefit finding and positive and negative adjustment domains. Disabil Rehabil 2005;27:985-997.

89. Warren S, Turpin K, Pohar S, Jones C, Warren K. Comorbidity and health-related quality of life in people with multiple sclerosis. Int J MS Care 2009;11:6-16.

90. Cross T, Rintell D. Children's perceptions of parental multiple sclerosis. Psychol Health Med 1999;4:355-360.

91. Coles AR, Pakenham KI, Leech C. Evaluation of an intensive psychosocial intervention for children of parents with multiple sclerosis. Rehabil Psychol 2007;52:133-142.

92. White CP, King K. Is Maternal Fatigue Mediating the Relationship between Maternal Depression and Child Outcomes? J Child Fam Stud 2011;20:844-853.

93. Ehrensperger MM, Grether A, Romer G, Berres M, Monsch AU, Kappos L, Steck B. Neuropsychological dysfunction, depression, physical disability, and coping processes in families with a parent affected by multiple sclerosis. Mult Scler 2008;14:1106-1112.

94. Hadjimichael O, Vollmer T, Oleen-Burkey M. Fatigue characteristics in multiple sclerosis: the North American Research Committee on Multiple Sclerosis (NARCOMS) survey. Health Qual Life Outcomes 2008;6:100.

95. Razaz N, Hertzman C, Marrie R, Tremlett H, Boyce W. Children of chronically ill parents: The Silence of Research. Child Care Health Dev 2014;40:753-754.

96. Sanderson S, Tatt ID, Higgins JP. Tools for assessing quality and susceptibility to bias in observational studies in epidemiology: a systematic review and annotated bibliography. Int J Epidemiol 2007;36:666-676.

97. Baker A, Young K, Potter J, Madan I. A review of grading systems for evidence-based guidelines produced by medical specialties. Clin Med (Northfield Il) 2010;10:358-363.

98. Robb G, Arroll B, Reid D, Goodyear-Smith F. Summary of an evidence-based guideline on soft tissue shoulder injuries and related disorders-Part 1: assessment. J Prim Health Care 2010;1:36-41.

99. Essex MJ, Boyce WT, Hertzman C, Lam LL, Armstrong JM, Neumann S, Kobor MS. Epigenetic vestiges of early developmental adversity: childhood stress exposure and DNA methylation in adolescence. Child Dev 2011;84:58–75.

100. Razaz N, Nourian R, Marrie RA, Boyce WT, Tremlett H. Children's and adolescents adjustment to parental multiple sclerosis: a systematic review. BMC Neurol 2014;14:107.

101. Roos LL, Nicol JP. A research registry: uses, development, and accuracy. J Clin Epidemiol 1999;52:39-47.

102. Jutte DP, Roos LL, Brownell MD. Administrative record linkage as a tool for public health research. Annu Rev Public Health 2011;32:91-108.

103. Forer B, Zumbo BD. Validation of multilevel constructs: Validation methods and empirical findings for the EDI. Soc Indic Res 2011;103:231-265.

104. Lloyd J. Bringing it together: Merging community-based, life-course, linked data, and social indicator approaches to monitoring child development. In: Centre ECLK, ed. Montréal, QC: Canadian Council on Learning, 2008.

105. Marrie RA, Yu N, Blanchard J, Leung S, Elliott L. The rising prevalence and changing age distribution of multiple sclerosis in Manitoba. Neurology 2010;74:465-471.

106. Duncan GJ, Dowsett CJ, Claessens A, Magnuson K, Huston AC, Klebanov P, Pagani LS, Feinstein L, Engel M, Brooks-Gunn J. School readiness and later achievement. Dev Psychol 2007;43:1428.

107. Janus M, Duku E. The School Entry Gap: Socioeconomic, Family, and Health Factors Associated with Children's School Readiness to Learn. Early Education 2007;18:375-403.

108. Measuring in support of early childhood development: The Normative II report 2012; The Offord Centre for Child Studies. Hamilton, Ontario Available at: http://www.offordcentre.com/readiness/files/updated_normative_II.pdf. Accessed April 1, 2013.

109. Guhn M, Zumbo BD, Janus M, Hertzman C. Validation theory and research for a population-level measure of children's development, wellbeing, and school readiness. Soc Indic Res 2011;103:183-191.

110. Forget-Dubois N, Lemelin J-P, Boivin M, Dionne G, Séguin JR, Vitaro F, Tremblay RE. Predicting early school achievement with the EDI: A longitudinal population-based study. Early Educ Dev 2007;18:405-426.

111. D'Angiulli A, Warburton W, Dahinten S, Hertzman C. Population-level associations between preschool vulnerability and grade-four basic skills. PLoS One 2009;4:e7692.

112. Brinkman SA, Gialamas A, Rahman A, Mittinty MN, Gregory TA, Silburn S, Goldfeld S, Zubrick SR, Carr V, Janus M. Jurisdictional, socioeconomic and gender inequalities in child

health and development: analysis of a national census of 5-year-olds in Australia. BMJ open 2012;2.

113. Martens P. Health Inequities in Manitoba: Is the Socioeconomic Gap in Health Widening Or Narrowing Over Time? Winnipeg: Manitoba Centre for Health Policy, University of Manitoba, 2010.

114. Marrie RA, Horwitz R, Cutter G, Tyry T, Campagnolo D, Vollmer T. Comorbidity, socioeconomic status and multiple sclerosis. Mult Scler 2008;14:1091-1098.

115. Kisely S, Lin E, Gilbert C, Smith M, Campbell LA, Vasiliadis HM. Use of administrative data for the surveillance of mood and anxiety disorders. Aust N Z J Psychiatry 2009;43:1118-1125.

116. Marrie RA, Yu BN, Leung S, Elliott L, Caetano P, Warren S, Wolfson C, Patten SB, Svenson LW, Tremlett H. Rising prevalence of vascular comorbidities in multiple sclerosis: validation of administrative definitions for diabetes, hypertension, and hyperlipidemia. Mult Scler 2012;18:1310-1319.

117. Santos R, Brownell MD, Ekuma O, Mayer T, Soodeen RA. The Early Development Instrument (EDI) in Manitoba: Linking Socioeconomic Adversity and Biological Vulnerability at Birth to Children's Outcomes at Age 5. Winniepg, MB: Manitoba Centre for Health Policy, University of Manitoba, 2012.

118. Lloyd J, Hertzman C. From kindergarten readiness to fourth-grade assessment: Longitudinal analysis with linked population data. Soc Sci Med 2008;68:111-123.

119. Hymel S, LeMare L, McKee W. The Early Development Instrument: An Examination of Convergent and Discriminant Validity. Soc Indic Res 2011;103:267-282.

120. Cents R, Diamantopoulou S, Hudziak J, Jaddoe V, Hofman A, Verhulst F, Lambregtse-van den Berg M, Tiemeier H. Trajectories of maternal depressive symptoms predict child problem behaviour: the Generation R study. Psychol Med 2013;43:13-25.

121. Razaz N, Tremlett H, Boyce WT, Guhn M, Joseph K, Marrie RA. Impact of parental multiple sclerosis on early childhood development: A retrospective cohort study. Mult Scler 2015;21:1172-1183.

122. Tremlett H, Zhao Y, Rieckmann P, Hutchinson M. New perspectives in the natural history of multiple sclerosis. Neurology 2010;74:2004-2015.

123. Janus M, Brinkman S, Duku E, Hertzman C, Antus R, Sayers M, Schoreder J, Walsh C. The Early Development Instrument: A population-based measure for communities. A book on development, properties, and use. Hamilton, ON: Offord Centre for Child Studies, 2007.

124. Marrie RA, Horwitz R, Cutter G, Tyry T, Campagnolo D, Vollmer T. The burden of mental comorbidity in multiple sclerosis: frequent, underdiagnosed, and undertreated. Mult Scler 2009;15:385-392.

125. Rutter M. Protective factors in children's responses to stress and disadvantage. Ann Acad Med Singapore 1979;8:324.

126. Odgers CL, Jaffee SR. Routine Versus Catastrophic Influences on the Developing Child. Annu Rev Public Health 2013;34:29-48.

127. Chen Y-C, Fish MC. Parental Involvement of Mothers With Chronic Illness and Children's Academic Achievement. J Fam Issues 2012;34:583-606.

128. Brownell MD, Chartier M, Santos R, Ekuma O, Au W, Sarkar J, MacWilliam L, Burland E, Koseva I, Guenette W. How are Manitoba's Children Doing? Winnipeg: Manitoba Centre for Health Policy, University of Manitoba, 2012.

129. Martens P, Fransoo R, McKeen N, Team TntK. The Manitoba RHA indicators atlas: Population-based comparisons of health and health care use. Winnipeg: Manitoba Centre for Health Policy, University of Manitoba, 2003.

130. Martens P, Fransoo R, McKeen N. Patterns of regional mental illness disorder diagnoses and service use in Manitoba: a population-based study. Winnipeg: Manitoba Centre for Health Policy, University of Manitoba, 2004.

131. Kingston D, Heaman M, Brownell M, Ekuma O. Predictors of Childhood Anxiety: A Population-Based Cohort Study. PLoS One 2015;10:e0129339.

132. Heaman M, Kingston D, Helewa ME, Brownell M, Derksen S, Bogdanovic B, McGowan K, Bailly A. Perinatal services and outcomes in Manitoba. Winnipeg: Manitoba Centre for Health Policy, University of Manitoba, 2012.

133. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005;62:593-602.

134. Lee EW, Wei L, Amato DA, Leurgans S. Cox-type regression analysis for large numbers of small groups of correlated failure time observations. In: Klein JP, G PK, eds. Survival analysis: State of the Art. Dordrecht, Netherlands: Kluwer Academic Publishers, 1992: 237-247.

135. Allison PD. Survival analysis using SAS: a practical guide: Sas Institute, 2013.

136. Baron RM, Kenny DA. The moderator–mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. J Pers Soc Psychol 1986;51:1173.

137. Preacher KJ, Hayes AF. SPSS and SAS procedures for estimating indirect effects in simple mediation models. Behav Res Methods Instrum Comput 2004;36:717-731.

138. Pakenham K, Cox S. Comparisons between youth of a parent with MS and a control group on adjustment, caregiving, attachment and family functioning. Psychol Health 2014;29:1-15.

139. Steck B, Grether A, Amsler F, Dillier AS, Romer G, Kappos L, Burgin D. Disease variables and depression affecting the process of coping in families with a somatically ill parent. Psychopathology 2007;40:394-404.

140. Pakenham KI, Tilling J, Cretchley J. Parenting difficulties and resources: The perspectives of parents with multiple sclerosis and their partners. Rehabil Psychol 2012;57:52-60.

141. Nilsagard Y, Bostrom K. Informing the children when a parent is diagnosed as having multiple sclerosis. Int J MS Care 2015;17:42-48.

142. Lix LM, De Coster C, Currie R. Defining and validating chronic diseases: an administrative data approach. Winnipeg: Manitoba Centre for Health Policy, 2006. Availabe at: http://mchp-appserv.cpe.umanitoba.ca/reference/chronic.disease.pdf

143. O'Donnell S, Vanderloo S, McRae L, Onysko J, Patten S, Pelletier L. Comparison of the estimated prevalence of mood and/or anxiety disorders in Canada between self-report and administrative data. Epidemiol Psychiatr Sci 2015:1-10.

144. Robertson E, Grace S, Wallington T, Stewart DE. Antenatal risk factors for postpartum depression: a synthesis of recent literature. Gen Hosp Psychiatry 2004;26:289-295.

145. Gavin NI, Gaynes BN, Lohr KN, Meltzer-Brody S, Gartlehner G, Swinson T. Perinatal depression: a systematic review of prevalence and incidence. Obstet Gynecol 2005;106:1071-1083.

146. Paulson JF, Bazemore SD. Prenatal and postpartum depression in fathers and its association with maternal depression: a meta-analysis. JAMA 2010;303:1961-1969.

147. Grigoriadis S, VonderPorten EH, Mamisashvili L, Tomlinson G, Dennis C-L, Koren G, Steiner M, Mousmanis P, Cheung A, Radford K. The impact of maternal depression during pregnancy on perinatal outcomes: a systematic review and meta-analysis. J Clin Psychiatry 2013;74:e321-341.

148. Association AP. The Diagnostic and Statistical Manual, Fifth Edition. Washington, DC: American Psychiatric Publishing, 2013.

149. Beck CT. Predictors of postpartum depression: an update. Nurs Res 2001;50:275-285.

150. Leinonen JA, Solantaus TS, Punamäki RL. Parental mental health and children's adjustment: the quality of marital interaction and parenting as mediating factors. J Child Psychol Psychiatry 2003;44:227-241.

151. Field T. Postpartum depression effects on early interactions, parenting, and safety practices: A review. Infant Behav Dev 2010;33:1-6.

152. Razaz N, Tremlett H, Boyce T, Guhn M, Marrie RA, Joseph KS. Incidence and determinants of mood or anxiety disorders in children of parents with multiple sclerosis (Under Review 2015).

153. McLaughlin TP, Khandker RK, Kruzikas DT, Tummala R. Overlap of anxiety and depression in a managed care population: Prevalence and association with resource utilization. J Clin Psychiatry 2006;67:1187-1193.

154. Zbozinek TD, Rose RD, Wolitzky‐Taylor KB, Sherbourne C, Sullivan G, Stein MB, Roy‐Byrne PP, Craske MG. Diagnostic overlap of generalized anxiety disorder and major depressive disorder in a primary care sample. Depress Anxiety 2012;29:1065-1071.

155. Olfson M, Druss BG, Marcus SC. Trends in Mental Health Care among Children and Adolescents. N Engl J Med 2015;372:2029-2038.

156. Sundquist J, Li X, Ohlsson H, Råstam M, Winkleby M, Sundquist K, Kendler KS, Crump C. Familial and neighborhood effects on psychiatric disorders in childhood and adolescence. J Psychiatr Res 2015;66-67:7-15.

157. Bjørk MH, Veiby G, Engelsen BA, Gilhus NE. Depression and anxiety during pregnancy and the postpartum period in women with epilepsy: A review of frequency, risks and recommendations for treatment. Seizure 2015;28:39-45.

158. Turner K, Piazzini A, Franza A, Fumarola C, Chifari R, Marconi AM, Canevini MP, Canger R. Postpartum depression in women with epilepsy versus women without epilepsy. Epilepsy Behav 2006;9:293-297.

159. Honarmand K, Feinstein A. Validation of the Hospital Anxiety and Depression Scale for use with multiple sclerosis patients. Mult Scler 2009;15:1518-1524.

160. Letourneau NL, Dennis C-L, Benzies K, Duffett-Leger L, Stewart M, Tryphonopoulos PD, Este D, Watson W. Postpartum depression is a family affair: addressing the impact on mothers, fathers, and children. Issues Ment Health Nurs 2012;33:445-457.

161. Lu E, Wang BW, Guimond C, Synnes A, Sadovnick AD, Dahlgren L, Traboulsee A, Tremlett H. Safety of disease-modifying drugs for multiple sclerosis in pregnancy: current challenges and future considerations for effective pharmacovigilance. Informa Healthcare 2013;13:251-261.

162. Harrison T, Stuifbergen A. Disability, social support, and concern for children: depression in mothers with multiple sclerosis. J Obstet Gynecol Neonatal Nurs 2002;31:444-453.

163. Gulick EE. Postpartum functioning in mothers with multiple sclerosis. West J Nurs Res 2007;29:589-602; discussion 603-512.

164. Morse CA, Buist A, Durkin S. First-time parenthood: influences on pre-and postnatal adjustment in fathers and mothers. J Psychosom Obstet Gynaecol 2000;21:109-120.

165. Garfield CF, Clark-Kauffman E, Davis MM. Fatherhood as a component of men's health. JAMA 2006;296:2365-2368.

166. Wickramaratne P, Gameroff MJ, Pilowsky DJ, Hughes CW, Garber J, Malloy E, King C, Cerda G, Sood AB, Alpert JE. Children of depressed mothers 1 year after remission of maternal depression: findings from the STAR* D-Child study. Am J Psychiatry 2011;168:593-602.

167. Hill AB. The environment and disease: association or causation? Proc R Soc Med 1965;58:295-300.

168. Falkov A. Parental psychiatric disorder: translating The Family Model into practice change. In: Reupert A, Maybery D, Nicholson J, Göpfert M, Seeman Frontmatter MV, eds. Parental Psychiatric Disorder: Distressed Parents and their Families. Cambridge, United Kingdom: Cambridge University Press, 2015: 277-287.

169. Shonkoff JP, Garner AS, Siegel BS, Dobbins MI, Earls MF, McGuinn L, Pascoe J, Wood DL. The lifelong effects of early childhood adversity and toxic stress. Pediatrics 2012;129:e232-e246.

170. Holden GW, Vittrup B, Rosen LH. Families, parenting, and discipline. In: Underwood MK, Rosen LH, eds. Social development. Relationships in infancy, childhood, and adolescence. New York: Guilford Publications, 2011: 127-152.

171. Evans GW, Li D, Whipple SS. Cumulative risk and child development. Psychol Bull 2013;139:1342-1396.

172. Rutter M. Stress, coping and development: some issues and some questions. J Child Psychol Psychiatry 1981;22:323-356.

173. Humphries KH, Rankin JM, Carere RG, Buller CE, Kiely FM, Spinelli JJ. Co-morbidity data in outcomes research: are clinical data derived from administrative databases a reliable alternative to chart review? J Clin Epidemiol 2000;53:343-349.

174. Beck CA, Metz LM, Svenson LW, Patten SB. Regional variation of multiple sclerosis prevalence in Canada. Mult Scler 2005;11:516-519.

175. Heim C, Binder EB. Current research trends in early life stress and depression: Review of human studies on sensitive periods, gene–environment interactions, and epigenetics. Exp Neurol 2012;233:102-111.

176. Hertzman C, Boyce T. How experience gets under the skin to create gradients in developmental health. Annu Rev Public Health 2010;31:347-349.

177. Kim-Cohen J, Caspi A, Moffitt TE, Harrington H, Milne BJ, Poulton R. Prior juvenile diagnoses in adults with mental disorder: developmental follow-back of a prospective-longitudinal cohort. Arch Gen Psychiatry 2003;60:709-717.

178. Marrie R, Yu BN, Leung S, Elliott L, Caetano P, Warren S, Wolfson C, Patten SB, Svenson LW, Tremlett H, Fisk J, Blanchard J. The Utility of Administrative Data for Surveillance of Comorbidity in Multiple Sclerosis: A Validation Study. Neuroepidemiology 2013;40:85-92.

Appendix

Supplementary Table A.1. Search strategies for the systematic review and results

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:

---

1 multiple sclerosis.mp. or exp Multiple Sclerosis/ (51343)
2 disseminated sclerosis.mp. or exp Multiple Sclerosis/ (40988)
3 sclerosis, disseminated.mp. or exp Multiple Sclerosis/ (40884)
4 sclerosis, multiple.mp. or exp Multiple Sclerosis/ (40934)
5 multiple sclerosis, acute fulminating.mp. or exp Multiple Sclerosis/ (40882)
6 exp Multiple Sclerosis, Relapsing-Remitting/ or Demyelination, demyelinization.mp. (2978)
7 exp Multiple Sclerosis/ or Dorsal sclerosis.mp. (40883)
8 exp family/ (220549)
9 exp Parents/ (65820)
10 exp Parent-Child Relations/ (43212)
11 exp "Child of Impaired Parents"/ (3814)
12 exp Nuclear Family/ (80078)
13 exp Caregivers/ (18985)
14 8 or 9 or 10 or 11 or 12 or 13 (234808)
15 1 or 2 or 3 or 4 or 5 or 6 or 7 (51460)
16 14 and 15 (540)

Supplementary Table A.2. Data extraction form

Study Information	Author & Year:	Citation:	
Type of Study	□ RCT □ Controlled Clinical Trial □ Quasi RCT □Retrospective Cohort □ Case-Control □ Case Series □ Cross-sectional		
	Inclusion	Exclusion	
Eligible Participants: Exposure Comparisons: Outcomes:			

Study Element	Description	Risk of Bias (Low, High, Unclear)
Participants: Age of Children Study Setting Geographical region Were the subjects asked to participate in the study representative of the entire population from which they were recruited? Were study subjects in different exposure groups recruited from the same population?		
Exposure status: Were exposure and comparison measures well described and valid? Were exposure and comparison factors measured prior to outcomes Did exposure/comparison status change during follow-up? Were case definitions well described and valid? Were other exposures similar in both groups during follow-up? Were all participants accounted for at study conclusion?		
Comparisons: Selected cases/ comparators representative of all eligible cases/comparators? Eligible population well described? Were relevant personal characteristics in participants reported?		
Outcomes: How were outcomes measured?		

Blinded outcome measurement? Were selected outcomes measurable and meaningful? Was follow-up time meaningful?		
Overall study quality		**Low, medium, high**

Supplementary Table A.3. List of ICD-9/10 codes used for identifying multiple sclerosis, demyelinating diseases; and Drug Identification Numbers (DIN) for identifying the disease-modifying drugs licensed for multiple sclerosis

Demyelinating-related disease or drug description	**ICD-9 codes**	**ICD-10 codes**	**Drug Identification Numbers (DIN)**
Multiple Sclerosis	340	G35	
Optic neuritis	377.3	H46	
Acute transverse myelitis	323.82	G37	
Acute disseminated encephalomyelitis	323	G36.9	
Demyelinating disease of CNS unspecified	341.9	G37.8	
Neuromyelitis optica	341.0	G36.0	
Other acute disseminated demyelination	341	G36	
glatiramer acetate, beta-interferon, natalizumb, fingolimod			02169649 02233014 02237317 02237319 02237320 02237770 02245619 02269201 02277492 02281708 02286386 02318253 02318261 02337819 02365480

Supplementary Table A.4. Summary of domains, subdomains, and example items on the Early Development Instrument (EDI).

EDI Domains	Subdomains	Example items
Physical Health and Well-being	Physical readiness for school day	arrives at school hungry
	Physical independence	has well-coordinated movements
	Gross and fine motor skills	is able to manipulate objects
Social Competence	Overall social competence	Is able to get along with other children
	Responsibility and respect	accepts responsibility for actions
	Approaches to learning	works independently
	Readiness to explore new things	Is eager to explore new items
Emotional Maturity	Prosocial and helping behaviour	helps other children in distress
	Anxious and fearful behaviour	appears unhappy or sad
	appears unhappy or sad	gets into physical fights
	Hyperactivity and inattention	is restless
Language and Cognitive Development	Basic literacy	Is able to write own name
	Interest in literacy/numeracy, and uses memory	Is interested in games involving numbers
	Advanced literacy	Is able to read sentences
	Basic numeracy	Is able to count to 20
Communication Skills and General Knowledge	(No subdomains)	Is able to clearly communicate one's own needs and understand others; shows interest in general knowledge about the world

Supplementary Table A.5. Definition, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of health claims data based case definitions as compared with medical record review

Comorbidity	Number of Years of Data	Algorithm: Number and Type of Claims	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95% CI)
Hypertension*[116]	2	≥1H or ≥2P	72.0 (59.8, 82.3)	96.6 (93.9, 98.3)	81.2 (69.6, 90.5)	94.2 (91.1, 96.5)
Diabetes*[116]	5	≥1H or ≥2P	85.7 (57.2, 98.2)	97.9 (95.6, 99.1)	60.0 (36.0, 80.9)	99.5 (98.1, 99.9)
Hyperlipidemia*[116]	5	≥1H or ≥2P or ≥2Rx	86.4 (75.0, 94.0)	92.7 (89.4, 95.2)	67.1 (55.4, 77.4)	97.5 (95.2, 98.9)
Chronic lung disease*[178]	5	≥1H or ≥2P or ≥2Rx	69.6 (47.1, 86.8)	91.9 (88.7, 94.4)	34.0 (20.9, 49.3)	98.0 (96.0, 99.2)
Depression$[37]	2	≥1 H or ≥5P OR (≥1P AND ≥7 Rx)	62.2 (52.4, 71.2)	86.7 (82.2, 90.4)	63.9 (54.1, 72.9)	85.8 (81.3, 89.6)
Anxiety$[37]	2	≥1 H or ≥2P OR (≥1P AND ≥2 Rx)	42.3 (23.3, 63.1)	82.2 (78.0, 85.9)	14.1 (7.25, 23.8)	95.4 (92.5, 97.4)

Hospital (H), physician (P), or prescription (Rx) claims. CI: confidence interval

* Definitions used in Chapters 3, 4 and 5

$ Definitions used in Chapter 3 and 4

Supplementary Table A.6. Summary of the previously validated algorithm used for identifying mood or anxiety disorders**.**

Diagnosis of mood or anxiety disorder was based on having at least one of the following within the study period.

a. 1+ hospitalizations with a diagnosis for depressive disorder, affective psychoses, neurotic depression or adjustment reaction:
    i. ICD–9–CM codes 296.2–296.8, 300.4, 309 or 311;
    ii. ICD–10–CA codes F31, F32, F33, F341, F38.0, F38.1, F41.2, F43.1, F43.2, F43.8, F53.0, F93.0 or with a diagnosis for a manic disorder, anxiety state, phobic disorders, obsessive– compulsive disorders or hypochondriasis:
    iii. ICD–9–CM codes 296.1, 300.0, 300.2, 300.3, 300.7;
    iv. ICD–10–CA codes F40, F41.0, F41.1, F41.3, F41.8, F41.9, F42
b. 1+ hospitalizations with a diagnosis for anxiety disorders:
    i. ICD–9–CM code 300;
    ii. ICD–10–CA codes F32, F341, F40, F41, F42, F44, F45.0, F45.1, F45.2, F48, F68.0, or F99 AND one or more prescriptions for an antidepressant, anxiolytic or mood stabilizer:
    iii. ATC codes N05AN01, N05BA, N06A
c. 1+ physician visits with a diagnosis for depressive disorder or affective psychoses:
    i. ICD–9–CM codes 296, 311
d. 1+ physician visits with a diagnosis for anxiety disorders:
    i. ICD–9–CM code 300 AND one or more prescriptions for an antidepressant, anxiolytic or mood stabilizer:
    ii. ATC codes N05AN01, N05BA, N06A
e. 3+ physician visits with a diagnosis for anxiety disorders or adjustment reaction:
    i. ICD–9–CM code 300, 309

Supplementary Table A.7. Agreement between the administrative definition of 1 year prevalence of depression (n=581, 5.84%) and Canadian National Population Health Survey (NPHS) mental health scales for depression, high distress scores and chronic distress scores in the Manitoba subset of the 1996/97 NPHS sample population.[130]

NPHS Scales	No.'s	Kappa	95% CI Kappa	Concordance %	Sensitivity	Specificity	Positive predictive value	Negative predictive value
High Probability of being depressed	409	0.26	0.23-0.30	93.1	0.37	0.95	25.8	97.2
High distress score	1,279	0.17	0.14-0.19	85.8	0.17	0.96	0.96	38.4
Chronic distress	447	0.06	0.03-0.09	90.8	0.12	0.94	9.81	95.8
Talked to a health professional in past 12 months about mental health	628	0.4	0.36-0.43	93.1	0.42	0.96	45.3	96.1