Epidemiology and Pharmacoepidemiology of Multiple Sclerosis in Saskatchewan

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Abstract

My PhD project involved examining the epidemiology and pharmacoepidemiology of multiple sclerosis (MS) in Saskatchewan through the use of health administrative data. First, I validated a case definition of MS for administrative data, and then used the validated definition to determine the incidence and prevalence of MS in Saskatchewan. Prior to my studies, Saskatchewan was thought to have one of the highest rates of MS in Canada, but province-wide estimates were not available.

I utilized the provincial MS cohort to then describe trends of healthcare utilization and the potential associations with comorbidities and use of disease-modifying therapies (DMTs) for MS using various study designs and methodologies. Both all-cause and MS-specific hospitalizations have decreased over time, but still remain higher than the general population.

DMTs were associated with a minimal reduction in all-cause and MS-specific hospitalizations, and did not impact the number of physician services used. Higher rates of all-cause hospitalizations were observed in individuals that are older, have a higher comorbidity burden, and have previous hospitalizations, whereas the rate of MS-related hospitalizations increased with male sex and younger age. Comorbidity burden increased the rate of all-cause hospitalizations in a dose-response manner, but did not impact MS-related admissions. Finally, decreases in both all-cause and MS-specific hospitalizations was observed with an increase in disease duration.

My research confirms that Saskatchewan has one of the highest rates of MS worldwide. While the introduction of DMTs has dramatically changed the management of MS, future research is needed to evaluate their true impact on subsequent healthcare utilization. Specific predictors, including individual comorbidities can be useful for identifying individuals with MS who are at higher risk for

hospitalization, and can help guide collaborative efforts to manage the disease and prevent future hospitalizations.

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List of Abbreviations

MS	Multiple sclerosis
CIS	Clinically isolated syndrome
RRMS	Relapsing remitting multiple sclerosis
PPMS	Primary progressive multiple sclerosis
SPMS	Secondary progressive multiple sclerosis
DMT	Disease modifying therapy
PML	Progressive multifocal leukoencephalopathy
DALY	Disability-adjusted life years
EDSS	Expanded Disability Status Scale
HUI3	Health Utility Index Mark 3
ED	Emergency department
RR	Relative risk
SD	Standard deviation
CI	Confidence interval
ICU	Intensive care unit
HR	Hazard ratio
OR	Odds ratio
IRR	Incidence rate ratio

MPR	Medication possession ratio
PDC	Proportion days covered
ICD	International Classification of Diseases
CDS	Chronic disease score
PPV	Positive predictive value
NPV	Negative predictive value
HSN	Health service number
RAI-MDS	Resident assessment instrument minimum data set
CDSS	Chronic disease surveillance system

1 INTRODUCTION

1.1 MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is a chronic, inflammatory neurological disease that affects the central nervous system.[1] It is considered to be the leading cause of non-traumatic neurologic disability in young adults,[1] and is typically diagnosed between 20-40 years of age, with a female predominance of 2.5:1.[2]

The exact cause of MS remains unknown but is assumed to be an interaction between genetic and environmental factors;[3] it has been suggested that MS develops in individuals that are genetically susceptible and have been exposed to a sufficient set of environmental factors.[4] Numerous environmental factors and exposures such as Epstein-Barr virus (EBV), adolescent obesity, smoking, vitamin D deficiency, or low sunlight or UV have been reported to increase the risk of MS. However, only a few of those findings were from well designed and adequately powered studies, and even less could be replicated consistently.[5] In a 2015 umbrella review that evaluated over 44 risk factors, only EBV and smoking showed consistent and significant association with developing MS.[6] EBV was found to be the strongest risk factor, and individuals infected during childhood or adolescence were 15 and 30 times more likely to develop MS, respectively. Smoking was also associated with developing MS, but the impact was modest.[5] The MS Society of Canada recommends daily vitamin D supplementation for individuals with MS or at risk of developing MS.[7] Higher serum levels of vitamin D have been associated with a lower risk of developing MS.[8]

MS is a degenerative disease where demyelination and axonal damage precipitate a variety of neurologic manifestations. Symptoms associated with MS vary, and can include pain, visual problems, fatigue, cognitive impairment, tremor, bladder and bowel dysfunction, sensory and gait disturbances, and spasticity.[9] A diagnosis of MS is reached after an individual demonstrates dissemination in time (two or more separate attacks based on clinical and/or imaging findings) and space (two or more lesions in different areas of the central nervous system) while excluding alternative diagnoses.[10] A relapse or attack is defined as new, or worsening of existing symptoms consistent with MS, that typically develop over the course of days to weeks, last at least 24-48 hours and are accompanied by an objective change in the neurological examination corresponding to a patient's symptoms.[2,11]

There are different types or "courses" of MS. The initial clinical presentation (or symptoms) is referred to as clinically isolated syndrome (CIS). CIS is a single clinical episode that presents with symptoms of inflammatory demyelination suggestive of MS but has not yet fulfilled the criteria of dissemination in time and space needed to confirm a diagnosis of MS (e.g. MRI evidence of multiple lesions in different areas of the brain indicating previous attacks or a second clinical attack).[12,13] Within 2 years, approximately 45% of individuals with CIS go on to develop MS.[10] Approximately 85% of patients have relapsing remitting MS (RRMS), where relapses are followed by recovery.[14,15] With time, recovery from relapses may be incomplete and disability start to accumulate. Within 10-15 years from diagnosis, most RRMS patients will enter the neurodegenerative secondary progressive phase of MS (SPMS) where the disease is less inflammatory in nature. Relapses and remissions become less defined and disability steadily progresses. Primary progressive MS (PPMS), is progressive from onset and is

distinguished by accumulating disability and the absence of relapses. Primary progressive MS affects approximately 15% of patients.[2]

1.2 DISEASE-MODIFYING THERAPY

There is currently no cure for MS, but in 1995 the first disease-modifying therapy (DMT) was approved for the treatment of relapsing remitting MS in Canada. Over the last two decades, 13 drugs have been approved for the treatment of MS in Canada (Table 1.1). These drugs act on the immune system to decrease inflammation, and in turn, reduce the frequency and severity of relapses, and slow disease progression.[16] Disease-modifying therapies are primarily used in RRMS, as they become less effective when the disease enters the less inflammatory, progressive phase.[2] However, one therapy has recently been approved for use in PPMS, and several DMTs have approval for use in patients with active SPMS who still experience relapses.[14,17-20] Research is now suggesting that treatment with DMTs begin at the CIS stage, as early clinical and subclinical activity contributes to long term disability.[16,21,22] However, in Saskatchewan, DMTs are currently only covered for patients with RRMS and PPMS who meet specific criteria.[23]

In Canada, the beta-interferons, glatiramer acetate, teriflunomide, dimethyl fumarate and ocrelizumab are all considered first line agents.[16] Fingolimod, natalizumab, and alemtuzumab, and cladrabine are reserved as second line agents for patients who have not responded to, or cannot tolerate, first-line agents.[16] With the exception of the recently introduced monoclonal antibody ocrelizumab,[24] first line therapies decrease relapse rates and disability by approximately 30-50% and 20-40% respectively.[25] Dimethyl fumarate, an oral first-

line DMT, appeared to have higher efficacy than other first-line DMTs in placebo-controlled studies, but when compared to glatiramer acetate in a head-to-head trial, the effect was not statistically significant.[26]

Injectable first line DMTs, such as the beta-interferons and glatiramer acetate, were the first DMTs introduced and are generally well tolerated.[25] They have the most long-term safety data available and appear to be relatively safe to use during pregnancy, although in North America, women are still counseled to stop DMT use 3 months before conception.[27] Side effects commonly associated with the beta-interferons are flu-like symptoms and injection site reactions.[28,29] Injection site reactions are also the most common side effect associated with glatiramer acetate.[30] Dimethyl fumarate and teriflunomide are first-line oral DMTs that were introduced in 2013.[31,32] The most common side effects associated with dimethyl fumarate are gastrointestinal events and flushing , which may diminish over time and with appropriate dose titration.[31] Teriflunomide is associated with several potential side effects including hepatotoxicity, neutropenia and leukopenia (for which it carries a black box warning); it is also a known teratogen.[32]

Second line agents have greater efficacy than the first-line agents (Table 1.2), but also have the potential to cause serious and sometimes fatal adverse effects.[33-35] Progressive multifocal leukoencephalopathy (PML), an often fatal viral infection of the white matter of the brain was first reported with natalizumab. The risk of PML increases in individuals who are positive for the John Cunningham (JC) virus, who have impaired immunity such as AIDS, malignancy, and previous or current immunosuppressive therapy, and who have been exposed to natalizumab for more than 2 years.[2] PML has also been reported in individuals who were

receiving dimethyl fumarate, fingolimod and ocrelizumab.[36] Several serious adverse events have been associated with fingolimod, including an increased risk of infection, particularly related to the herpes zoster virus, and cardiovascular events. As such, individuals starting fingolimod must follow a strict monitoring program which includes confirming immunity to the varicella zoster virus and a minimum of 6 hours of cardiovascular monitoring after the first dose is administered.[33,37,38] There are several potential safety concerns associated with alemtuzumab including autoimmune reactions (thyroid disorders, immune thrombocytopenia), infections, and malignancies, for which it carries a black box warning. Laboratory monitoring is required monthly during the treatment period and for 48 months after the last infusion.[35] Ocrelizumab is the first DMT approved for the treatment of early PPMS and is also a first line option for RRMS. However, there is an increased risk of infections including respiratory infections and herpes with ocrelizumab, and it may increase the risk of malignancy. It is also contraindicated in individuals with active hepatitis B infection.[40]

Ideally, treatment should be started with the safest agent that is able to control clinical and radiological disease activity (i.e. decrease number and severity of relapses and decrease brain lesion formation identified on MRI).[41] Treatment should be individualized based on the patient's disease status, preference, and contraindications or safety issues.[25] Treatment can be escalated to a second line agent if the patient exhibits breakthrough disease activity (relapses or accumulating disability) after an adequate course of first line treatment, or if there are tolerability or safety concerns.[25] In Saskatchewan, specific criteria must be met for individuals to receive, and maintain coverage for their DMT (Appendix A – B.1-4).[23]

Table 1. 1 Disease modifying therapies currently approved for multiple sclerosis in Canada (listed chronologically)

Disease modifying therapy	Year of approval in Canada	Place in therapy	Health Canada indication	Administration
Interferon beta 1b[28] (Betaseron)	1995	First line	CIS RRMS SPMS	Subcutaneous injection on alternating days
Glatiramer acetate[30] (Copaxone)	1997	First line	CIS RRMS	Daily subcutaneous injection
Interferon beta 1a[29] (SC) (Rebif)	1998	First line	CIS Relapsing forms of MS	3 times weekly subcutaneous injection
Interferon beta 1a[42] (IM) (Avonex)	1998	First line	CIS Relapsing forms of MS	Once weekly intramuscular injection
Natalizumab[34] (Tysabri)	2006	Second line	RRMS	Monthly IV infusions
Interferon beta 1b[43] (Extavia)	2010	First line	CIS RRMS SPMS	Subcutaneous injection on alternating days
Fingolimod[33] (Gilenya)	2011	Second line	RRMS	Oral capsule once daily

Teriflunomide[32] (Aubagio)	2013	First line	RRMS	Oral tablet once daily
Dimethyl fumarate[31] (Tecfidera)	2013	First line	RRMS	Oral capsule twice daily
Alemtuzumab[35] (Lemtrada)	2014	Second line	RRMS	2 cycles by infusion*
Peginterferon beta 1a[44] (Plegridy)	2015	First line	RRMS	Subcutaneous injection every 2 weeks
Daclizumab[39] (Zinbryta)	2016 *Withdrawn 2018*	Second line	RRMS	Monthly subcutaneous injection
Cladribine [45] (Mavenclad)	2017	Second line	RRMS	Two oral courses per year for two years
Ocrelizumab (Ocrevus)	2018	First line	RRMS/PPMS	Two infusions within 2 weeks followed by bi-annual infusions

CIS, clinically isolated syndrome; RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; MS, multiple sclerosis; SC, subcutaneous; IM, intramuscular; IV, intravascular

* First cycle is one infusion per day for 5 days. Second cycle is one year later; one infusion per day for 3 days.

** Initial dose: 300 mg intravenous infusion, followed two weeks later by a second 300 mg infusion followed by a single 600 mg infusion every six months

Table 1. 2 Efficacy of disease modifying therapies

DMT	RR in ARR compared to placebo	RR in Disability Progression when compared to placebo	RR in ARR compared to active comparison	RR in Disability Progression compared to active comparison
First-line				
Interferon beta-1b[46,47]	34%	29%*	24% *vs. interferon beta-1a i.m* 3%* *vs. glatiramer acetate*	44% *vs. interferon beta-1a i.m* 5%* *vs. glatiramer acetate*
Interferon beta-1a[48]	18%	37%	-	-
Interferon beta-1a[49-51]	32%	32%	16% *vs. interferon beta-1a i.m* 3%* *vs. glatiramer acetate*	13%* *vs. interferon beta-1a i.m* 25%* *vs. glatiramer acetate*
Peginterferon-1a[52]	36%	36%	-	-
Glatiramer acetate[53]	29%	12%*	-	-
Teriflunomide[54,55]	31-36%	24-26%	4%*	-

			vs. interferon-beta 1a s.c	
Dimethyl fumarate[26,56]	44-53%	24*-41%	24%* *vs. glatiramer acetate*	17%* vs. glatiramer acetate
Ocrelizumab[24]	73-80%	-	46-47% *vs. interferon-beta 1a s.c*	40% *vs. interferon-beta 1a s.c*
Second-line				
Fingolimod[37,57,58]	48-55%	14-28%	52% vs. *interferon beta-1a i.m*	25%* vs. *interferon beta-1a i.m*
Natalizumab[59]	68%	42%	-	-
Alemtuzumab[60,61]	-	-	49-55% *vs. interferon-beta 1a s.c*	30*-42% *vs. interferon-beta 1a s.c*
Daclizumab[62,63]**	54%	-	45% *vs. interferon-beta 1a s.c*	54% *vs. interferon-beta 1a s.c*
Cladribine[64]	55-58%	31-33%	-	-

Adapted from Torkildsen O, Myhr KM, Bo L. Disease-modifying treatments for multiple sclerosis - a review of approved medications. *European Journal of Neurology.* 2016; 23 Suppl 1:18-27.

RR: Relative reduction; ARR: Annual relapse rate; i.m intramuscular; s.c: subcutaneous

*Result was not statistically significant

** Daclizumab was withdrawn in 2018 and is no longer on the market

1.3 COMORBIDITIES AND MS

Comorbidity refers to the total burden of chronic disease other than the underlying condition of interest.[65] Comorbidities are common among the MS population and have been attributed as a potential cause of some of the outcome heterogeneity in MS.[66] Comorbidities can impact an individual's disease course and prognosis, including diagnostic delays and greater disability at diagnosis, [67] more progressive disease,[68-70] increase in changes on MRI, decrease in quality of life and cognitive function,[71] and increased mortality.[72] The most commonly reported comorbidities in MS include depression, anxiety, hypertension, dyslipidemia and chronic lung disease.[73] MS is also associated with an increased risk of infection such as respiratory, urinary tract, and skin infections, sepsis,[74-76] and cardiovascular disease.[77]

Comorbidities are common even before the onset of MS. Participants in the North American Research Committee on Multiple Sclerosis (NARCOMS) registry self-reported their comorbidities, and at the initial MS symptom onset 28% percent reported a physical comorbidity and 8.4% reported a psychiatric comorbidity. This went up to 35% and 18%, respectively, by time of diagnosis.[78] Because prevalence of physical comorbidities increases with age,[66] these percentages are expected to rise with time.

Comorbidities can also increase relapse rates in MS. Findings from a multi-center study that prospectively followed individuals with RRMS reported that comorbidity (3 or more comorbidities) was associated with an increase in relapse rate (adjusted rate ratio: 1.45, 95% confidence interval [CI]: 1.00–2.08). Similar increases were seen when the individual

comorbidities were examined, including migraine (adjusted rate ratio: 1.38; 95% CI: 1.01 – 1.89) and hyperlipidemia (adjusted rate ratio: 1.67; 95% CI: 1.07 – 2.61).[79]

Comorbidity also impacts the treatment and management of MS. While observational studies have confirmed high prevalence of comorbidity in individuals with multiple sclerosis, clinical trials of DMTs often exclude individuals with comorbidities.[80] Therefore, the safety and efficacy of DMTs in individuals with comorbid conditions is uncertain. The emergence of secondary comorbidities with DMT use such as infections, autoimmune disease, vascular comorbidity, or neoplasm is also a concern. Presence of comorbidities have been found to impact time to initiation of a DMT. For example, anxiety and ischemic heart disease were associated with reduced initiation of a DMT, while having depression increased the likelihood of starting a DMT.[81]

1.4 BURDEN OF MS

The disabling and long-term nature of MS is not only a burden to patients and their families, but also has a significant impact on the healthcare system and society (Table 1.3).[82,83] Within 10-15 years of diagnosis, approximately 80% of MS patients experience some degree of impaired mobility,[84] which can be due to difficulty walking, imbalance, muscle spasms, fatigue, or weakness.[84,85] Increases in disability have been associated with an increase in unemployment, making it difficult for individuals with MS to support themselves and their families financially.[86] [87] Furthermore, MS patients are now living longer lives, contributing to a growing aging population.[88] Due to the progressive nature of the disease, older MS patients can develop disability more than ten times that of their aging counterparts,[89] putting an even greater strain on the healthcare system and society.

Table 1. 3 Examples of symptoms associated with multiple sclerosis and their complications

Symptom	Potential Clinical Complication(s)	Potential Social Complication(s)
Visual problems (optic neuritis; sudden loss of vision, blurred vision, or diplopia)	• Loss of vision • Eye pain	• Unemployment • Decreased ability to participate in everyday activities.
Bladder and bowel dysfunction (urine incontinence, fecal incontinence, and constipation)	• Recurrent urinary tract infections • Kidney failure • Urosepsis • Fecal impaction, haemorrhoids.	• Social isolation • Risk for nursing home placement
Sensory problems (numbness, tingling, burning, pain, fatigue)	• Injuries, risk of burns, falls • Sexual dysfunction	• Difficulty with ADLs • Strain on relationships
Cognitive impairment (memory, judgement, attention, concentration)		• Unemployment • Difficulty taking care of one's self
Dysarthria and Dysphagia	• Communication difficulties • Swallowing impairment • Malnutrition Risk for aspiration • Pneumonia	• Social isolation • Difficulty with relationships
Muscle weakness, spasticity, fatigue, and altered mobility	• Pain • Falling episodes • Walking difficulties • Obesity • Pressure sores • Hygiene issues • Increased fatigue and functional disability	• Risk of injuries • Difficulty with ADLs • Unemployment • Financial problems • Social isolation •
Emotional changes (depression, anxiety, and bipolar disorders)	• Sleep disturbances • Eating disorders • Anger	• Loss of self-esteem • Difficulty with ADLs • Social isolation • Risk of suicide

Adapted from MS Society of Canada-Symptoms and Marion Brandis, M. A., and M. S. N. Rachael Stacom. "Long-term care in the home for people with multiple sclerosis." *Care Management Journals* 10.3 (2009): 128.

ADL: Activities of daily living

The Public Health Agency of Canada estimated the total annual cost associated with MS to be $950 million for the years 2000-2001,[90] and with MS patients living longer lives, contributing to a growing aging population,[88,89] and with rising hospital costs in MS,[91] those costs are expected to rise to 2 billion by 2030.[92] Multiple sclerosis not only impacts direct healthcare costs such as hospital care, physician care, and medication use, but also impacts non-direct and intangible costs such as those related to disability, disease-related time off from work, employment insurance, and earlier retirement.[93] Because MS typically affects individuals during their most productive years, the productivity loss and need for assistance can have a significant impact on society.[93] When estimating the disability-adjusted life years (DALYs), a summary measure of years of life lost due to premature mortality and healthy years of life lost due to disability,[90] MS ranks in the top six for neurological conditions.[90] Individuals with MS also self-report poorer health.[94] When comparing Health Utility Index Mark 3 (HUI3) scores, a classification system that summarizes health related quality of life[95] for several chronic diseases in Canada, the burden related to MS was found to be considerably greater than that of diabetes, stroke, heart disease, and arthritis combined.[94]

The direct healthcare costs in Canada associated with MS in 2001 were $58.4 million for hospital care, $12.1 million for physician care and $68.7 million for medications.[90] Increases in healthcare costs are observed with more advanced stages of the disease. The Expanded Disability Status Scale (EDSS) reports scores from 0-10 where higher scores indicate a higher level of disability and disease progression.[96] The average cost per year for MS patients in Canada was measured according to EDSS score in 2012, and estimated that the annual cost associated with mild disability (EDSS 0-3) was $30,836, moderate disability (EDSS 4-6.5) was

$46,622, and increased to almost $78,000 for patients with severe disability (EDSS 7-9).[83] In the UK, direct and indirect costs were also observed to increase with an increase in disability, with costs dramatically rising with EDSS scores of 6.5 or greater.[97] Similarly, a 2005 study assessing overall direct and indirect costs associated with MS in nine European countries found costs increased with an increasing EDSS score; €18,000 for individuals with an EDSS less than 4, €36,500 for an EDSS score of 4.0-6.5 and €62,000 for those with an EDSS score of 7 or greater.[98]

1.5 HEALTHCARE UTILIZATION IN THE MS POPULATION

Patients with MS are approximately twice as likely to be hospitalized, visit a medical professional, or consult a mental health professional as compared to the general population.[94,99] The Canadian Longitudinal Study on Aging (CLSA) is a population-based prospective national research study that included 51,382 individuals between the ages of 45-85. The study evaluated burden of neurologic disease, comorbidity and healthcare utilization in the aging Canadian population. Participants were asked to self-report their diagnoses and were given 10 self-report questions on their healthcare utilization in the last 12 months. Individuals with MS were found to have higher specialist visits (prevalence ratio 1.62; 95% CI: 1.50–1.74), emergency department visits (prevalence ratio 1.20; 95% CI: 0.97–1.48), and inpatient hospitalizations (prevalence ratio 1.61; 95% CI: 1.16–2.25).[100]

Higher rates of healthcare utilization were found with more severe disease/disability.[101] An American study reported that patients with EDSS scores >5.0 had more consultations with primary care physicians and specialists as well as more hospitalizations within the previous year compared to patients with EDSS scores between 3.0-5.0.[101] Patients with higher relapse activity also have higher healthcare utilization and costs; patients with two or more relapses per year were more likely to have a hospitalization (23.4% vs. 11.7%, p-value=<0.0001) or emergency department (ED) visit (38.0% vs.22.6%, p-value= <0.0001) compared to patients that had fewer relapses.[102]

This increased healthcare utilization has been observed as far as 5 years prior to the diagnosis of MS.[103] In a population-based study from Manitoba comparing physician service

utilization between the MS population and a matched cohort from the general population, physician service utilization in 2008 was higher in the MS population, with 12.9 physician visits/person year vs. 8.4 physician visits/person-year (rate ratio 1.53; 95% CI 1.52-1.55). Physician visits peaked during the year of MS diagnosis with 19 visits/person-year and decreased thereafter, but remained higher than before the diagnosis of MS.[103] In an American study comparing health resource utilization within the first year of MS diagnosis between newly diagnosed patients and a matched "healthy comparison" group, MS patients were 3.5 times more likely to be hospitalized, twice as likely to have an ED visit, and 2.4 times more likely to receive rehabilitation services (physical, occupational or speech therapy).[104] The mean number of physician visits was approximately two times higher in the MS group compared to the healthy control group (8.08 (SD 6.69) vs. 3.44 (SD 3.92), p-value =<0.0001).[104] The MS patients also had higher utilization of non-DMT prescription drugs that included anticonvulsants, antidepressants, antipsychotics and amphetamines.[104]

Healthcare utilization is also high among children with MS. In a population-based Canadian study comparing health care utilization between children with MS and matched controls from the general population in Ontario, children with MS were more likely to be hospitalized (odds ratio 15.2; 95%CI: 12.0, 19.1) and had higher rates of physician visits (rate ratio 4.58; 95%CI: 4.26, 4.92); the odds of hospitalization were highest during year of diagnosis (odds ratio 40.1; 95%CI: 27.1, 59.5).[105]

Hospitalizations in the MS population

Hospitalizations are the largest component of healthcare resource use, and can be surrogate measures for disease worsening, comorbidity, and overall demand on the healthcare system.[106,107] The total number of all-cause hospitalizations in the general Canadian population has increased over the past several decades but after accounting for the aging population and population growth, hospitalization rates have actually declined.[108] Hospitalization rates in the MS population have also decreased over the same time period, but still remain higher than the general population.[109]

A population-based study from Manitoba used administrative data to compare acute care hospitalization rates between the MS population and a matched cohort from the general population between 1984-2011.The decline in hospitalization rates over this time period was larger in the MS population than in the matched cohort (-0.80; 95% CI: -0.93 to -0.67 vs. -0.38; 95% CI: -0.23 to -0.17).[109] Hospital admissions related to MS also decreased.[109] A study from British Columbia found the overall rate of all-cause admissions between 1988-2008 to be 32.4 per 100 MS patients and this rate declined by 1.4% annually.[107] In Portugal, the rate of MS-related hospitalizations decreased from 15.9/100 person-years (95% CI: 14.9–16.9) to 8.9/100 person-years (95% CI: 8.2–9.6) between 2008 and 2013.[110] The decline in hospitalization rates [107,109,110] may be due changes in healthcare policy, the emergence of DMTs, and shifting the treatment and management of MS patients to the outpatient setting.[109,111]

Intensive care unit (ICU) admissions are a main driver of medical costs.[112] A population-based study from Manitoba compared the incidence of ICU admission, mortality post-ICU

admission, and critical illness in the MS population vs the general population. The study found individuals with MS were at higher risk of ICU admission (HR 1.45; 95% CI: 1.10-1.32) and had higher 1-year mortality (RR 2.06 95% CI: 1.32-3.07) than the general population. Individuals with MS were also more likely to be admitted to the ICU due to infection than the matched general population control group (OR 1.82; 95% CI 1.10–1.32).[113]

Individuals with MS are at higher risk for infection and infection-related hospitalizations.[74-76] In a matched population-based study from British Columbia that compared infection-related healthcare utilization between individuals with and without MS, MS patients were twice as likely to be hospitalized for an infection (adjusted OR 2.39; 95% CI: 2.16-2.65). They also had 41% more infection-related physician visits (adjusted RR): 1.41; 95% CI: 1.36–1.47) and 57% more prescriptions for antimicrobials (adjusted RR: 1.57; 95% CI: 1.49–1.65).[74] In an American study, veterans with MS were 52% (HR 1.52; 95% CI 1.37-1.70) more likely to have a serious infection requiring a hospitalization for respiratory infections, urinary tract infections or sepsis, and were at much greater risk of a fatal infection (HR 1.85; 95% CI 1.08-3.85) than veterans who did not have MS.[75] This was similar to the study in Manitoba where bacterial pneumonia, influenza, and urinary tract infections were more common in the individuals with MS than the matched cohort.[109]

Comorbidities, which are common in the MS population, also appear to increase the risk of hospitalization. The presence of comorbidities in the Manitoba MS population increased the rate of hospital admissions by almost 3-fold (RR 2.88; 95% CI 1.41-3.43). A dose-response relationship was observed where an increase in the rate of hospitalizations was seen with an increase in number of comorbidities.[114] Furthermore, in a study that evaluated patient

characteristics of a MS clinic cohort from British Columbia, fatigue and high comorbidity burden (≥3 comorbidities) were significantly associated with higher rates of physician visits (adjusted rate ratio: 1.37 and 1.52, respectively) and hospitalizations (adjusted RR: 4.02 and 3.45 respectively).[115]

Length of Hospital Stay

The average length of hospital stays has declined over the years in the Canadian general population with a national average of 7.2 days between 2011-2012,[108] but results from the MS population specifically are conflicting. A study from British Columbia showed an increase in length of hospital stay with an average length of stay of 10.2 days (SD 24.8) between 1986 and 2008 suggesting that it is sicker patients that are being hospitalized in the more recent years.[107] The average length of stay also increased for MS patients in Portugal from 3 days in 2008 to 4 days in 2013 (p-value=<.001).[110] However, a study from Manitoba reported that the average length of stay for hospitalizations has declined over time (-0.11 days/year).[109] This is similar to results from an American study where the mean length of stay decreased from 6.9 days in 1993 to approximately 5 days in 2006.[91] In both Canadian studies from Manitoba and British Columbia, hospitalizations related to MS were longer than those that were not related to MS.[107,109]

Long-Term Care

Approximately 20-25% of the MS population will need some form of supportive living environments during the course of their disease, such as home care, respite care, assisted living, adult day care, or help with transportation and meals.[116,117] Approximately 5% of

individuals with MS will require a nursing home or be admitted to a long-term care facility,[118] which can be isolating and difficult to adjust to,[119] as well as decrease an individual's quality of life and self-autonomy.[120] A longitudinal study in 2015 examining nursing home placement among patients at the Saskatoon MS clinic found that approximately 14% of patients were institutionalized in a long term care facility during the follow up period (mean follow-up period=13.7 years; SD=7.9 years).[120]

Individuals with MS admitted to long-term care are more likely to be younger at admission, more cognitively intact, and have higher rates of depression than other facility residents.[121,122] Long term care residents with MS also receive more rehabilitation services than the residents who do not have MS.[123] In a population based cross-sectional study describing the proportion and predictors associated with receiving rehabilitation in long term care facilities across Canada, residents with MS received physical therapy and more intense (higher frequency and duration) rehabilitation than residents with other medical conditions such as stroke.[123]

Disease-modifying therapy and healthcare utilization

The rationale behind using disease-modifying therapy in MS is to decrease early clinical and subclinical activity that is assumed to contribute to long term disability.[16,21] Shorter term goals are to decrease the number and severity of relapses, decrease impairment from relapses, and reduce the number of lesions on MRI.[25] The long-term goal is to prevent or delay disease progression.[2] Clinical trials have confirmed DMTs can achieve the short-term goals but there is still debate about whether or not the DMTs prevent long-term progression of the disease.[124-133] One possible explanation is that the efficacy of drugs established through clinical trials is usually

greater than the effectiveness of the drug from real world settings, often due to strict inclusion criteria for participants and vigorous support and follow up for participants.[131]

It has been suggested that the use of DMTs can reduce healthcare utilization and healthcare costs by decreasing the number of relapses[82] and slowing progression of disease.[83] A study from Manitoba reported that DMTs have been associated with a decreased risk of ICU admission compared to non DMT-users[134] while a study from British Columbia found no difference in hospitalizations between beta-interferon users and non-users (adjusted IRR 1.018: 95% CI 0.803-1.290).[135] An American study reported that between 2001 and 2010, a time when the use of DMTs became widespread, hospitalizations due to MS increased by 40%.[136] However, these results are difficult to interpret as the authors reported the crude number of hospitalizations and the increase could have been due to an increased prevalence of MS rather than an increase in the rate of hospitalizations. A recent study examined DMT use and healthcare utilization among Medicare MS patients in the United States and found that DMT use was associated with a decrease in inpatient hospitalizations and emergency department visits.[137] Further research on association between DMT use and subsequent healthcare utilization is needed before any conclusions can be drawn.

1.6 STUDY DESIGNS IN MS RESEARCH

Randomized controlled trials (RCTs) are considered the gold standard in determining the efficacy and safety of medications. With randomization, baseline characteristics should be equally distributed between study groups. The same equal distribution should occur for unknown or unmeasured factors, thus reducing the potential for confounding.[138] While RCTs maximize internal validity, several limitations exist.[139] The generalizability of results can be argued. Several populations are under-represented or excluded from clinical trials including children, the elderly, and those with comorbidity other than the condition under study. Clinical trials also focus on short-term results in relatively small populations, limiting the ability to identify long-term or rare adverse events. As well, clinical trials are conducted in controlled settings that are quite different from real-world clinical practice.[140]

In situations where RCTs are not feasible, or more generalizable results are needed, observational studies are an alternative.[139,141] Observational studies examine and evaluate the impact of an exposure on an outcome.[142] They can have a cohort, case-control, or cross-sectional design.[143] In cohort studies, subjects identified by exposure are followed over time to examine the effect of the exposure on the development of an outcome. They can assess associations and evaluate multiple outcomes for a given exposure. Disadvantages of cohort studies include the need for large sample sizes, long durations for follow-up, and they are prone to bias, and confouding.[142] Case-control studies involve identifying cases (subjects identified to have outcome) and controls (subjects that do not have the outcome) from the same population and examining their exposure to a risk factor(s) retrospectively.[142] They are relatively quick and

easy to conduct, less expensive, and can examine associations for rare outcomes. Disadvantages of case-controls are that they are prone to recall bias and selection of controls may be difficult.[139] Cross-sectional studies examine exposure and outcome(s) at a certain point in time. While cross-sectional studies are easy and quick to conduct, a temporal relationship cannot be established between exposure and outcome, therefore this type of design cannot identify associations.[143]

Use of Administrative Data for Observational Studies

Observational research using healthcare databases has increased dramatically over the last several decades and has helped give insight into "real-world" conditions.[140] It has provided information regarding long-term safety and effectiveness of drugs, as well as healthcare utilization patterns in more diverse populations, thus complementing the knowledge initially acquired from RCTs.[139] Health administrative data, which are primarily collected for health system management and reimbursement purposes,[144] has become a valuable resource in epidemiological studies because it is large-scale, or even population-based in countries with universal healthcare, relatively easy to access and use. It can also provide longitudinal data over many years, allowing for the examination of changes over time.[145] Health administrative data can also be used to provide an accurate estimation of disease incidence and prevalence.[146]

However, there are limitations with administrative data that should be considered. Selection bias may be a problem with non-population-based healthcare databases where the subjects being studied are often employed and/or insured, and therefore may be healthier compared to non-insured or non-employed subjects.[140] Using population-based administrative

databases can reduce this potential bias. Misclassification bias can occur, as the validity or accuracy of results are only as good as the accuracy of data entered. Potential misclassification of clinical data can be evaluated through validation studies.[140]

Confounding is another limitation inherent in all observation studies. Confounders that may affect outcomes may not be captured or available in administrative databases. This can be somewhat controlled through restriction, matching, standardization, stratification, and the use of propensity scores or multivariate modeling; however, the potential for confounding will always remain.

Saskatchewan Health Administrative Databases[147]

Canada has a universal healthcare program that requires provinces to provide hospital and physician care free of charge to residents under the federal Canada Health Act. Covered services include hospitalizations, physician visits, diagnostic tests, and procedures. Drug programs are not included in the Canada Health Act and are administered individually by the provinces and territories. Information related to the health services provided are captured by varying degrees in databases in each individual province.

Saskatchewan, a central Canadian province, has a stable population of 1.16 million people.[148] Almost all of Saskatchewan residents are entitled to receive benefits through the provincial healthcare system. The remaining population is covered federally and includes members of the Canadian Forces, Royal Canadian Mounted Police, and federal inmates. Saskatchewan has a drug plan that is available to residents regardless of age or income level. Approximately 85-90% of the Saskatchewan population is eligible for prescription drug

coverage; ineligible residents are primarily registered First Nations and recognized Inuit people whose drug costs are funded by another government agency.[149]

Health administrative databases maintained by the government of Saskatchewan include a population registry, prescription drug data, hospital services data, physician services data, cancer registry, the Resident Assessment Instrument Minimum Data Set (RAI-MDS) and vital statistics. Patients are identified through unique, lifelong health service numbers (HSN). All databases are linkable by the individual HSN, allowing for accurate population-based and longitudinal patient histories, with minimal loss to follow up.

The *population registry* captures demographic and residency/coverage data on all beneficiaries and is updated daily for any changes. Insured health transactions are checked against the population registry for eligibility and accuracy of information. Information provided includes sex, marital status, date of birth, start and stop dates for health coverage, and reasons for health coverage termination (e.g. death, emigration). The discharge abstract database provides diagnostic, treatment, and other health information on every hospital separation (discharge, transfer, or death) and day surgery case. It includes data from acute inpatient care, long-term care for patients that occupy a hospital bed, day surgeries, psychiatric inpatients, rehabilitation in general hospitals, and hospital separations that occurred outside the province involving a Saskatchewan beneficiary. Diagnostic information is reported with International Classification of Disease (ICD) codes.[150] ICD-9 codes were used until March, 31, 2002, and effective April 2002, ICD-10-CA codes are used. Other information includes procedures performed during the hospitalization, and admission and discharge dates. The medical services branch (MSB) provides information on physician billing claims. It includes physician and patient

information, services provided, and a diagnosis using three digit ICD-9 codes.[147] Some physicians that have alternate payment arrangements (i.e. non-fee-for service) may submit shadow (dummy) claims, although not all services may be captured reliably. A further limitation of the MSB is that only one ICD-9 claim can be recorded per physician visit. The prescription drug plan captures all prescriptions dispensed in outpatient settings. The provincial formulary lists drugs that are covered by the "Drug Plan", some of which are listed under restricted status and are only covered when certain criteria are met (known as Exceptional Drug Status), including the disease-modifying therapies for MS (Appendix A – B.1-4). The prescription drug plan provides information on the patient, drug name, dose, quantity dispensed, prescriber, dispensing pharmacy, cost, and date dispensed. Non-prescription medications are not reliably captured by the database, nor are drugs dispensed through hospital pharmacies. *The Resident Assessment Instrument Minimum Data Set (RAI-MDS)* provides information regarding care and function of long-term care facility residents. This includes diagnoses for medical conditions that affect everyday life, including a specific code for MS. Data are collected upon admission to the long-term care facility, and are updated quarterly or annually, as well as when there is a change in health status. The RAI-MDS documentation is mandatory in Saskatchewan; it was initiated in 2001 and fully implemented by 2004.[151]

1.7 THE INCIDENCE AND PREVALENCE OF MULTIPLE SCLEROSIS IN CANADA

It is estimated that 2.3 million people worldwide have MS, with an estimated 100,000 in Canada.[152] In 2013, Canada was estimated to have the highest prevalence of MS in the world with an overall prevalence of 291 per 100,000.[152] Prevalence has increased over the years[153] with somewhat stable incidence.[154] This increased prevalence may be attributed to earlier diagnosis[155] due to increased access to neurologists[3] and the emergence of more accurate diagnostic techniques (i.e. MRI),[156] and longer survival, rather than an actual increased risk of disease.[154]

Since the 1980s, many studies have attempted to estimate the prevalence of MS in Canadian regions using a variety of sources and methodologies such as self-report, medical chart reviews, and health administrative databases (Table 1.4). Chart reviews are considered to be the gold standard for the identification of MS[157] but are not feasible at the population level because of high cost and consent requirements.[158] Self-report without clinical confirmation is subject to inaccuracy and recall bias.[158,159] Health administrative databases can be an excellent source for population-based estimates of MS but need validated case definitions to obtain accurate results and are limited by the data available within each database.[159]

Table 1. 4 Incidence and Prevalence Studies of MS in Canada

Region	Author (year)	Study period	Data source	Incidence[a]	Crude overall prevalence[a] (95% CI)	Age adjusted overall prevalence[a] (95% CI)	Method of case ascertainment
Newfoundland [160]	Pryse-Phillips (1986)	1960-1984	Hospital/clinic, Neurologists, Other physician, Patient associations	3.0	56.4 (50-63)	-	Clinical assessment, Chart review
Alberta[161] **Barrhead County**	Warren (1992)	January 1st 1990[b]	Hospital/clinic, Other physicians, Nursing home/LTC, Patient associations	4.2	196 (118-305)	-	Clinical assessment, Chart review
Alberta[162] **Westlock County**	Warren (1993)	January 1st 1991[b]	Hospital/clinic, Other physicians, Nursing home/LTC, Patient associations	7.3	200 (127-300)	-	Clinical assessment
Alberta[163] **Crowsnest Pass and Cardston**	Klein (1994)	June 21, 1989[b]	Hospital/clinic, Neurologists, Other physicians		217 (121.5-358) 88	-	Clinical assessment, Chart review
Alberta[164]	Svenson (1994)	(1984-1989)	Administrative database		216 (NR)	-	Administrative data codes
Manitoba[165] **aboriginals**	Mirsattari (2001)	1970-1996	Hospital/clinic		40 (NR)	-	Clinical assessment and tests
Canada[158] **(overall)**	Beck (2005)	2000-2001	Canadian Community Health Survey	-	240 (210-280)	-	Self-report

Quebec				-	180 (90-260)	-	
Atlantic Canada				-	350 (230-470)	-	
Ontario				-	230 (130-250)	-	
Prairies				-	340 (240-440)	-	
British Columbia				-	240 (160-320)	-	
Newfoundland and Labrador[166]	Sloka (2005)	1996-2003	Neurologists, Administrative data	5.6	94.4 (90.2-98.7)	-	Chart review
Alberta[167] **First nations**	Svenson (2007)	1994-2002	Administrative Database		335 (328.5-341.5) 99.9 (78.4-121.4)		Administrative data codes
Saskatoon[168]	Hader (2007)	1970-2004	Neurologists, Other physicians, Administrative databases, Nursing homes, Patient associations, Registry	9.5 (8.8-10.4)	298 (274.7-323.6	329 (NR)	Chart review
Alberta[156]	Warren (2008)	1990-2004	Administrative data	23.9 (NR)	-	357.6 (351.0-364.2)	Administrative data codes
Manitoba[88]	Marrie (2010)	1984-2006	Administrative data	11.4 (10.7-12.0)	260 (NR)	262.4 (253.1-271.7)	Chart review, administrative data codes, questionnaire

Nova Scotia[169]	Marrie (2013)	1990-2010	Administrative data	5.17 (3.78-6.56)	-	266.9 (257.1-277.1)	Chart review, administrative data codes, questionnaire
Ontario[170]	Widdifield (2015)	2000-2010	Administrative data	19.4 (18.5-20.3)	223.7 (221.0-226.6)	207.3 (204.6-210.0)	Administrative data codes, Chart review
British Columbia[171]	Kingwell (2015)	1991-2010	Administrative data	7.8 (7.6-8.1)	-	179.9 (176.0-183.3)	Administrative data codes
Manitoba First Nations[172]	Marrie (2018)	1984-2011	Administrative data			188.5 (146.6–230.4)	Administrative data codes
Ontario[173] **Pediatric MS**	Marrie (2018)	2003-2014	Administrative data	0.99 (0.65-1.43) 1.24 (0.86-1.72)		4.03 (3.33-4.85) 6.8 (5.87-7.84)	Administrative data

Adapted from Evans C, Beland SG, Kulaga S, Wolfson C, Kingwell E, Marriott J, et al. Incidence and prevalence of multiple sclerosis in the Americas: a systematic review. *Neuroepidemiology*. 2013; 40: 195-21.

LTC, Long term care; NR, not reported;

[a] Per 100,000; [b] point prevalence

Determining incidence and prevalence of a disease with administrative data involves applying an algorithm or case definition to identify the 'affected' cohort.[174] Case definitions need to be validated to ensure that they are correctly capturing the individuals with the disease, and not capturing individuals without the disease. Validation evaluates the performance of the case definition and is typically done by computing the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and concordance.[145] Sensitivity indicates the proportion of true positives among all positive disease cases identified by the case definition, whereas, specificity indicates the proportion of true negatives among all disease negative cases identified by the case definition.[151] Positive predictive value indicates the proportion of disease positive cases identified by the case definition to truly have the disease and NPV is the proportion of disease negative cases identified by the administrative case definition who truly do not have the disease.[145,151] Concordance, which measures the level of agreement between a gold standard and new technique/method (e.g. medical records and administrative data) rather than accurateness of results, can be measured using methods such as Bland Altman's graphs and Cohen's Kappa.[175] Cohen's Kappa is recommended for categorical data, while Bland Altman's graphs are recommended for continuous data.[175,176] Pearson's coefficient, though commonly used, is inappropriate to measure concordance as it measures the strength of a relationship between two methods and not the agreement.[175,177]

Multiple sclerosis cases can be identified in administrative data, and several case definitions have been used across Canada (Table 1.5).[88,156,170] These definitions range from using one MS specific claim code (ICD-9: 340 or ICD-10: G35) for hospital and physician

claims[156,170] to requiring several MS-specific claims (with or without prescription drug claims).[88,169,171]

In a study conducted in Alberta, MS cases were defined as an individual with one or more hospital diagnoses of MS (ICD-9: 340), two or more physician claims for MS, or a diagnosis by a neurologist, although this definition was not validated. This study estimated the prevalence of MS in Alberta in 2004 was 357.6 per 100,000 (95% CI 351.0-364.2).[156] In Ontario, MS-specific claims (ICD-9 340 or ICD-10 G35) from one hospitalization or five physician billing claims over a two-year period were used to identify MS cases. This definition had a sensitivity of 84.2%, specificity of 100%, positive predictive value (PPV) of 86% and a negative predictive value (NPV) of 99%, and required the least amount of follow-up time for determining a case.[170] The age and sex standardized prevalence and incidence of MS in 2010 was 207.3 per 100,000 (95% CI: 204.6-210.0) and 19.4 per 100,000 (95% CI: 18.5-20.3), respectively.[170]

Other MS case definitions have been validated in Manitoba[88] and Nova Scotia,[169] and recently used to estimate the incidence and prevalence of MS in British Columbia.[171] Validation results can be found in Table 1.5. The case definition that was applied in Manitoba identified MS cases if an individual had ≥7 claims for MS prior to 1997 or ≥3 claims after 1997. A claim could come from hospital, physician, or prescription drug databases. Two definitions were developed because as of 1998, a provincial healthcare program was developed for MS patients that did not require their physicians submit fee for service claims or "shadow billing".[147] The average annual incidence rate in Manitoba between 1998 and 2006 was 11.4 per 100,000 (95% CI: 10.7-12.0) and the age adjusted prevalence in 2006 was 226.7 per 100,000 (95% CI: 218.1-235.3). The case definition used in Nova Scotia and British Columbia was ≥7 hospital or

physician claims for ≥3 years of residency following the first MS claim, and ≥3 claims for individuals with <3 years of residency. The average annual incident rate and adjusted prevalence reported for Nova Scotia in 2010 was 5.17 per 100,000 (96% CI 3.78-6.56) and 266.9 per 100,000 (95% CI 257.1-277.1), respectively. In British Columbia the average incident rate between 1996 and 2008 was 7.8 per 100,000 (95% CI 7.6-8.1)and the age standardised prevalence in 2008 was 179.9 per 100,000 (95% CI 176.0-183.3).[169,171] The Canadian Chronic Disease Surveillance System (CDSS) recently developed and released a case definition for MS for conducting national surveillance which requires ≥1 hospitalization or ≥5 physician claims for MS (ICD-9 340 or ICD-10 G35) within a two year period.[178]

The prevalence of MS in Saskatchewan is unknown, although a study by Hader et al. estimated the prevalence in the Saskatoon area in 2005 to be 298 per 100,000 (95% CI: 274.7 to 323.6). This estimate came from medical records from three local hospitals in Saskatoon between 1969 and 2005, chart reviews from long term care facilities, the MS rehabilitation clinic in Saskatoon, and local family physicians and neurologists, as well as through the memberships of the MS Society in Saskatoon.[168] A study by Beck *et al*. estimated the prevalence of MS in the Prairie region (Alberta, Manitoba and Saskatchewan) to be 340 per 100,000 - one of the highest in Canada.[158] Cases were identified from the Canadian Community Health Survey, a population based survey where participants were contacted by phone and asked to self-report their medical conditions. Self-reports of MS were not clinically confirmed, and the accuracy of the results is limited by the small number of cases with MS (n=332) from a total of 131,535 participants. Also, the survey excluded individuals residing in long term care facilities, which likely underestimates the true prevalence of MS. Differences in data sources for

case ascertainment and case definitions, and varying reporting of results (sex- and age-standardized vs. crude) make the comparison of incidence and prevalence between provinces difficult,[159] and highlights the need for a uniform and standardized approach for estimating and report the incidence and prevalence of MS.

Table 1. 5 Administrative case definitions used to estimate incidence and prevalence in Alberta, Manitoba, Nova Scotia, British Columbia, and Ontario

	Databases used	Administrative Case definition evaluated.	Comparator population	Sensitivity	Specificity	PPV	NPV
Alberta[156]	Hospital claims, Physician claims	≥1 hospitalization, ≥2 physician claims for MS or received diagnosis from neurologist	-	-	-	-	-
Manitoba[88]	Hospital claims, Physician claims, Prescription claims	≥7 separate claims (initial medical contact of MS before 1997), ≥3 separate claims (initial contact of MS after 1997)	General population	92.4% 90.2%	76.7% 55.9%	91.6% 74.5%	78.6% 80.0%
Nova Scotia[169]	Hospital claims, Physician claims	≥7 hospital or physician claims for ≥3 years of residency following first MS claim, and ≥3 claims for people with <3 years of residency	MS Clinic	88%	68%	89%	67%
British Columbia[171]	Hospital claims, Physician claims	≥7 hospital or physician claims for ≥3 years of residency following first MS claim, and ≥3 claims for people with <3 years of residency	-	88%	68%		
Ontario[170]	Hospital claims, Physician claims	≥1 hospitalization or ≥5 physician claims within a 2 year period.	General population	84.2%	100%	86%	99%

Ontario[173] Pediatric MS	Hospital claims, Physician claims, drug claims	≥1 hospitalization or ≥5 physician claims within a 2-year period	ADS cohort and healthy children	81%	100%	100%	86%
		≥3 hospital, physician or drug claims		89.2%	100%	100%	91.5%

PPV, positive predictive value; NPV, negative predictive value; MS, multiple sclerosis

ADS cohort: acquired demyelinating syndromes (ADS) prospective multicenter study cohort

1.8 AIMS AND OBJECTIVES

This PhD project aims to investigate the epidemiology and pharmacoepidemiology of MS in Saskatchewan and has four separate objectives, each achieved through individual studies.

Objective 1: Establish the incidence and prevalence of MS in Saskatchewan

Although Saskatchewan is estimated to have one of the highest prevalence of MS worldwide, the actual province-wide incidence and prevalence of MS is unknown. Obtaining accurate estimates using validated and systematic approaches that that have been applied in other Canadian provinces will help identify current knowledge gaps and enable comparison between different Canadian regions. This could help identify temporal trends in incidence and prevalence of MS that could also help estimate the impact of current or future interventions on the occurrence of the disease and aid in the search for the etiology of MS.[3,159]

Objective 2: Examine healthcare utilization patterns in the Saskatchewan MS cohort and the impact of impact of disease-modifying therapies on healthcare utilization at the population level

The introduction of DMTs has dramatically changed the treatment of MS. It has been suggested that by decreasing the number and severity of relapses and slowing disease progression that there should also be a decreased burden on the healthcare system, yet the current literature is conflicting. Therefore, understanding the impact that DMTs have on

healthcare utilization at a population level will help guide health policy decisions related to issues such as the reimbursement or coverage of therapies.

Objective 3: Identify predictors of hospitalizations in the Saskatchewan MS cohort

Hospital admissions place a significant burden on the healthcare system and understanding predictors and causes of hospitalization can guide efforts by clinicians and the health system to prevent hospitalizations and help with future planning and resource allocation.

Objective 4: Examine the impact of comorbidities on healthcare utilization in the Saskatchewan incident MS cohort

Comorbidities, which are common in the MS population, have been found to increase the risk of hospitalization almost 3-fold.[114] Limited studies have evaluated the effect of comorbidities on healthcare utilization, thus we also aim to evaluate the association between comorbidities and hospitalization rates in MS patients in Saskatchewan.

Identifying the incidence and prevalence of MS and evaluating the healthcare utilization the MS population in Saskatchewan will help fill knowledge gaps and assist in policy making and future planning needed to improve MS care in the province.

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1.10 APPENDICES

Appendix A. Criteria for coverage of first line disease modifying therapies for multiple sclerosis in Saskatchewan[23]

Have clinically definite relapsing and remitting multiple sclerosis *AND;*
Have had at least two documented attacks of MS during the previous two years (an attack is defined as the appearance of new symptoms or worsening of old symptoms, lasting at least 24 hours in the absence of fever, preceded by stability for at least one month) *AND;*
Are fully ambulatory for 100 meters without aids (canes, walkers or wheelchairs). Expanded Disability Status Scale (EDSS) 5.5 or less *AND;*
Are ages 18 or older (applications for patients under 18 will be considered.)

EDSS, Expanded Disability Status Scale

Appendix B.1 Criteria to obtain and maintain coverage for natalizumab in Saskatchewan[23]

EDSS ≤ 5.0
Has failed to respond to a full and adequate course (i.e. at least six months) of at least ONE disease modifying therapy listed on the Saskatchewan Formulary as initial therapy OR has contraindications/intolerance to at least TWO disease modifying therapies listed on the Saskatchewan Formulary as initial therapy *AND;*
Has had ONE of the following types of relapses in the past year: • The occurrence of one relapse with partial recovery during the past year AND has at least ONE gadolinium enhancing lesion on brain MRI, OR significant increase in T2 lesion load compared to a previous MRI; • The occurrence of two or more relapses with partial recovery during the past year; • The occurrence of two or more relapses with complete recovery during the past year AND has at least ONE gadolinium enhancing lesion on brain MRI, OR significant increase in T2 lesion load compared to a previous MRI.
Patients must be stable or have experienced no more than 1 disabling attack/relapse and have an EDSS score of ≤ 5.0 to be eligible for annual renewal.

EDSS, Expanded Disability Status Scale

Appendix B.2 Criteria to obtain and maintain coverage for fingolimod in Saskatchewan23

EDSS ≤ 5.5
Have failed to respond to a full and adequate course (i.e. at least six months) of: at least ONE disease modifying therapy (DMT) listed on the SK Formulary listed as initial therapy, OR has contraindications/intolerance to at least TWO disease modifying therapies listed on the SK Formulary as initial therapy AND;
One or more clinically disabling relapses in the previous year
Significant increase in T2 lesion load compared with that from a previous MRI scan (i.e. 3 or more new lesions) or at least one gadolinium enhancing lesion
Exclusion Criteria: • Patients who have had a heart attack or stroke in the last 6 months of funding request, history of sick sinus syndrome, atrioventricular block, significant QT prolongation, bradycardia, ischemic heart disease, or congestive heart failure • Patients taking class 1A or III anti-arrhythmic drugs, immunocompromised due to immunosuppressant or cancer or AIDS, severe hepatic impairment, concurrent malignancies, pregnancy/anticipated pregnancy/breast feeding, or active infectious disease such as tuberculosis or hepatitis. • Patients with a history of cardiovascular disease, immunocompromised state, severe hepatic impairment, concurrent malignancies, anticipated pregnancy/breastfeeding or have an active infectious disease such as tuberculosis or hepatitis cannot be approved for fingolimod.
Patients must be stable or have experienced no more than 1 disabling attack/relapse and have an EDSS score of ≤ 5.5 to be eligible for annual renewal.

EDSS, Expanded Disability Status Scale

Appendix B.3 Criteria to obtain and maintain coverage for alemtuzumab in Saskatchewan[23]

EDSS ≤ 5.0 AND
Active disease defined by clinical and imaging features (i.e., one new lesion) AND;
At least one relapse while on at least six months of a disease modifying therapy within the last 10 years AND;
At least two attacks (first episode or relapse) in the previous two years, with at least one attack in the previous year AND;
The medication is being prescribed by a neurologist with experience in the treatment of multiple sclerosis AND;
An inadequate response to a treatment course at least six months in length (i.e., at least one attack) to at least ONE disease modifying therapy listed on the Saskatchewan Formulary;
Patients are prescribed medication for 2 years (8 vials) and retreatment may be considered.

EDSS, Expanded Disability Status Scale

Appendix B.4 Criteria to obtain and maintain coverage for ocrelizumab in Saskatchewan[23]

For treatment of RRMS
EDSS ≤ 5.5 AND
have had a clinical relapse and/or new MRI activity in the last two years AND;
are fully ambulatory for 100 meters without aids (canes, walkers, or Wheelchairs)
For treatment of PPMS
EDSS score between 3.0 and 6.5 AND;
Has a confirmed diagnosis of PPMS (based on McDonald criteria);
Score of at least 2.0 on the Functional Systems scale for the pyramidal system due to lower extremity findings;
Disease duration of less than: 15 years for those with an EDSS greater than 5.0; OR o 10 years for those with an EDSS of 5.0 or less
The patient is under the care of a neurologist with experience in the diagnosis and management of multiple sclerosis.
Treatment should be discontinued for patients with an EDSS score of equal to or greater than 7.0.

EDSS, Expanded Disability Status Scale; RRMM, Relapsing remitting multiple sclerosis; PPMS, Primary progressive multiple sclerosis

2 Establishing the Incidence and Prevalence of Multiple Sclerosis in Saskatchewan

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LAS, CE and RAM designed the study. LAS conducted data analyses. LAS and CE drafted the manuscript. LAS, CE, RAM, DB and KK were involved in the interpretation of data, critically revising the manuscript, and have approved the final version to be published.

2.1 ABSTRACT

Objective: To validate a case definition of multiple sclerosis (MS) using health administrative data and to provide the first province-wide estimates of MS incidence and prevalence for Saskatchewan, Canada.

Methods: We used population-based health administrative data between January 1, 1996 and December 31, 2015 to identify individuals with MS using two potential case definitions: 1) ≥3 hospital, physician or prescription claims (Marrie definition); 2) ≥1 hospitalization or ≥5 physician claims within 2 years (Canadian Chronic Disease Surveillance System [CCDSS] definition). We validated the case definitions using diagnoses from medical records (n=400) as the gold standard.

Results: The Marrie definition had a sensitivity of 99.5% (95% CI 92.3-99.2), specificity of 98.5% (95% CI 97.3-100.0), positive predictive value (PPV) of 99.5% (95% CI 97.2-100.0) and negative predictive value (NPV) of 97.5% (95% CI 94.4-99.2). The CCDSS definition had a sensitivity of 91.0% (95% CI 81.2-94.6), specificity of 99.0% (95% CI 96.4-99.9), PPV of 98.9% (95% CI 96.1-

99.9) and NPV of 91.7% (95% CI 87.2-95.0). Using the more sensitive Marrie definition, the average annual adjusted incidence per 100,000 between 2001 and 2013 was 16.5 (95% CI 15.8-17.2), and the age and sex-standardized prevalence of MS in Saskatchewan in 2013 was 313.6 per 100,000 (95% CI 303.0-324.3). Over the study period, incidence remained stable while prevalence increased slightly.

Conclusion: We confirm Saskatchewan has one of the highest rates of MS in the world. Similar to other regions in Canada, incidence has remained stable while prevalence has gradually increased.

2.2 INTRODUCTION

With approximately 100,000 affected individuals, Canada has one of the highest rates of multiple sclerosis (MS) in the world.[1] Despite the high prevalence, precise estimates of epidemiology are missing for some Canadian regions. The etiology of MS remains elusive but evidence suggests geographic and environmental factors, including genetic heterogeneity, may play an important role.[2] Establishing incidence and prevalence in specific regions can contribute to the understanding of etiologic factors and inform decisions related to resource allocation and access to MS care and supports.[3]

Several methods exist for determining the incidence and prevalence of a disease, including the use of health administrative data. In Canada, two well-recognized definitions for identifying cases of MS from administrative data exist, with differing potential strengths and limitations, and have been used to estimate the incidence and prevalence in several provinces.[4,5]

The province of Saskatchewan is often cited as having one of the highest rates of MS in Canada,[6,7] yet population-wide estimates have never been reported from this region. The purpose of this study was twofold: to test two case definitions of MS using health administrative databases; and to establish valid estimates of the incidence and prevalence of MS in Saskatchewan.

2.3 METHODS

Data Source

Saskatchewan has a stable population of just over one million people.[8] Almost all (99%) residents of Saskatchewan are entitled to publicly funded provincial health care benefits apart from those covered federally, including members of the Canadian Forces, Royal Canadian Mounted Police, and federal inmates.[9] The Saskatchewan government maintains several databases that record health services delivered to provincial beneficiaries including physician claims, hospital visits, prescription drugs, vital statistics, and population registry information.[9] Diagnoses are recorded using International Classification of Disease (ICD) codes. In the hospital discharge database, diagnoses were reported using the ninth revision (ICD-9) until 2002, and currently use ICD-10-CA. Diagnoses in physician claims data are recorded using three-digit ICD-9 codes.[9] The prescription drug database records medication dispensations for medications. All demographic information was obtained from the population registry.[9]

Identification of Cases and Controls for Validation

A random sample of 200 patients with clinically definite MS were identified from the provincial MS clinic in Saskatchewan. Patients received their diagnosis from specialists providing clinical services according to prevailing diagnostic criteria.[10-13] Also, 200 individuals without an MS diagnosis ("controls") were randomly selected from the Inpatient Rehabilitation Center database. This database captures diagnostic information (via tick boxes) on numerous chronic diseases, one of which is MS.[14] Health region employees not involved with the study randomly selected cases and controls from these databases, and only de-identified information was released to researchers.

Case Definitions and Validation

Two case definitions for MS were applied to cases and controls between January 1, 1996 and December 31, 2015. The first definition required ≥3 hospital, physician or drug claims, and has been previously validated by Marrie *et al*, and used in other Canadian provinces and observational research.[15-21] The second definition, released by the Canadian Chronic Disease Surveillance System (CCDSS), required ≥1 hospitalization or ≥5 physician claims within 2 years.[5] Hospital transfers and re-admissions within one day of a discharge date were considered as one hospitalization episode and collapsed into a single hospital claim. We selected these definitions because they have been previously validated or used in other Canadian studies.[15,20-22] As a complementary analysis, we also tested several other case definitions (Supplemental - Table 1) to allow for comparability with other Canadian studies or for situations where a potentially more sensitive or more specific definition may be warranted.

For each administrative case definition, the sensitivity (proportion of true positives correctly identified), specificity (proportion of true negative correctly identified), positive predictive value (PPV) and negative predictive value (NPV) (with a 95%CI) were calculated as compared to the reference standard. A Kappa statistic was used to estimate the agreement between the administrative case definition and the medical records identification for each case definition where neither was considered the gold standard. We estimated that a sample of 200 MS cases and 200 non-MS controls would allow us to detect a sensitivity of 90% and specificity of 85%.

Incidence

Because MS is a diagnosis of exclusion, patients may present with symptoms suggesting

the disease before a confirmed diagnosis. Thus, for all patients meeting the case definition of MS, the date of diagnosis ("index date") was identified as the earlier of: the first date of medical contact for MS (ICD-9: 340/ICD-10: G35), or a diagnosis of a related demyelinating conditions [acute disseminated demyelination (ICD-10: G36), neuromyelitis optica (ICD-9: 341.0/ICD-10: G36.0), demyelinating disease of CNS unspecified (ICD-9: 341.9/ICD-10: G37.9), acute disseminated encephalomyelitis (ICD-9: 323/ICD-10: G36.9), optic neuritis (ICD-9: 377.3/ICD-10: H46), and acute transverse myelitis (ICD-9: 323.82/ICD-10: G37)].[15] This allowed for a more accurate date of incidence based on disease onset rather than disease diagnosis, which may be delayed.[15]

The incident MS population consisted of those meeting the case definition with an index date in the given calendar year. Population figures on January 1 for the respective year were used as the denominator, with prevalent MS cases from previous years removed. Results were standardized to the 2001 Canadian Census to allow for comparability with previous studies. A five-year run-in period with no other claims for MS or demyelinating conditions was used to ensure that the identified cases were indeed incident. However, because the CCDSS recommended an 8-year run-in period to detect incidence in MS,[5] a sensitivity analysis using an 8-year run-in period was also conducted to evaluate the effect of different run-in periods on incidence estimates.

Prevalence

Prevalent MS cases were identified for each calendar year from 2001 to 2013 using both case definitions. Cases of MS were considered prevalent until their death or loss of health coverage (emigration). Population figures from January 1 for each year were used as the

denominator. Prevalence was estimated annually and adjusted for sex and age via the direct method[23] to the 2001 Canadian census.

This study was approved by the University of Saskatchewan's Biomedical Research Ethics Board. Data access was approved by the Saskatchewan Ministry of Health and the Saskatchewan Health Quality Council.

2.4 RESULTS

Validation of definitions

Four hundred cases and controls were identified from the Saskatoon MS Clinic (n=200) and the Inpatient Rehabilitation Centre database (n=200). There were more females in the MS case group (66.5%) compared to the non-MS control group (35.0%), and the control group was older, with a mean age of 65.0 (SD 19.2) years compared to 53.8 (SD 12.6) years. The Marrie definition (≥3 hospital, physician, or drug claims) had a sensitivity of 99.5% (95%CI 92.3-99.2), specificity of 98.5% (95%CI 97.3-100.0), PPV of 99.5 % (95%CI 97.2-100.0) and NPV of 97.5% (95%CI 94.4-99.2). The CCDSS definition (≥1 hospitalization or ≥5 physician claims within 2 years) had a sensitivity of 91.0% (95%CI 81.2-94.6), specificity of 99.0% (95%CI 96.4-99.9), PPV of 98.9% (95%CI 96.1-99.9) and NPV of 91.7% (95%CI 87.2-95.0). Agreement between the clinical and administrative cohorts was high with a Kappa of 0.97 (95%CI 0.95-0.99) for the Marrie definition and 0.90 (95%CI 0.85-0.94) for the CCDSS definition. The complementary analyses revealed that, in general, sensitivity was higher for those definitions requiring fewer claims and those with a longer, or unlimited timeframe (Supplemental-Table 2).

Incidence

Between 2001 and 2013, 2226 incident cases of MS were identified with the Marrie definition and 1903 were identified with the CCDSS definition. Approximately 70% of identified cases were women, with a mean age of 43 years during the year of "diagnosis". Other characteristics of identified cases were similar between the definitions (Table 2.1). In 2013, the age and sex-standardized incidence of MS per 100,000 was 16.3 (95%CI 13.8 – 18.8) for the Marrie definition and 12.1 (95%CI 9.9 – 14.2) for the CCDSS definition (Table 2.2). Between 2001 and 2013, the average annual adjusted incidence per 100,000 was 16.5 (95%CI 15.8-17.2) using the Marrie definition, and 14.1 (95%CI 13.5-14.8) with the CCDSS definition (Table 2.3 and 2.4). For both definitions, incidence was highest in 2001, and became relatively stable after 2005 (Figure 2.1). Peak incidence occurred between the ages of 35-39 for both sexes and was similar between definitions with 24.2 (95%CI 21.1-27.4) per 100,000 for Marrie and 22.1 (95%CI 19.1-25.1) per 100,000 for CCDSS (Table 2.2, Table 2.3 and 2.4). The incidence of MS in females was higher than in males with an overall rate ratio of 2.21 (95%CI 2.02-2.42) for the Marrie definition, and 2.13 (95%CI 1.94-2.35) for the CCDSS definition (Table 2.3 and 2.4).

The annual change in incidence rate over time was similar regardless of whether a 5 or 8-year run-in period was applied for the Marrie (-0.0503 [SE 0.0176] vs -0.0569 [SE 0.0270]) and CCDSS definitions (-0.0622 [SE 0.0192] vs -0.0745 [SE 0.0296]).

Prevalence

As of July 1, 2013, 3,456 individuals with MS resided in Saskatchewan according to the Marrie definition, versus 2,998 based on the CCDSS definition. In 2013, the age and sex-

standardized prevalence of MS per 100,000 was 313.6 (95%CI 303.0-324.3) using the Marrie definition, and 248.7 (95%CI 239.2-258.2) using the CCDSS definition (Table 2.5). The prevalence was higher in females than in males, with a female to male ratio of 2.42 (95%CI 2.37-2.48) with the Marrie definition and 2.36 (95%CI 2.30-2.42) with the CCDSS definition (Supplemental -Table 2.4 and Supplemental -Table 2.5). Irrespective of the definition used, the prevalence increased gradually between 2001 and 2010 but stabilized thereafter (Figure 2.2). For both definitions, the age at which prevalence peaked increased over time (Figure 2.3).

2.5 DISCUSSION

The results of this first-ever province-wide examination of incidence and prevalence confirm that Saskatchewan has one of the highest rates of MS in Canada, and worldwide. We found that the Marrie definition (≥3 claims for MS) had a higher sensitivity, PPV, and NPV when compared to the CCDSS definition (≥1 hospitalization or ≥5 physician claims within 2 years); specificity was similar between the two definitions. The estimated incidence and prevalence of MS in Saskatchewan were higher using the more sensitive Marrie definition compared to the CCDSS definition. Although differences in the rates appear small, the Marrie definition identifies an additional 450 prevalent cases in 2013 out of a provincial population of 1.1 million. As a result, the Marrie definition may be preferred from a health policy perspective considering the high costs associated with MS will have a significant impact on health system resources.[24,25]

In 2013, 314 individuals per 100,000 in Saskatchewan were identified as having MS. A previous study estimated a prevalence of 340 per 100,000 but examined the prairie region, combining

data from the 2000/2001 Canadian Community Health Survey for Alberta, Saskatchewan, and Manitoba, and relied on a very small number of cases (n<80).[7] Hader *et al.* used medical records to estimate a prevalence of 298 per 100,000 but only included the Saskatoon area, not the entire province.[6]

The prevalence of MS has been determined in several Canadian provinces, but methodological differences in disease surveillance can make comparisons difficult. Therefore, we utilized two case definitions that have been previously applied to health administrative data in Canada – to allow for comparability across provinces. The first definition by Marrie *et al*, was initially validated in Manitoba,[15] has been used in other provinces, and is regularly used.[16-21] The age-adjusted prevalence of MS in Manitoba in 2006 was 262 per 100,000 and the average age-adjusted annual incidence was 13.4 per 100,000 between 1998 and 2006.[15] The estimates observed in Saskatchewan using this same definition were higher: the standardized prevalence of MS was 302 per 100,000 in 2006, and the standardized annual incidence was 16.5 per 100,000 between 2001 and 2013.

The second definition has been validated in Ontario,[22] and is the definition that has been recently recommended by the Canadian Chronic Disease Surveillance System in part because it does not require prescription claims, which are not universally available across Canada.[5] The age and sex-standardized prevalence of MS in Ontario in 2010 was 207 per 100,000, compared with 256 per 100,000 in Saskatchewan for the same year.[22]

In British Columbia and Nova Scotia, MS cases were defined as having ≥7 claims for MS for individuals with >3 years of residency or ≥3 claims if ≤3 years of residency. In Nova Scotia,

the age-standardized prevalence of MS in 2010 was estimated to be 267 per 100,000 with an average annual incidence was 9.77 per 100,000 from 1995 to 2010. When a three claim definition (regardless of residency time) was tested, the crude prevalence in 2010 was 326.3 per 100,000.[21] In British Columbia, the age-standardized prevalence of MS in 2008 was 180 per 100,000 with an average annual incidence of 7.8 per 100,000 from 1996 to 2008.[20] Similar to Nova Scotia, the more sensitive ≥3 claim definition revealed a higher standardized annual incidence (10.9 per 100,000) and prevalence (235.8 per 100,000).[20]

Regional variation in the prevalence of MS across Canada has been demonstrated previously, and may be due to environmental differences and variations in the ethnic makeup (i.e. inherited risk of developing MS) of the populations.[3,7,22] This may help to explain the differences seen between the prevalence in British Columbia and Nova Scotia, both of which are coastal provinces compared to landlocked Saskatchewan. Interestingly, the incidence and prevalence of MS was higher in Saskatchewan than Manitoba – two provinces of similar location, size, and population demographics. However, variations in genetic and environmental risks could still play a role, as has been noted in other countries over small geographic distances.[26] Another possible explanation for this inconsistency may be differences in healthcare policies and practice patterns between provinces.

Similar to other provinces, we observed a relatively stable incidence, but a gradual increase in prevalence. This increase in prevalence may be attributed to earlier diagnosis[27] due to improved access to neurologists[3] and the emergence of more accurate diagnostic techniques (i.e. MRI),[28] and longer survival, rather than an actual increased risk of disease.[29] Duration of observation may also affect the prevalence estimate; a longer observation period may capture

milder or inactive cases of MS.[30] A shifting in peak prevalence to older ages over time (representing an aging population) is also consistent with findings from Manitoba, Nova Scotia, and British Columbia,[15,20,21] and studies of mortality rates, which suggest an improved survival in individuals with MS.[31,32] We observed a "peak" in incidence in 2001, the same year new diagnostic criteria introduced the use of MRI to facilitate the diagnosis of MS, which may have contributed to the increase in MS cases rather an actual increase in disease risk during that period. However, as this was the first year that incidence was measured, it is also likely that prevalent cases were incorrectly identified as incident during this year.

Although health administrative data are considered a reliable method for estimating incidence and prevalence, individuals who do not have frequent contact with the health care system may be missed, resulting in an underestimation of the disease. Indeed, a previous study in Quebec found that the prevalence of systematic lupus erythematosus, another relapsing remitting disease where contacts with the health system varied, was underestimated when using an observation period of 5 years versus 15 years.[30] This is more likely to have happened in our study with the CCDSS definition which required claims occur within a two-year period, compared to the Marrie definition which had no time limit, and was able to utilize almost two decades of data. This may also have been augmented due to billing practices in Saskatchewan; although many physicians who receive alternate payments (i.e. non-fee-for-service) submit shadow (dummy) claims which are captured in health administrative data, the physicians at the provincial MS clinic did not shadow bill during the study period. Therefore, not all encounters for MS may have been captured reliably. This is more likely to have impacted the CCDSS definition which may result in estimates that could possibly underestimate of the true burden

of MS. The two reference data sources captured diagnoses differently which could introduce ascertainment bias. However, clinicians prospectively recorded the diagnoses in both cases which would be expected to limit the bias. A further limitation is the potential for misclassifying prevalent cases as incident. However, in a sensitivity analysis, we used an 8-year run-in period to identify incident cases, and found the change in incidence rates over time estimated with the 5-year run-in period to be very similar.

We confirmed that Saskatchewan has one of the highest rates of MS in Canada, and worldwide. The Public Health Agency of Canada estimated the annual per capita health care cost (excluding out-of-pocket expenses) for adults in 2011 was approximately $16,800 for individuals with MS, compared to $2,500 for those without a neurological condition.[25] This, combined with a high prevalence and longer survival means MS will continue to place a significant burden on society and the health care system.[24] A more complete understanding of the burden of MS in Saskatchewan will not only help with future health care planning and resource allocation, but will also contribute towards research attempting to better understand the etiology of MS.

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Table 2. 1 Characteristics of incident (2001-2013) and prevalent MS cases (2013) for Marrie and CCDSS definitions

Incident Cases (2001-2013)	**Marrie Definition N=2226**	**CCDSS Definition N=1903**
Sex, n (%)		
Women	1537 (69)	1299 (68)
Mean age at incidence, years (SD)	42.8 (13.8)	43.1 (14.5)
Mean time to meet case definition[a], years (SD)	0.90 (1.48)	0.98 (1.40)
Prescription for a DMT, n (%)		
Ever	834 (38)	805 (42)
Within 3 years of first MS claim	695 (31)	672 (35)
Socioeconomic status at incidence date, n (%)[b]		
Lowest	367 (16)	336 (18)
Second lowest	342 (19)	372 (20)
Middle	387 (17)	331 (17)
Second highest	464 (21)	398 (21)
Highest	414 (19)	328 (17)
Unknown	162 (7)	138 (7)
Prevalent Cases (July 1st, 2013)	**Marrie Definition N=3,456**	**CCDSS Definition N=2,998**
Sex, n (%)		
Women	2463 (71)	2119 (71)

Mean age, years (SD)	53.1 (13.3)	53.2 (13.5)
Prescription for a DMT, n (%) Ever	1281 (37)	1256 (42)
Socioeconomic status quintile, n (%)[b]		
Lowest	512 (15)	455 (15)
Second lowest	667 (19)	581 (19)
Middle	620 (18)	522 (17)
Second highest	706 (20)	633 (21)
Highest	693 (20)	584 (19)
Unknown	258 (7)	223 (7)

Marrie definition: ≥ hospital, physician or drug claims. CDSS definition: ≥1 hospital or ≥5 physician claims in 2 years
MS: multiple sclerosis; CCDSS: Canadian Chronic Disease Surveillance System; SD: Standard deviation; DMT: Disease modifying therapy; SES: socioeconomic status
a. Time between first MS claim and satisfying the case definition
b. Sum of percentages may not add up to 100 as the figures were rounded. Chi square test for homogeneity was used to test for equal distribution between SES quintiles (missing cases were excluded), p-value = <.0001.

Table 2. 2 Age and sex standardized incidence of MS in Saskatchewan per 100,000, 2001 – 2013

Standardized Incidence per 100,000 – Marrie definition (≥3 hospital, physician, or drug claims)							**Standardized Incidence per 100,000 – CCDSS definition** (≥1 hospitalization or ≥5 physician claims within 2 years)					
Year	**Both**	**95% CI**	**Males**	**95% CI**	**Females**	**95% CI**	**Both**	**95% CI**	**Males**	**95% CI**	**Females**	**95% CI**
2001	24.20	21.05-27.35	13.11	9.81-16.41	35.33	29.95-40.72	22.14	19.13-25.14	11.98	8.84-15.13	32.32	27.19-37.45
2002	20.60	17.70-23.50	11.27	8.20-14.33	30.07	25.12-35.01	17.16	14.51-19.80	9.22	6.43-12.01	25.20	20.69-29.72
2003	19.67	16.84-22.50	11.16	8.15-14.18	28.23	23.42-33.03	17.64	14.96-20.32	10.49	7.57-13.41	24.82	20.31-29.32
2004	20.39	17.50-23.29	13.30	10.00-16.60	27.51	22.75-32.26	19.01	16.22-21.79	12.54	9.35-15.73	25.48	20.91-30.04
2005	21.97	18.95-24.98	15.43	11.86-19.00	28.51	23.66-33.36	18.95	16.16-21.75	15.14	11.62-18.66	22.76	18.43-27.09
2006	17.08	14.42-19.74	11.41	8.30-14.51	22.79	18.47-27.11	14.94	12.46-17.42	10.60	7.62-13.58	19.32	15.35-23.30
2007	17.96	15.22-20.70	8.49	5.86-11.12	27.40	22.61-32.19	14.65	12.18-17.13	6.44	4.15-8.74	22.85	18.47-27.22
2008	16.82	14.19-19.45	11.33	8.29-14.37	22.33	18.04-26.62	13.61	11.23-15.98	9.79	6.96-12.63	17.44	13.63-21.25
2009	14.59	12.18-17.01	9.03	6.33-11.73	20.23	16.22-24.25	12.69	10.44-14.93	8.60	5.96-11.24	16.85	13.20-20.49
2010	13.51	11.20-15.81	7.06	4.70-9.41	20.05	16.07-24.03	11.64	9.49-13.79	6.56	4.28-8.85	16.78	13.12-20.43
2011	14.01	11.64-16.38	9.57	6.84-12.30	18.52	14.64-22.39	11.88	9.70-14.06	7.99	5.46-10.52	15.83	12.27-19.39
2012	13.76	11.46-16.07	8.15	5.72-10.58	19.54	15.59-23.49	10.64	8.62-12.66	6.35	4.23-8.47	15.04	11.58-18.50
2013	16.27	13.77-18.77	12.00	9.00-15.00	20.65	16.64-24.67	12.05	9.91-14.18	8.33	5.85-10.82	15.85	12.36-19.35

Table 2. 3a. Average annual incidence of MS in Saskatchewan by age and sex per 100,000, 2001 – 2013 (Marrie definition)

	Both			Male			Female			Female: male	
Age Group (years)	**No. cases 2001-2013**	**AAI**	**95% CI**	**No. cases 2001-2013**	**AAI**	**95% CI**	**No. cases 2001-2013**	**AAI**	**95% CI**	**Rate Ratio**	**95% CI**
≤19	47	1.29	0.92-1.66	13	0.70	0.32-1.07	34	1.91	1.27-2.55	2.74	1.45-5.19
20-24	141	14.16	11.82-16.49	38	7.42	5.06-9.78	103	21.29	17.18-25.41	2.87	1.98-4.16
25-29	224	24.62	21.40-27.84	67	14.42	10.97-17.87	157	35.27	29.75-40.78	2.45	1.84-3.26
30-34	236	27.82	24.27-31.37	77	17.93	13.92-21.93	159	37.95	32.05-43.85	2.12	1.61-2.78
35-39	306	35.42	31.45-39.39	95	21.88	17.48-26.28	211	49.10	42.47-55.72	2.24	1.76-2.86
40-44	320	33.89	30.18-37.61	86	18.10	14.28-21.93	234	49.89	43.50-56.28	2.76	2.15-3.53
45-49	306	30.74	27.29-34.18	89	17.66	13.99-21.33	217	44.15	38.27-50.02	2.50	1.95-3.20
50-54	248	26.91	23.56-30.26	79	16.87	13.15-20.59	169	37.29	31.67-42.91	2.21	1.69-2.89
55-59	155	20.11	16.94-23.28	54	13.80	10.12-17.48	101	26.63	21.43-31.82	1.93	1.39-2.69
60-64	94	15.32	12.22-18.41	38	12.36	8.43-16.30	56	18.28	13.49-23.06	1.48	0.98-2.23
65-69	57	11.40	8.44-14.36	23	9.38	5.55-13.22	34	13.34	8.86-17.82	1.42	0.84-2.41
70-74	40	9.11	6.29-11.93	12	5.76	2.50-9.03	28	12.13	7.64-16.62	2.10	1.07-4.14
75-79	25	6.49	3.95-9.04	11	6.36	2.60-10.12	14	6.60	3.14-10.06	1.04	0.47-2.29
≥80	27	4.41	2.75-6.07	7	3.12	0.81-5.44	20	5.16	2.90-7.42	1.65	0.70-3.90
Total	2226	16.51	15.82-17.19	689	10.26	9.49-11.03	1537	22.70	27.57-23.84	2.21	2.02-2.42

Marrie definition: ≥3 hospital, physician, or drug claims; AAI: average annual incidence

Table 2. 4b. Average annual incidence of MS in Saskatchewan by age and sex per 100,000, 2001 – 2013 (CCDSS definition)

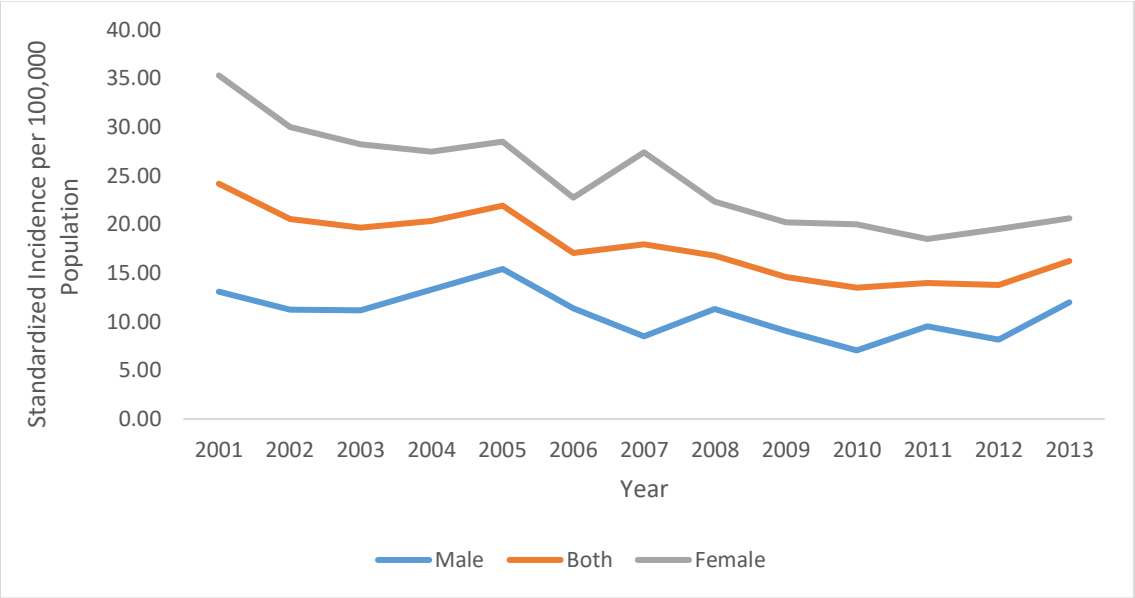
	Both			Male			Female			Female: male	
Age Group (years)	**No. cases 2001-2013**	**AAI**	**95% CI**	**No. cases 2001-2013**	**AAI**	**95% CI**	**No. cases 2001-2013**	**AAI**	**95% CI**	**Rate Ratio**	**95% CI**
≤19	46	1.26	0.90-1.63	12	0.64	0.28-1.01	34	1.91	1.27-2.55	2.97	1.54-5.74
20-24	121	12.15	9.98-14.31	31	6.05	3.92-8.18	90	18.60	14.76-22.45	3.07	2.04-4.62
25-29	199	21.87	18.83-24.91	56	12.05	8.89-15.21	143	32.11	26.85-37.37	2.66	1.96-3.63
30-34	187	22.03	18.87-25.19	63	14.66	11.04-18.29	124	29.58	24.38-34.79	2.02	1.49-2.73
35-39	261	30.19	26.53-33.85	83	19.11	15.00-23.22	178	41.38	35.30-47.46	2.17	1.67-2.81
40-44	272	28.79	25.36-32.21	77	16.20	12.58-19.82	195	41.52	35.69-47.34	2.56	1.97-3.34
45-49	250	25.09	21.98-28.20	75	14.87	11.51-18.24	175	35.55	30.28-40.81	2.39	1.82-3.13
50-54	193	20.92	17.97-23.87	65	13.87	10.50-17.24	128	28.19	23.31-33.08	2.03	1.51-2.74
55-59	128	16.59	13.72-19.46	49	12.51	9.01-16.01	79	20.79	16.21-25.38	1.66	1.16-2.37
60-64	89	14.49	11.48-17.50	36	11.71	7.88-15.53	53	17.27	12.62-21.92	1.48	0.97-2.25
65-69	58	11.59	8.61-14.57	19	7.75	4.26-11.23	39	15.29	10.49-20.09	1.97	1.14-3.42
70-74	36	8.19	5.52-10.87	15	7.20	3.56-10.85	21	9.09	5.20-12.98	1.26	0.65-2.45
75-79	33	8.57	5.64-11.49	16	9.25	4.72-13.78	17	8.01	4.20-11.82	0.87	0.44-1.71
≥80	30	4.90	3.15-6.65	7	3.12	0.81-5.43	23	5.93	3.50-8.35	1.90	0.81-4.42
Total	1903	14.11	13.48-14.75	604	8.99	8.28-9.71	1299	19.19	18.14-20.23	2.13	1.94-2.35

CCDSS definition: ≥1 hospitalization or ≥5 physician claims within 2 years; AAI: average annual incidence

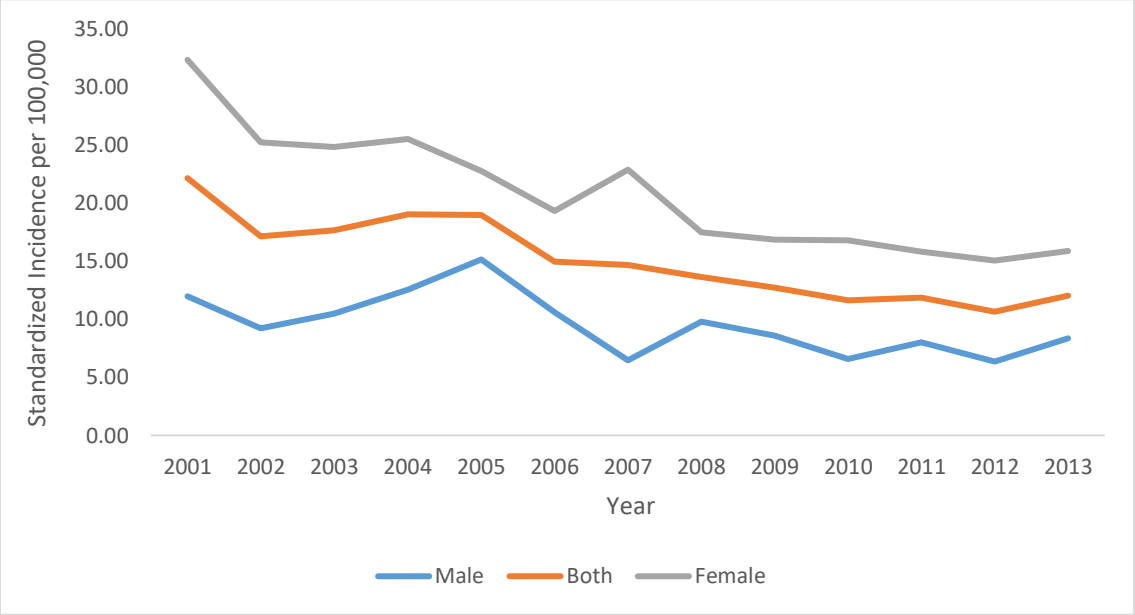
Table 2. 5 Age standardized prevalence of MS in Saskatchewan per 100,000 by sex, 2001-2013

Standardized Prevalence per 100,000 – Marrie Definition (≥3 hospital, physician, or drug claims)							**Standardized Prevalence per 100,000 – CCDSS Definition** (≥1 hospitalization or ≥5 physician claims within 2 years)					
Year	**Both**	**95% CI**	**Males**	**95% CI**	**Females**	**95% CI**	**Both**	**95% CI**	**Males**	**95% CI**	**Females**	**95% CI**
2001	253.98	243.74-264.21	152.41	141.18-163.64	356.02	338.89-373.14	215.39	205.96-224.82	131.15	120.73-141.57	299.89	284.15-315.62
2002	266.09	255.67-276.52	157.00	145.66-168.33	375.89	358.38-393.39	224.61	215.04-234.19	133.89	123.42-144.36	315.77	299.72-331.83
2003	274.77	264.23-285.31	158.37	147.04-169.70	392.10	374.31-409.89	230.53	220.87-240.18	135.28	124.80-145.76	326.42	310.18-342.66
2004	287.48	276.68-298.28	165.79	154.18-177.39	409.32	391.12-427.52	239.57	229.71-249.43	140.49	129.80-151.18	338.62	322.06-355.18
2005	295.53	284.63-306.43	172.83	161.03-184.63	418.62	400.29-436.95	245.05	235.12-254.98	146.01	135.15-156.86	344.26	327.63-360.89
2006	302.35	291.37-313.34	177.73	165.84-189.62	427.56	409.08-446.04	249.30	239.32-259.28	149.95	139.02-160.88	348.94	332.24-365.64
2007	310.06	298.91-321.21	180.00	167.98-192.01	440.05	421.30-458.81	253.98	243.89-264.07	151.41	140.38-162.44	356.35	339.47-373.23
2008	312.34	301.27-323.41	179.71	167.84-191.58	445.61	426.92-464.30	255.14	245.13-265.15	149.86	139.01-160.72	360.78	343.95-377.61
2009	312.34	301.37-323.31	178.45	166.74-190.16	447.36	428.77-465.95	253.52	243.63-263.41	148.09	137.41-158.77	359.72	343.04-376.40
2010	317.30	306.29-328.32	182.90	171.07-194.74	452.92	434.30-471.53	256.43	246.51-266.34	151.58	140.78-162.37	362.12	345.45-378.78
2011	315.96	305.07-326.84	179.06	167.50-190.63	454.72	436.22-473.22	254.67	244.88-264.46	147.90	137.36-158.45	362.83	346.28-379.38
2012	310.98	300.32-321.64	178.05	166.66-189.44	446.18	428.08-464.28	249.16	239.60-258.72	145.72	135.38-156.06	354.30	338.15-370.46
2013	313.62	302.97-324.28	177.98	166.68-189.27	451.90	433.73-470.06	248.69	239.19-258.19	143.73	133.55-153.92	355.60	339.48-371.73

Figure 2.1 Age-standardized incidence of MS per 100,000 in Saskatchewan, 2001-2013

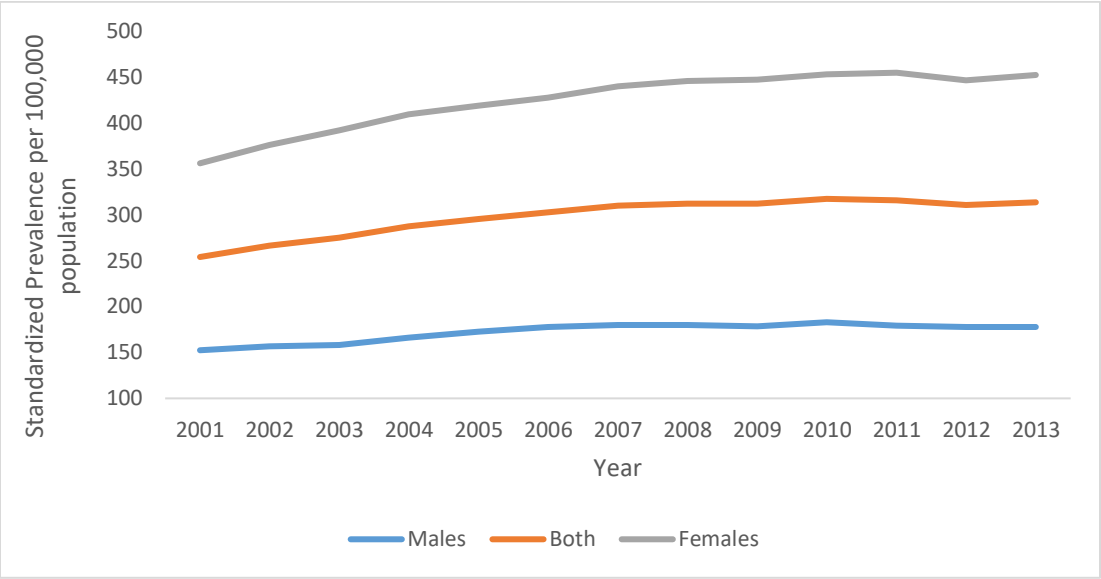


Marrie definition: ≥3 hospital, physician, or drug claims

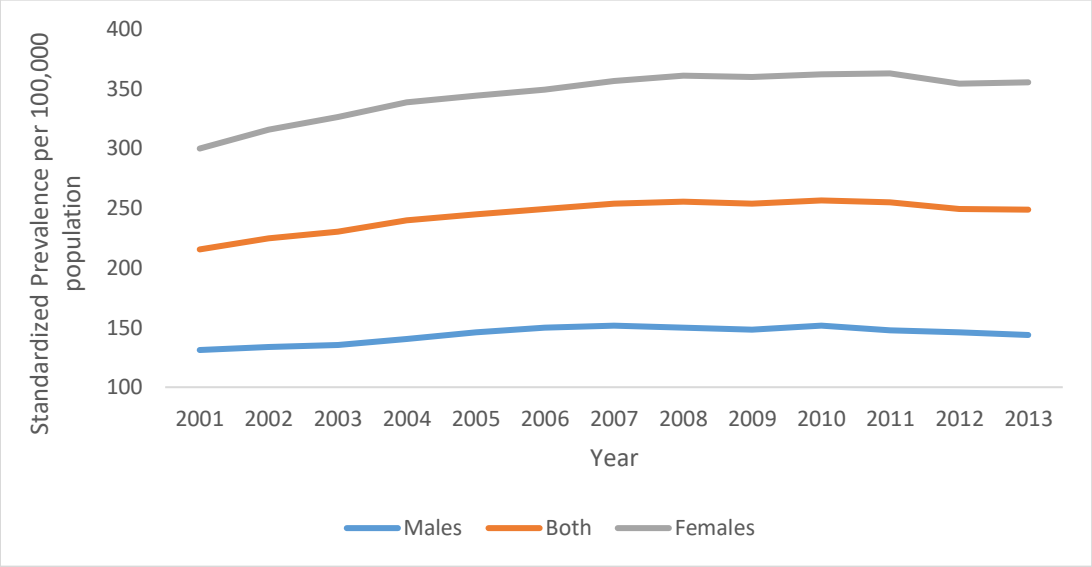


CCDSS definition: ≥1 hospitalization or ≥5 physician claims within 2 years

Figure 2.2 Age Standardized Prevalence for MS in Saskatchewan per 100,000 between 2001-2013

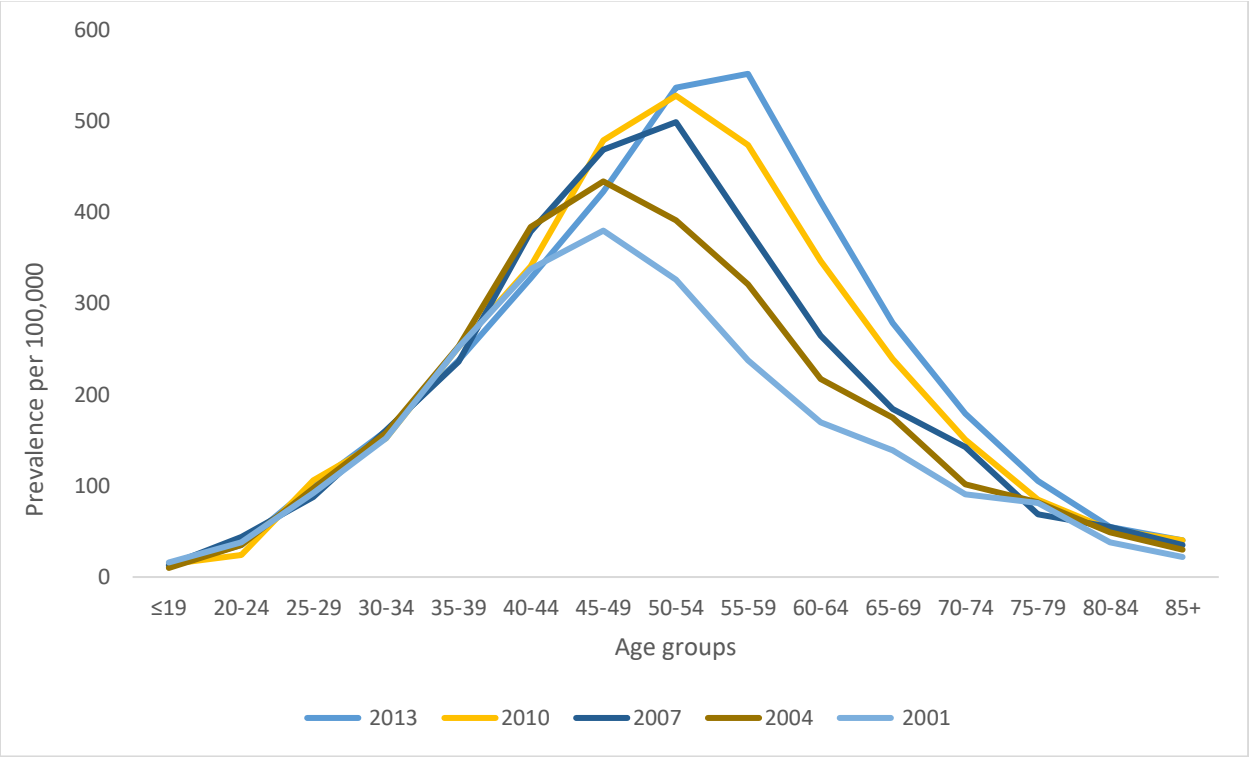


Marrie definition: ≥3 hospital, physician or drug claims
Change in prevalence over time = 4.84

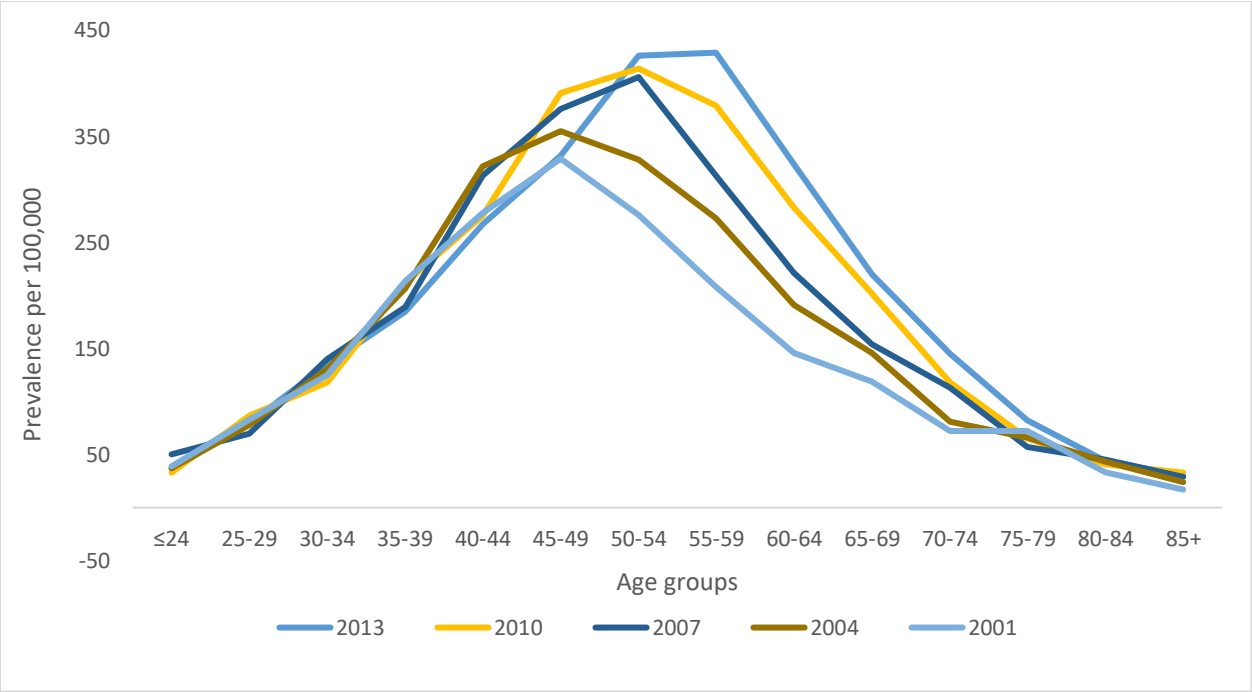


CCDSS definition: ≥1 hospitalization or ≥5 physician claims within 2 years

Figure 2.3 Age specific prevalence of MS in Saskatchewan per 100,000, 2001-2013



Marrie definition: ≥3 hospital, physician, or drug claims



CCDSS definition: ≥1 hospitalization or ≥5 physician claims within 2 years

Supplemental Table 2. 1 Administrative case definitions tested to identify MS cases in Saskatchewan

Case definition	Within a 1-year period	Within a 2-year period	Within a 3-year period
≥2 hospital or physician claims for MS	X	X	X
≥1 hospital or ≥2 physician claims for MS	X	X	X
≥3 hospital or physician claims for MS	X	X	X
≥1 hospital or ≥3 physician claims for MS	X	X	X
≥5 hospital or physician claims for MS	X	X	X
≥1 hospital or ≥5 physician claims for MS	X	X	X
≥7 hospital or physician claims for MS	X	X	X
≥1 hospital or ≥7physician claims for MS	X	X	X
≥3 hospital, physician or prescription claims for MS over entire period			

Supplemental Table 2. 2 Validation results for administrative case definitions used to identify MS cases

Algorithm	Sensitivity (95% CI)		Specificity (95% CI)		PPV (95% CI)		NPV (95% CI)		Kappa (95% CI)	
≥7 hospital or physician claims in 3 years	86.5	80.97-90.91	99.5	97.25-99.99	99.43	96.84-99.99	88.05	83.1-91.98	0.86	0.81-0.91
≥7 hospital or physician claims in 2 years	82.5	76.51-87.5	99.5	97.25-99.99	99.40	96.69-99.98	85.04	79.82-89.36	0.82	0.76-0.88
≥7 hospital or physician claims in 1 year	75.5	68.94-81.29	99.5	97.25-99.99	99.34	96.39-99.98	80.24	74.73-85.01	0.75	0.69-0.81
≥5 hospital or physician claims in 3 years	92.0	87.33-95.36	99.5	97.25-99.99	99.46	97.03-99.99	92.56	88.2-95.69	0.92	0.88-0.95
≥5 hospital or physician claims in 2 years	90.5	85.56-94.18	99.5	97.25-99.99	99.45	96.98-99.99	91.29	86.72-94.67	0.90	0.86-0.94
≥5 hospital or physician claims in 1 year	84.0	78.17-88.79	99.5	97.25-99.99	99.41	96.75-99.99	86.15	81.01-90.33	0.84	0.78-0.89
≥3 hospital or physician claims in 3 years	96.0	92.27-98.26	99.5	97.25-99.99	99.48	97.15-99.99	96.14	92.53-98.32	0.95	0.92-0.98
≥3 hospital or physician claims in 2 years	96.0	92.27-98.26	99.5	97.25-99.99	99.48	97.15-99.99	96.14	92.53-98.32	0.95	0.92-0.98
≥3 hospital or physician claims in 1 year	94.0	89.75-96.86	99.5	97.25-99.99	99.47	97.09-99.99	94.31	90.28-97.03	0.94	0.90-0.97
≥2 hospital or physician claims in 3 years	97.5	94.26-99.18	99.5	97.25-99.99	99.49	97.19-99.99	97.55	94.37-99.2	0.97	0.95-0.99
≥2 hospital or physician claims in 2 years	97.0	93.58-98.89	99.5	97.25-99.99	99.49	97.18-99.99	97.07	93.74-98.92	0.97	0.94-0.99

Algorithm	Sensitivity (95% CI)		Specificity (95% CI)		PPV (95% CI)		NPV (95% CI)		Kappa (95% CI)	
≥2 hospital or physician claims in 1 year	97.0	93.58-98.89	99.5	97.25-99.99	99.49	97.18-99.99	97.07	93.74-98.92	0.96	0.93-0.99
≥1 hospital or ≥7 physician claims in 3 years	87.5	82.1-91.74	99.0	96.43-99.88	98.87	95.98-99.86	88.79	83.9-92.61	0.86	0.81-0.91
≥1 hospital or ≥7 physician claims in 2 years	83.5	77.62-88.36	99.0	96.43-99.88	98.82	95.79-99.86	85.71	80.53-89.96	0.82	0.76-0.87
≥1 hospital or ≥7 physician claims in 1 year	77.0	70.54-82.64	99.0	96.43-99.88	98.72	95.45-99.84	81.15	75.67-85.85	0.76	0.69-0.82
≥1 hospital or ≥5 physician claims in 3 years	92.5	87.93-95.74	99.0	96.43-99.88	98.93	96.19-99.87	92.96	88.65-96.01	0.91	0.87-0.95
≥1 hospital or ≥5 physician claims in 2 years (CCDSS definition)	91.0	86.15-94.58	99.0	96.43-99.88	98.91	96.13-99.87	91.67	87.15-94.99	0.90	0.85-0.94
≥1 hospital or ≥5 physician claims in 1 year	84.5	78.73-89.22	99.0	96.43-99.88	98.83	95.84-99.86	86.46	81.34-90.61	0.83	0.78-0.88
≥1 hospital or ≥3 physician claims in 3 years	96.0	92.27-98.26	99.0	96.43-99.88	98.97	96.33-99.87	96.12	92.49-98.31	0.95	0.91-0.98
≥1 hospital or ≥3 physician claims in 2 years	96.0	92.27-98.26	99.0	96.43-99.88	98.97	96.33-99.87	96.12	92.49-98.31	0.95	0.91-0.98
≥1 hospital or ≥3 physician claims in 1 years	94.5	90.37-97.22	99.0	96.43-99.88	98.95	96.27-99.87	94.74	90.78-97.34	0.93	0.89-0.97
≥1 hospital or ≥2 physician claims in 3 years	97.5	94.26-99.18	99.0	96.43-99.88	98.98	96.38-99.88	97.54	94.35-99.2	0.97	0.94-0.99

Algorithm	Sensitivity (95% CI)		Specificity (95% CI)		PPV (95% CI)		NPV (95% CI)		Kappa (95% CI)	
≥1 hospital or ≥2 physician claims in 2 years	97.0	93.58-98.89	99.0	96.43-99.88	98.98	96.36-99.88	97.06	93.71-98.91	0.96	0.93-0.99
≥1 hospital or ≥2 physician claims in 1 years	97.0	93.58-98.89	99.0	96.43-99.88	98.98	96.36-99.88	97.06	93.71-98.91	0.96	0.93-0.98
≥3 hospital, physician, or drug through whole period (Marrie definition)	97.5	94.26-99.18	99.5	97.25-99.88	99.49	97.19-99.99	97.55	94.37-99.2	0.97	0.95-0.99

PPV: Positive predictive value, NPV: Negative predictive value, CCDSS: Canadian Chronic Disease Surveillance System

Supplemental Table 2. 3 Average annual incidence of MS in Saskatchewan by age and sex per 100,000, 2004 – 2013 (Marrie definition) with an 8-year run-in period

	Both			Males			Females			Female: male	
Age Group (years)	No. cases 2004-2013	AAI	95% CI	No. cases 2004-2013	AAI	95% CI	No. cases 2004-2013	AAI	95% CI	Risk Ratio	95% CI
≤19	36	1.30	0.87-1.72	11	0.78	0.32-1.23	25	1.85	1.12-2.57	2.38	1.17-4.84
20-24	111	14.31	11.65-16.98	33	8.28	5.45-11.10	78	20.70	16.10-25.29	2.50	1.66-3.76
25-29	160	22.28	18.83-25.73	54	14.71	10.79-18.63	106	30.19	24.44-35.94	2.05	1.48-2.85
30-34	180	27.23	23.25-31.21	58	17.30	12.85-21.76	122	37.44	30.80-44.09	2.16	1.58-2.96
35-39	207	32.22	27.83-36.61	70	21.63	16.56-26.70	137	42.97	35.78-50.17	1.99	1.49-2.65
40-44	214	30.37	26.30-34.44	55	15.52	11.42-19.62	159	45.39	38.33-52.45	2.92	2.15-3.97
45-49	231	29.89	26.03-33.74	76	19.47	15.09-23.85	155	40.52	34.14-46.89	2.08	1.58-2.74
50-54	191	25.83	22.17-29.49	60	15.97	11.93-20.01	131	36.02	29.85-42.19	2.26	1.66-3.06
55-59	113	17.97	14.66-21.29	40	12.51	8.63-16.39	73	23.62	18.20-29.04	1.89	1.28-2.78
60-64	69	13.95	10.66-17.24	28	11.26	7.09-15.43	41	16.66	11.56-21.76	1.48	0.91-2.39
65-69	45	11.55	8.18-14.93	17	8.88	4.66-13.11	28	14.12	8.89-19.36	1.59	0.87-2.90
70-74	35	10.48	7.01-13.95	10	6.30	2.39-10.20	25	14.28	8.68-19.87	2.27	1.09-4.72
≥75	27	3.49	2.17-4.80	11	3.55	1.45-5.64	16	3.44	1.76-5.13	0.97	0.45-2.09
Total	1619	15.51	14.76-16.27	523	10.06	9.20-10.92	1096	20.93	19.69-22.17	2.08	1.87-2.31

Marrie definition: ≥3 hospital, physician, or drug claims; AAI: average annual incidence

Supplemental Table 2. 4 Average annual incidence of MS in Saskatchewan by age and sex per 100,000, 2004 – 2013 (CCDSS definition) with an 8-year run-in period

	Both			Males			Females			Female: male	
Age Group (years)	No. cases 2004-2013	AAI	95% CI	No. cases 2004-2013	AAI	95% CI	No. cases 2004-2013	AAI	95% CI	Risk Ratio	95% CI
≤19	35	1.26	0.84-1.68	10	0.70	0.27-1.14	25	1.85	1.12-2.57	2.62	1.26-5.45
20-24	95	12.25	9.79-14.71	28	7.02	4.42-9.62	67	17.78	13.52-22.03	2.53	1.63-3.93
25-29	143	19.91	16.64-23.17	45	12.26	8.68-15.84	98	27.90	22.38-33.42	2.28	1.60-3.24
30-34	143	21.62	18.08-25.17	48	14.32	10.27-18.37	95	29.14	23.28-35.00	2.04	1.44-2.88
35-39	173	26.91	22.90-30.92	59	18.23	13.58-22.88	114	35.72	29.16-42.28	1.96	1.43-2.68
40-44	176	24.96	21.27-28.64	50	14.11	10.20-18.02	126	35.92	29.65-42.19	2.55	1.83-3.53
45-49	189	24.43	20.94-27.91	63	16.13	12.15-20.12	126	32.88	27.14-38.62	2.04	1.51-2.76
50-54	144	19.45	16.27-22.63	46	12.23	8.70-15.77	98	26.90	21.57-32.22	2.20	1.55-3.12
55-59	92	14.62	11.63-17.60	38	11.88	8.10-15.66	54	17.44	12.79-22.10	1.47	0.97-2.22
60-64	65	13.12	9.93-16.31	27	10.85	6.76-14.95	38	15.42	10.51-20.32	1.42	0.87-2.33
65-69	44	11.28	7.95-14.62	14	7.31	3.48-11.14	30	15.12	9.71-20.53	2.07	1.10-3.90
70-74	30	8.98	5.76-12.19	13	8.18	3.73-12.63	17	9.70	5.09-14.31	1.19	0.58-2.44
75-79	20	6.80	3.82-9.79	9	6.78	2.35-11.2	11	6.83	2.79-10.87	1.01	0.42-2.44
≥80	16	3.34	1.70-4.98	6	3.40	0.68-6.13	10	3.30	1.26-5.35	0.97	0.35-2.67
Total	1365	13.08	12.39-13.77	456	8.77	7.96-9.57	909	17.36	16.23-18.49	1.98	1.77-2.21

CCDSS definition: ≥1 hospitalization or ≥5 physician claims within 2 years; AAI: average annual incidence

Supplemental Table 2. 5 Average annual prevalence of MS in Saskatchewan by age and sex per 100,000, 2001 – 2013 (Marrie Definition)

	Both			Males			Female			Female: Male	
Age Group (years)	**No. cases 2001-2013**	**AAP**	**95% CI**	**No. cases 2001-2013**	**AAP**	**95% CI**	**No. cases 2001-2013**	**AAP**	**95% CI**	**Rate Ratio**	**95% CI**
≤19	154	4.22	3.55-4.89	59	3.16	2.35-3.97	108	6.06	4.92-7.21	1.92	1.40-2.64
20-24	470	47.17	42.90-51.43	107	20.88	16.93-24.84	363	74.99	67.28-82.70	3.59	2.89-4.45
25-29	1239	136.00	128.42-143.57	314	67.53	60.06-75.00	925	207.35	193.99-220.71	3.07	2.70-3.49
30-34	2056	241.75	231.30-252.20	533	123.94	113.42-134.47	1523	362.25	344.06-380.45	2.92	2.65-3.23
35-39	3220	371.31	358.48-384.14	929	213.50	199.77-227.22	2291	530.25	508.53-551.96	2.48	2.30-2.68
40-44	4615	486.44	472.41-500.47	1278	268.30	253.59-283.01	3337	706.40	682.43-730.37	2.63	2.47-2.81
45-49	5842	583.46	568.49-598.42	1544	305.42	290.19-320.66	4298	866.97	841.05-892.89	2.84	2.68-3.01
50-54	5976	644.44	628.10-660.78	1728	367.62	350.29-384.95	4248	929.00	901.06-956.94	2.53	2.39-2.67
55-59	5110	658.93	640.86-677.00	1513	385.15	365.74-404.56	3597	939.99	909.27-970.71	2.44	2.30-2.59
60-64	3704	600.12	580.79-619.45	1165	377.72	356.03-399.41	2539	822.28	790.29-854.26	2.18	2.03-2.33
65-69	2579	513.29	493.48-533.10	850	345.56	322.33-368.79	1729	674.16	642.38-705.94	1.95	1.80-2.12
70-74	1713	388.76	370.35-407.17	603	288.86	265.80-311.91	1110	478.70	450.54-506.86	1.66	1.50-1.83
75-79	1072	277.70	261.08-294.33	371	214.14	192.35-235.93	701	329.46	305.07-353.85	1.54	1.36-1.74
≥80	1092	178.09	167.53-188.65	285	126.97	112.23-141.71	807	207.61	193.29-221.94	1.64	1.43-1.87
Total	38842	288.03	285.17-290.89	11279	167.97	164.87-171.06	27576	407.30	402.5-412.095	2.42	2.37-2.48

Marrie definition: ≥3 hospital, physician, or drug claims; AAP: average annual prevalence

Supplemental Table 2. 6 Average annual prevalence of MS in Saskatchewan by age and sex per 100,000, 2001 – 2013 (CCDSS Definition)

	Both			Male			Female			Female: male	
Age Group (years)	**No. cases 2001-2013**	**AAP**	**95% CI**	**No. cases 2001-2013**	**AAP**	**95% CI**	**No. cases 2001-2013**	**AAP**	**95% CI**	**Rate Ratio**	**95% CI**
≤19	117	3.21	2.63-3.79	31	1.66	1.08-2.24	86	4.83	3.81-5.85	2.91	1.93-4.38
20-24	398	39.94	36.02-43.87	87	16.98	13.41-20.55	311	64.25	57.11-71.39	3.78	2.98-4.80
25-29	1024	112.40	105.51-119.28	252	54.20	47.51-60.89	772	173.06	160.85-185.26	3.19	2.77-3.68
30-34	1696	199.42	189.93-208.91	428	99.53	90.10-108.96	1268	301.60	285.00-318.20	3.03	2.72-3.38
35-39	2659	306.50	294.85-318.16	812	186.61	173.77-199.44	1846	427.25	407.76-446.74	2.29	2.11-2.49
40-44	3797	399.69	386.97-412.41	1112	233.45	219.73-247.17	2680	567.32	545.84-588.80	2.43	2.27-2.61
45-49	4773	476.69	463.17-490.22	1311	259.33	245.30-273.37	3462	698.34	675.08-721.60	2.69	2.53-2.87
50-54	4848	522.91	508.19-537.63	1443	306.99	291.15-322.83	3406	744.86	719.85-769.88	2.43	2.28-2.58
55-59	4167	537.33	521.02-553.65	1250	318.20	300.56-335.84	2917	762.29	734.63-789.95	2.40	2.24-2.56
60-64	3057	495.29	477.74-512.85	979	317.41	297.53-337.29	2078	672.98	644.04-701.91	2.12	1.97-2.29
65-69	2142	426.31	408.26-444.37	697	283.36	262.32-304.39	1445	563.42	534.37-592.47	1.99	1.82-2.18
70-74	1379	312.96	296.44-329.48	473	226.58	206.16-247.00	906	390.72	365.28-416.17	1.72	1.54-1.93
75-79	859	222.53	207.64-237.41	299	172.58	153.02-192.15	560	263.19	241.39-284.99	1.53	1.33-1.75

	Both			Male			Female			Female: male	
Age Group (years)	**No. cases 2001-2013**	**AAP**	**95% CI**	**No. cases 2001-2013**	**AAP**	**95% CI**	**No. cases 2001-2013**	**AAP**	**95% CI**	**Rate Ratio**	**95% CI**
≥80	888	144.82	135.30-154.35	236	105.14	91.72-118.55	652	167.74	154.86-180.61	1.60	1.37-1.85
Total	31799	235.28	233.21-238.39	9410	140.13	137.30-142.96	22389	330.69	326.36-335.01	2.36	2.30-2.42

CCDSS definition: ≥1 hospitalization or ≥5 physician claims within 2 years; AAP: average annual prevalence

3 The Association Between Disease-modifying Therapies for Multiple Sclerosis and Healthcare Utilization on a Population Level: A Retrospective Cohort Study

Al-Sakran L, Marrie RA, Blackburn D, Knox K, Evans C. Association between disease-modifying therapies for multiple sclerosis and healthcare utilisation on a population level: a retrospective cohort study. BMJ Open 2019;9:e033599. doi: 10.1136/bmjopen-2019-033599

LAS, CE and RAM designed the study. LAS conducted data analyses. LAS and CE drafted the manuscript. LAS, CE, RAM, DB and KK were involved in the interpretation of data, critically revising the manuscript, and have approved the final version to be published.

3.1 ABSTRACT

Objective: The use of disease-modifying therapies (DMT) in multiple sclerosis (MS) has increased significantly. However, the impact of DMTs on healthcare use is limited and conflicting, and rarely examined at a population level. The purpose of this study was to examine the association between DMTs and healthcare utilization at the population level.

Methods: We used population-based health administrative data from Saskatchewan, Canada from 1997–2016, and identified two cohorts. The general population cohort included all Saskatchewan residents ≥18 years who were drug plan beneficiaries. The MS cohort included individuals ≥18 years, identified using a validated definition (≥3 hospital, physician or drug claims for MS). To test for an association between the total number of DMT dispensations per year and the total number of hospitalizations we used negative binomial regression fitted with generalized estimating equations (GEE); only hospitalizations that occurred after the date of MS

diagnosis (date of first claim for MS or demyelinating disease) were extracted. To test for an association between the number of DMT dispensations and physician claims, negative binomial distributions with GEE were fit as described above. Results were reported as rate ratios (RR), with 95% confidence intervals, and calculated for every 1000 DMT dispensations.

Results: The number of DMT dispensations was associated with a decreased risk for all-cause (RR=0.994; 95% CI:0.992 – 0.996) and MS-specific (RR=0.909; 95% CI:0.880 – 0.938) hospitalizations. The number of DMT dispensations was not associated with the number of all-cause (RR=1.006; 95% CI: 0.990 – 1.022) or MS-specific (RR=0.962; 95% CI:0.910 – 1.016) physician claims.

Conclusion: Increased DMT use in Saskatchewan was associated with a reduction in hospitalizations, but did not impact the number of physician services used. Additional research on cost-benefit and differing treatment strategies would provide further insight into the true impact of DMTs on healthcare utilization at a population level.

3.2 INTRODUCTION

Multiple sclerosis (MS) is considered to be the leading cause of non-traumatic neurologic disability in young adults,[1] and it is estimated that Canada has among the highest prevalence of MS worldwide.[2] Although the prevalence of MS is relatively low compared to other chronic diseases, the disabling and long-term nature of the disease, high health care utilization and treatment costs, and lost productivity places a significant strain on the healthcare system and society.[3 4] In Canada, the total estimated health care cost per capita in 2011 was $16,800 for adults with MS compared to $2,500 for individuals without a neurological condition; total annual costs are expected to rise from an estimated $950 million in 2001, to $2 billion by 2031.[5 6]

Although there is currently no cure for MS, disease-modifying therapies (DMTs) have dramatically changed the treatment of MS over the last two decades. The DMTs are costly, and have been described as a great economic burden for patients and society.[7] However, other studies have suggested DMTs are cost-effective[8] as their use should lead to a reduction in relapses and progression,[9-11] and ultimately a decrease in subsequent healthcare utilization and costs.[3 4 12]

Regardless of the uncertainty surrounding the cost-effectiveness of DMTs, it is known that healthcare utilization is higher for individuals living with MS compared to the general population.[13-18] The use of DMTs continues to increase as new therapies become available, and with the recommendations for treatment of early disease.[8 9 11 19-22] Therefore, understanding the impact that DMTs have on healthcare utilization at a population level will help guide health

policy decisions related to issues such as the reimbursement or coverage of therapies. This study aimed to examine healthcare utilization patterns, and to describe the association between DMTs and healthcare utilization at the population level, using data from Saskatchewan, Canada.

3.3 MATERIALS AND METHODS

Data Source

This retrospective cohort study used population-based data from Saskatchewan, Canada. The Saskatchewan government maintains linkable electronic health administrative databases, which have accessible data on hospitalizations (Discharge Abstract Database), fee-for-service physician services, prescription drug claims, and registration information. In Saskatchewan, almost all 1.1 million residents receive publicly funded provincial health care benefits, with the exception of those covered federally (members of the Canadian Forces, Royal Canadian Mounted Police, and federal inmates). Approximately 85-90% of the Saskatchewan population is eligible for prescription drug coverage; ineligible residents are primarily registered First Nations and recognized Inuit people whose drug costs are funded by another government agency.[23]

The Discharge Abstract Database records diagnoses during hospitalizations using the ninth revision of the International Classification of Disease (ICD) codes (ICD-9) until 2002, and the ICD-10-Canadian modification (CA) onwards. Up to 25 diagnoses may be captured for each hospitalization, with the primary diagnosis considered the one most responsible for the admission. The Physician Database records a single diagnosis using only three-digit ICD-9 codes,

as well as general provider information. The Physician Database is not limited to claims for face-to-face visits, rather it reports all claims submitted for reimbursement including services such as laboratory reviews and phone consultations. Information related to outpatient medication dispensations, including the drug information number (DIN), dose, quantity and date dispensed is captured in the Prescription Database.

Study cohorts

This retrospective study utilized two cohorts. The *general population cohort* included all Saskatchewan residents who were beneficiaries of the provincial drug plan and were ≥18 years old. The *MS cohort* included drug plan beneficiaries ≥18 years old who were identified to have MS between January 1, 1996 and December 31, 2016, based on a previously validated algorithm requiring ≥3 hospital (ICD-9: 340, ICD-10-CA: G35), physician (ICD-9: 340) or drug claims (Appendix C) for MS.[24]

Study outcomes

Healthcare utilization patterns in the general population cohort

Inpatient (requiring a minimum of one-night stay) hospitalization rates were examined between January 1, 1997 and December 31, 2016. All hospitalizations were included, except for those admissions related to childbirth (ICD-9: V27, ICD-10: Z37). To prevent double-counting of hospitalizations, admissions occurring within one day of a previous discharge were collapsed into a single hospitalization. The mean length of inpatient all-cause hospitalization stays was also examined.

Healthcare utilization patterns in the MS cohort

Hospitalizations and physician claims were examined in the MS cohort over the same study period, using the methods outlined above. However, only those hospitalizations and physician claims that occurred after the date of MS diagnosis, assigned as the date of the first claim for MS or a demyelinating disease [Appendix D][25] were extracted. A hospitalization was identified as MS-specific if an MS code (ICD-9: 340 or ICD-10-CA: G35) was recorded as the primary or secondary diagnosis code. Physician claims for the same subject, with the same date and provider, were collapsed into a single claim. We further examined physician claims by identifying the rate of all-cause (i.e. non-MS-specific) and MS-specific claims. A claim was identified as MS-specific if an MS code (ICD-9: 340) was recorded as the diagnostic code. Physician claims were only examined in the MS cohort as the large number of physician claims in the general population made analyses and interpretations difficult.

Association of DMT use on healthcare utilization in the MS cohort

Utilization of DMTs (Appendix C) was measured for each year between 1997 and 2016 and reported as the total number of dispensations for any DMT, and the total number of individuals receiving at least one DMT dispensation. Although the first DMT (interferon-beta-1b) was approved for use in Canada in 1996, it was not available through the Saskatchewan drug plan until December 1997 (Appendix C). In Saskatchewan, prescriptions are primarily dispensed in one-month quantities, including the DMTs that were available during the study period.

We examined the potential association of DMT use on three specific outcomes related to healthcare utilization in the MS cohort. First, we tested for an association between the total number of DMT dispensations per year and the total number of inpatient hospitalizations (all-cause and MS-specific) per year. A hospitalization was identified as MS-specific if an MS code (ICD-9: 340 or ICD-10-CA: G35) was recorded as the primary or secondary diagnosis code. Second, we tested for an association between the total number of DMT dispensations per year, and the mean length of all-cause inpatient hospital stays. Finally, we examined the association between the total number of DMT dispensations per year and the total number of physician claims (all-cause and MS-specific) per year.

Analyses

Hospitalization rates were standardized to the Canadian 2006 census (closest census to mid-point) for age and sex via the direct method,[26] and reported per 100,000 population. Physician claim rates were calculated and standardized in the same manner, but reported as per person, to allow for easier interpretation. Linear regression models were used to evaluate the change in rates over time. The coefficient of determination (i.e. adjusted R^2 statistic) was reported for each model to estimate the degree to which the model fit the observed data. The estimated slope of the regression line with 95% confidence intervals was reported to describe the direction of the change.

The association between DMT use and healthcare utilization was examined on a population-level, rather than individual-level. As such, individual-level covariates were not included in the models. Negative binomial regressions fitted with generalized estimating

equations (GEE) with an exchangeable correlation matrix were used to test if an association existed between the total number of DMT dispensations per year and all-cause and MS-specific hospitalizations at the population level. Subjects were stratified by age group (18-39, 40-59, ≥60 years) and sex. The independent variable was the total number of DMT dispensations per year for each strata; the dependent variable was either the total number of all-cause or MS-specific hospitalizations per year, and was obtained for each strata. To account for changing population size, and to control for age and sex, the population of each stratum was included as an offset in the model. Calendar year (as a continuous variable) was also included as a covariate in the models. When the outcome was MS-specific hospitalizations, we also included the number of annual all-cause hospitalizations in the general population as a covariate to account for potential changes in hospital utilization trends. To test for an association between the number of DMT dispensations and the average length of all-cause inpatient hospitalizations, Poisson models with GEE with an autocorrelation matrix were fit in the same manner as above. Because the length of an inpatient hospitalization could not have a value of zero, we subtracted 1 from the length of each hospitalization, to allow the use of a Poisson model.[26] Finally, to test for an association between the number of DMT dispensations and physician claims, negative binomial distributions with GEE were fit using the same age and sex strata and offset as described for hospitalizations above, with adjustment for calendar year. Results were presented as rate ratios (RR), with 95% confidence intervals, and calculated for every 1000 DMT dispensations.

This study was approved by the University of Saskatchewan's Biomedical Research Ethics Board. Data was accessed at the Saskatchewan Health Quality Council under data sharing agreements with the Saskatchewan Ministry of Health and eHealth Saskatchewan. Statistical

analyses were performed with SAS 9.4 (SAS Institute Inc., Cary, NC). Due to the retrospective nature, and design of the study it was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination of our research.

3.4 RESULTS

The population of Saskatchewan in 2016 was 1,098,352, an increase of approximately 100,000 over the study period.[27] The incidence of MS in Saskatchewan is similar to other provinces in Canada,[25 28-30] and remained stable during the study period; a slight increase in prevalence was observed, with an estimated age- and sex-standardized prevalence of 313.6 per 100,000 (95% CI: 303.0 – 324.3) in 2013.[24] Between January 1, 1997 and December 31, 2016 there were 159,396 DMT dispensations in Saskatchewan, a crude increase from 27 in 1997 to 9,246 in 2016 ($p<0.0001$; adjusted $R^2=0.73$). The crude number of individuals receiving at least one DMT dispensation also increased from 23 in 1997 to 945 in 2016 ($p<0.0001$; adjusted $R^2=0.85$).

Hospitalization rates in both the general population cohort and the MS cohort decreased over the study period. The age- and sex-standardized rate for all-cause hospitalizations in the general population cohort was 14,240 per 100,000 (95% CI: 14,135 – 14,346) in 1997 and 9,935 per 100,000 (95% CI: 9,870 – 10,000) in 2016 ($p<0.0001$; adjusted $R^2=0.96$) (Figure 3.1). Within the MS cohort, the age- and sex-standardized rate of all-cause hospitalizations in 1997 was 32,311 per 100,000 (95% CI: 27,513 – 37,109) and 16,544 per 100,000 (95% CI: 14,945 – 18,144) in 2016 ($p<0.0001$; adjusted $R^2=0.79$) (Figure 3.1). There was a slight increase in the mean length of all-cause hospitalization stays for the general population

during the study period from 7.6 days in 1997 to 8.1 days in 2016 ($p<0.0001$; adjusted $R^2=0.72$). An increase in the mean length of stay was also observed for the MS population from 6.8 days in 1997 to 9.6 days in 2016 ($p=0.0001$; adjusted $R^2=0.55$) (Figure 3.2). The age- and sex-standardized rate of MS-specific physician claims in the MS cohort decreased from 6.8 per person (95% CI: 5.8 – 8.8) in 1997 to 3.5 per person (95% CI: 3.2 – 3.7) in 2016 ($p<0.0001$; adjusted $R^2=0.70$). The rates for non-MS claims remained constant throughout the study period from 10.2 per person (95% CI: 8.8 – 11.3) in 1997 to 10.3 per person (95% CI: 9.4 – 11.2) in 2016 ($p=0.52$; adjusted $R^2=-0.03$) (Figure 3.3).

The number of DMT dispensations was associated with a decreased risk for both all-cause (RR=0.994; 95% CI: 0.992 – 0.996, $p<0.0001$) and MS-specific (RR=0.909; 95% CI: 0.880 – 0.938, $p<0.0001$) hospitalizations in the MS cohort (Table 3.1). An association between the number of DMT dispensations and an increased length of all-cause inpatient stay was observed (RR=1.077; 95% CI: 1.024 – 1.132, $p=0.004$) (Table 3.1). Finally, the number of DMT dispensations was not associated with the number of all-cause or MS-specific physician claims in the MS cohort ($p>0.10$ for both) (Table 3.1).

3.5 DISCUSSION

In this retrospective population-based cohort study, we observed trends in healthcare utilization over a 20-year period in Saskatchewan, Canada, and examined the impact of DMTs for MS on this utilization at a population level. As DMT use increased, decreases in both all-cause and MS-specific hospitalizations were observed, although an increase in the length of all-

cause inpatient hospitalizations was also seen. There was no association between DMT utilization and the number of physician claims.

We noted a reduction in hospitalizations over time in both the general population cohort and the MS cohort, with a more pronounced decrease seen in MS-specific hospitalizations. This is similar to findings reported in two other Canadian provinces, Manitoba and British Columbia.[13] [14] Despite this reduction, healthcare utilization was still higher in the MS cohort compared to the general population cohort, which is consistent with the existing literature demonstrating individuals living with MS are approximately twice as likely to be hospitalized, visit a medical professional, or consult a mental health professional as compared to the general population.[16] [17]

The decrease in hospitalizations associated with increased DMT use was seen even after adjustment for time (i.e. calendar year). Our findings are similar to other studies that have noted a reduction in hospitalizations with the use of DMTs. A recent study by Sanchirico, *et al*. examined DMT use and healthcare utilization among Medicare MS patients in the United States and found that DMT use was associated with a decrease in inpatient hospitalizations and emergency department visits.[31] In Canada, similar results were reported in matched-control studies with lower hospitalization rates[32] and intensive care unit admissions.[33] Our study is unique in that the reductions we observed were at a population, rather than individual, level.

Despite a reduction in hospitalization rates, we observed an increase in the length of inpatient stays. This is in contrast to both the Sanchirico study,[31] and a 2018 Finnish study that described an overall decreased length of hospital stays in their MS cohorts with DMT use.[34]

Different study populations (non-population-based in the Sanchirico study) and healthcare systems and policies may be responsible for the discrepancy. For example, the mean inpatient stay was 4.2 days (SD 5.2) in the Finnish study,[34] but was 8.4 days (SD 0.94) in our study. Further, in Canada, a 6.9% increase in the length of inpatient hospital stays in the general population has been reported over a 15-year period from 1995-96 to 2010-11.[35] We have also previously shown an increasing length of stay in a cohort of MS patients in British Columbia, although DMT use was not specifically evaluated in that study.[13] So although hospitalization rates have decreased over time, it appears that those individuals who are hospitalized are sicker, and require more complex care.[13] It is also possible that some individuals with MS remain in hospital longer as they wait for placement in a long-term care facility, or are receiving inpatient rehabilitation.[36]

Interestingly, we did not find an association between DMT use and the number of physician claims. Aside from the actual prescribing of medications, many of the DMTs require regular monitoring and follow-up; therefore, it is not unrealistic to expect that DMT use would increase the number of physician claims. Although we were unable to differentiate the types of physician services that were delivered, all physician services submitted for reimbursement were captured in our data, which provides a more comprehensive assessment of actual resource utilization. It is therefore possible that any increase related to DMT prescribing and monitoring may be offset by a reduction in physician services in other areas, such as relapse management.

This study has limitations that should be considered. Registered First Nations and recognized Inuit people in Saskatchewan have their drug costs paid for by another government

agency and were excluded from the analyses as we could not accurately determine their DMT claims. The prevalence of MS in the Indigenous population is low[37] and we do not expect their exclusion to have an impact on our results related to the association between DMT and healthcare utilization. Some physicians in Saskatchewan receive alternate payment plans (i.e. salary), rather than fee-for-service. Although it is required that these physicians "shadow bill" for tracking purposes, some may not, and therefore not all physician service encounters may have been captured reliably. However, this number would be small and would not be expected to impact population-level results. It was not possible to examine the utilization of other healthcare professional services, such as nurses and therapists, as these data are not systematically captured by the Saskatchewan government. We also did not have access to laboratory monitoring or MRI data, which would be important outcomes to include in future research examining the newer DMTs that require increased surveillance. We did not evaluate the effects of other factors, such as comorbidity and adherence, which would be more appropriate for an individual-level analysis. However, in our previous work, we have shown that optimal adherence to the DMTs was 80% for the Saskatchewan MS population.[38] As is common with administrative data, we did not have access to important clinical factors that may affect hospitalization rates such as type of MS[13] and disease severity.[39] However, because we were evaluating healthcare utilization at the population level, this individual-level data was not necessary. Finally, we considered a class effect of the DMTs and therefore were not able to differentiate outcomes related to specific DMTs.

This study is novel in that it examined the association of DMTs and healthcare utilization in an MS cohort on a population, rather than individual, level. This allowed us to examine the

impact of DMT use on the healthcare system, and from a policy perspective, rather than just on the individual subjects. This ecological approach is similar to other studies that have looked at population-level drug utilization and outcomes in other diseases such as heart failure.[40] Outcomes related to healthcare utilization, and in particular hospitalizations, are of interest to payers and policy makers; hospitalizations are the largest component of healthcare resource use, and can also be surrogate measures for disease worsening.[13 41] Our study demonstrates that increased DMT use over two decades in Saskatchewan has been associated with a reduction in all-cause and MS-specific hospitalizations, but has not impacted the number of physician services used. Further research into areas such as cost-benefit and different treatment strategies (e.g. escalation vs. initial highly active therapy) would provide additional insight into the true impact of DMTs on healthcare utilization at a population level.

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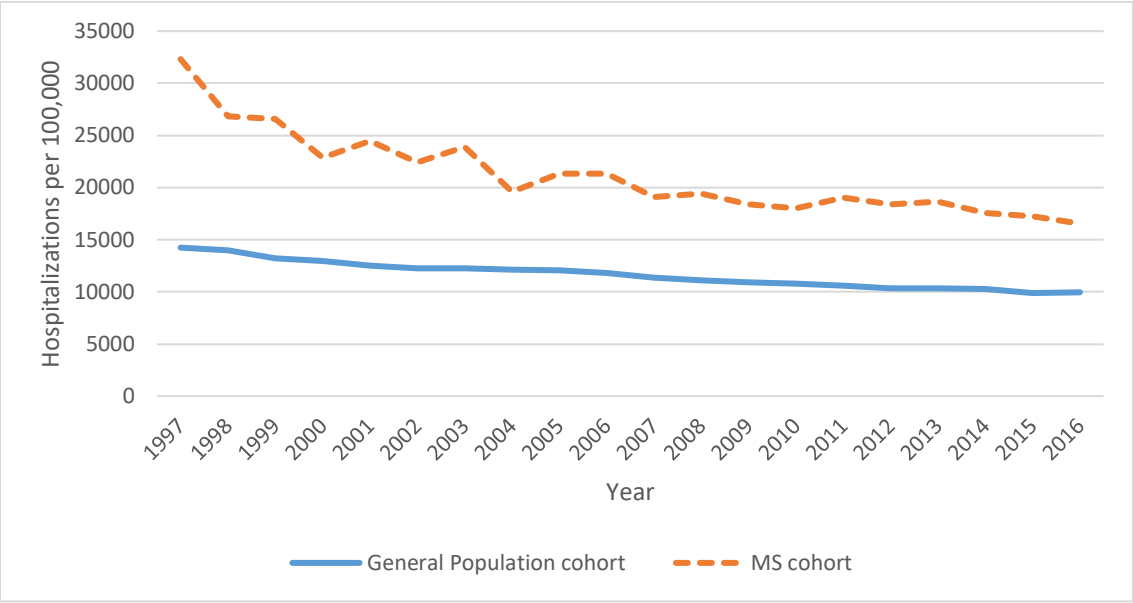
Table 3. 1 Association between disease-modifying therapy dispensations and health care utilization in the multiple sclerosis cohort in Saskatchewan

Variable	Risk Ratio	95% Confidence Intervals	p-value
All-cause hospitalizations[a]			
Per 1000 DMT dispensations	0.994	0.992 to 0.996	<0.0001
Calendar year	0.978	0.974 to 0.983	<0.0001
MS-specific hospitalizations[a]			
Per 1000 DMT dispensations	0.909	0.880 to 0.938	<0.0001
Calendar year	0.940	0.924 to 0.957	<0.0001
All-cause hospitalizations[b]	1.000	1.000 to 1.000	0.090
All-cause mean length of stay (days)[c]			
Per 1000 DMT dispensations	1.077	1.024 to 1.132	0.004
Calendar year	0.999	0.993 to 1.005	0.781
All-cause physician claims[a]			
Per 1000 DMT dispensations	1.006	0.990 to 1.022	0.477
Calendar year	0.982	0.977 to 0.987	<0.0001
MS-specific physician claims[a]			
Per 1000 DMT dispensations	0.962	0.910 to 1.016	0.165
Calendar year	0.954	0.935 to 0.975	<0.0001

a. Negative binomial regression fitted with GEE
b. Adjusted for all-cause hospitalizations in the Saskatchewan general population to account for changes in hospitalization trends
c. Poisson regression fitted with GEE

DMT: disease-modifying therapy

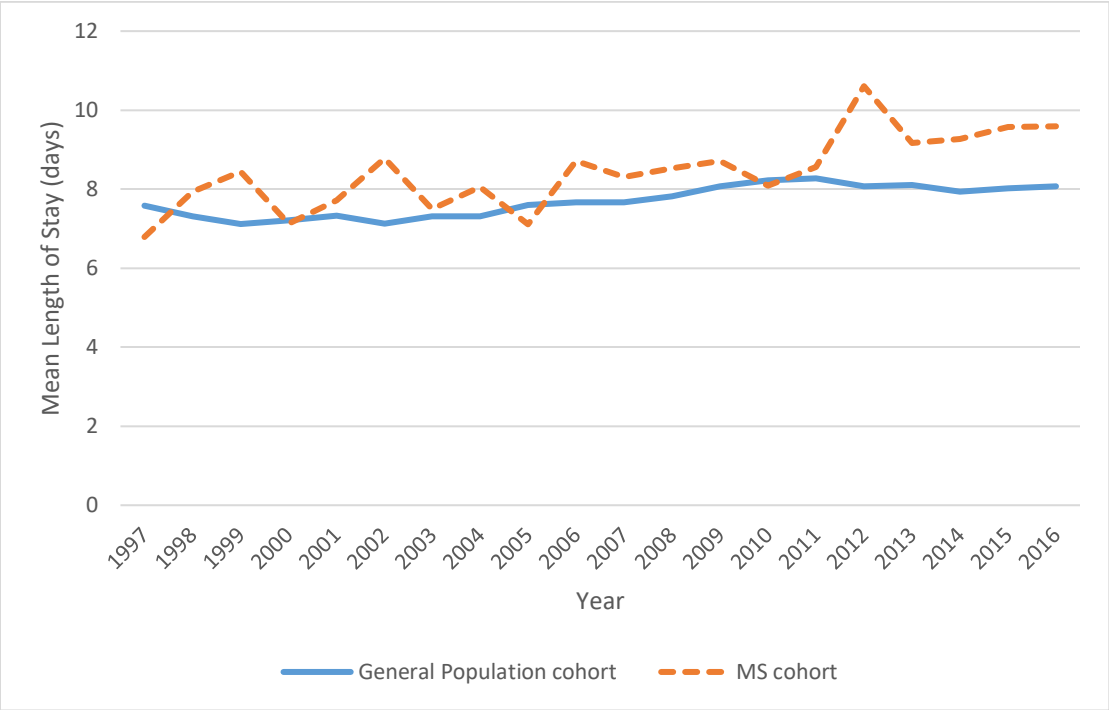
Figure 3. 1 Age and sex standardized inpatient hospitalizations per 100,000 in the Saskatchewan general population cohort and MS cohort (1997– 2016)



MS cohort: Estimate: -605.3 (95% CI:-744.6 to -466.0)

General population cohort: Estimate: -215.5 (95% CI: -235.2 to -195.9)

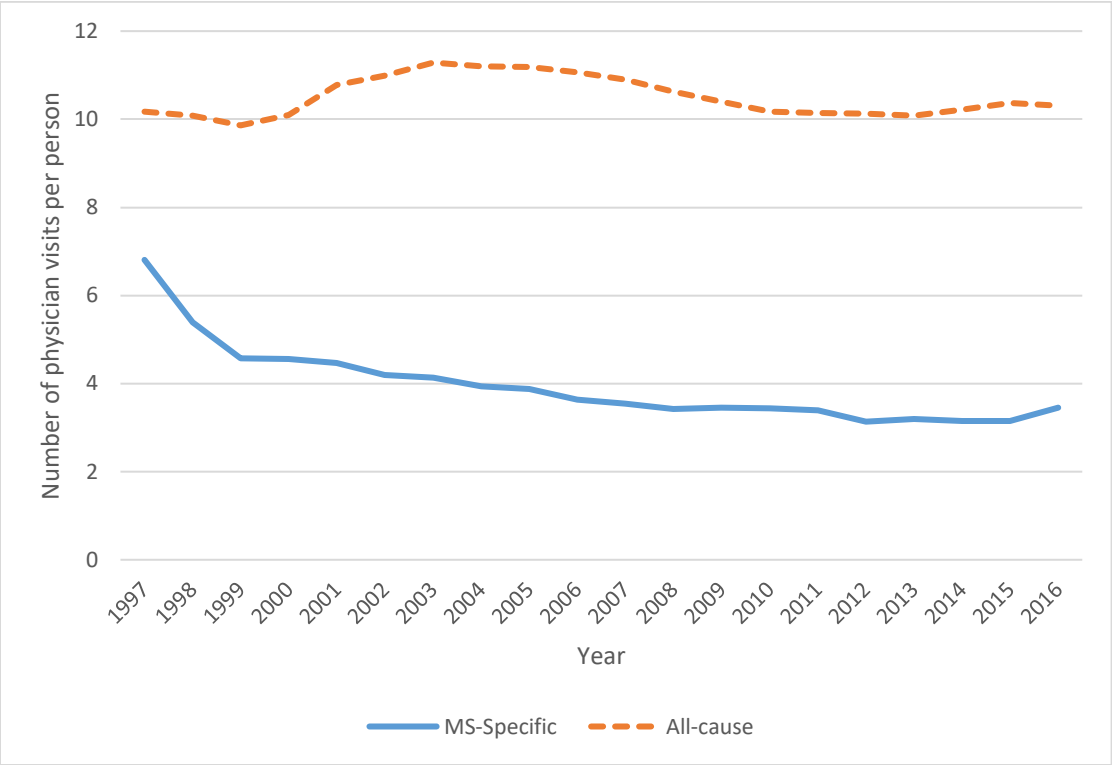
Figure 3. 2 Mean length of all-cause hospital stay in the Saskatchewan general population cohort and MS cohort (1997 – 2016)



MS cohort: Estimate: 0.121 (95% CI: 0.072 to 0.170)

General population cohort: Estimate: 0.056 (95% CI: 0.040 to 0.0722)

Figure 3. 3 Age and sex standardized physician claims (all-cause and MS-specific) per person in the Saskatchewan MS cohort (1997-2016)



All-cause: Estimate: -0.119 (95% CI: -0.047 to 0.232)

MS-specific: Estimate: -0.129 (95% CI: -0.166 to -0.091)

Appendix C. Disease modifying drugs available in Canada (1997 – 2016)

Drug Identification Number (DIN)	Drug	First Date Available on Saskatchewan Formulary (dd-mm-yyyy)
02169649	Interferon beta 1b (Betaseron) 0.3 mg/vial	01/12/1997
02269201	Interferon beta 1a (Avonex) 30mcg/0.5 ml	15/10/1998
02237319	Interferon beta 1a (Rebif) 22 mcg/0.5 ml	01/07/1998
02237320	Interferon beta 1a (Rebif) 44mcg/0.5 ml	01/07/1998
02318253	Interferon beta 1a (Rebif) 66 mcg/1.5 ml	01/07/1998
02318261	Interferon beta 1a (Rebif) 132 mcg/1.5 ml	01/07/1998
02337819	Interferon beta 1b (Extavia) 0.3 mg/ml	01/01/2011
02245619	Glatiramer acetate (Copaxone) 20 mg/1 ml	01/07/2002
02233014	Glatiramer acetate (Copaxone) 20 mg/vial	01/11/1997
02456915	Glatiramer acetate (Copaxone) 40 mg/1 ml	Not available during study period
02404508	Dimethyl fumarate (Tecfidera)120 mg	01/05/2014
02420201	Dimethyl fumarate (Tecfidera) 240 mg	01/05/2014
02416328	Teriflunomide (Aubagio) 14 mg	01/11/2014
02286386	Natalizumab (Tysabri) 300 mg/15ml	01/07/2009
02365480	Fingolimod (Gilenya) 0.5 mg	01/04/2012

02418320	Alemtuzumab (Lemtrada) 12mg/1.2ml	01/07/2016

Appendix D. ICD codes associated with MS and demyelinating disease

ICD-9	ICD-10-CA	Disease or Condition
340	G35	Multiple sclerosis
341	G36.0	Neuromyelitis optica
-	G36.0	Acute disseminated demyelination
341.9	G37.8	Demyelinating disease of unspecified origin
323	G36.9	Acute disseminated encephalomyelitis
323.82	G37	Acute transverse myelitis
377.3	H46	Optic neuritis

ICD: International Classification of Diseases

4 Predictors of Hospitalization in a Canadian MS Population: a Matched Cohort Study

Al-Sakran L, Marrie RA, Blackburn D, Knox K, Evans C. Predictors of Hospitalization in a Canadian MS Population: a Matched Cohort Study. *Abstract presented at endMS Conference, December 10, 2019, Calgary.*

LAS, CE and RAM designed the study. LAS conducted data analyses. LAS and CE drafted the manuscript. LAS, CE, RAM, DB and KK were involved in the interpretation of data, critically revising the manuscript, and have approved the manuscript.

4.1 ABSTRACT

Objective: Hospitalizations are the most costly component of healthcare in Canada, and hospitalization rates are higher in the multiple sclerosis (MS) population compared to the general population. This study aimed to examine predictors of hospitalizations in the MS population in Saskatchewan, Canada.

Methods: This retrospective cohort study used population-based health administrative data from Saskatchewan, Canada from 1996–2016. Subjects with MS were identified using a validated definition (≥3 hospital, physician, or drug claims for MS). Up to five general population controls were identified for each MS case and matched on sex, age, and geographical location. The rate of hospitalizations and reason for admission were determined for each case and control. Negative binomial (hospitalization rate) and binary logistic (reason for admission) regression models fitted with generalized estimating equations were used to test

the following potential predictors: sex, age, median household income, calendar year, prior hospitalizations, and comorbidity status.

Results: We identified 4,878 MS cases (11,744 hospitalizations), and 23,662 matched controls (32,541 hospitalizations). Higher comorbidity burden, older age, and prior hospital admissions were associated with an increased rate of all-cause hospitalizations for both cohorts. Males were more likely to be hospitalized than females for all-cause (adjusted rate ratio: 1.20; 95% CI: 1.07 – 1.34) and MS-specific (adjusted odds ratio: 1.34; 95% CI 1.15 – 1.55) hospitalizations. The rate of MS-specific hospitalizations decreased with age, and there was no association with comorbidity or prior hospitalizations. A diagnosis of MS was associated with decreased odds of hospitalization due to neoplasms, diseases of the circulatory system, and mental health and behavioural disorders.

Conclusion: Increased age, comorbidity, and prior hospital admissions are predictors of all-cause hospitalizations. Conversely, MS-related hospitalizations decreased as subjects aged, and there was no association with comorbidity. Our results highlight that reasons for hospitalizations can differ by age, and clinicians should consider this when managing patients, as they make efforts to reduce hospitalizations in the MS population.

4.2 INTRODUCTION

Multiple sclerosis (MS) is a chronic, progressive neurologic disease that is typically diagnosed between the ages of 20 and 50 years.[1] The long-term and potentially disabling nature of MS is not only a burden to affected individuals and their families, but also has a significant impact on the healthcare system.[2,3] In 2001, the total annual health care costs of MS in Canada was 950 million[4] and those costs are projected to rise to 2 billion by 2030.[5]

Hospitalizations are the most costly component of healthcare resource use,[6] and represent an important aspect of demand on the healthcare system.[7,8] According to the Andersen behavioral model, the use of healthcare services is driven by enabling factors (e.g. access), predisposing factors (e.g. age, sex), and the need for healthcare (e.g. illness).[9] While the rates of hospitalizations in both the MS and general population have decreased over the years in Canada, hospitalization rates in the MS population remain higher than in the general population.[10] Furthermore, individuals with MS are now living longer,[11,12] potentially adding even more strain on the healthcare system.

Previous studies in Canada have examined some predictors of hospitalization in the MS population.[8,10] In Manitoba, increased all-cause hospitalization rates were associated with an increase in age, and a decrease in income, whereas MS-specific hospitalizations were associated with younger age and lower income.[10] In British Columbia an increase in both all-cause and MS-specific hospitalization rates was associated with primary progressive MS, older age, and longer MS duration.[8] Differences in findings may be attributed to different study designs, data sources, and study populations. As treatment and practice patterns are known to differ between Canadian provinces,[13] evaluating additional predictors and in various regions,

can provide additional insight to help guide collaborative efforts to prevent future hospitalizations and inform resource allocation decisions. This study aimed to expand on the existing literature by examining predictors of hospitalizations in the MS population in Saskatchewan, Canada.

4.3 METHODS

Data Source

This population-based study used health administrative data from Saskatchewan, Canada. Saskatchewan has a population of just under 1.2 million,[14] and all residents are eligible to receive provincial health care benefits except those covered federally (members of the Canadian Forces, Royal Canadian Mounted Police, and federal inmates). The government of Saskatchewan maintains electronic health administrative databases that can be linked using an encrypted unique identifier. Databases include the Discharge Abstract Database (hospitalizations), physician claims, prescription drug claims, and registration information.

The Discharge Abstract Database records dates of admission and discharge, and up to 25 diagnoses and procedures occurring during hospitalizations, with the primary diagnosis considered the most responsible reason for admission. Diagnoses were recorded using the ninth revision of the International Classification of Disease (ICD) codes (ICD-9) until 2002, and the ICD-10-Canadian modification (CA) thereafter. The physician claims database reports a single diagnosis using three-digit ICD-9 codes, date of service, and general information about the provider. The prescription database provides information related to prescription medications dispensed in an outpatient setting.

Study Population

This study used a retrospective matched cohort design. The MS cohort included all Saskatchewan beneficiaries identified with MS between January 1, 1997 and December 31, 2016 using a validated case definition of ≥3 hospital (ICD-9: 340, ICD-10-CA: G35), physician (ICD-9: 340) or drug claims for MS (Appendix E).[15] The date of first medical contact for any MS or demyelinating disease claim (Appendix F) during the study period was considered the date of "diagnosis", and designated as the index date.[11] Up to five general population controls were identified for each MS case and matched on sex, age (year of birth) and geographical location, estimated by the first three digits of the postal code. Subjects identified as potential controls were excluded if they had ≥1 claim for MS or a demyelinating disease any time during the study period to ensure that we would not include controls who later were diagnosed with MS. The index date identified for the MS case was also assigned to the matched control(s). Both cases and matched controls were required to have at least one year of continuous coverage (i.e. residency) before the assigned index date to allow for calculation of baseline characteristics, such as comorbidity status. Subjects were followed from their index date until the study end date (the earliest of death, loss of beneficiary status, or December 31, 2016).

Study Outcomes

All inpatient hospitalizations that occurred between January 1, 1997 and December 31, 2016, except those related to childbirth (ICD-9: V27, ICD-10-CA: Z37), were extracted from the Discharge Abstract Database. Only admissions occurring after the index date were included in

the analyses. Hospitalizations occurring within one day of a previous discharge were collapsed into a single hospitalization episode to prevent double counting. The total number of hospitalizations per year was determined for each individual case and control. We also examined the length of hospitalizations and reason for admission in cases and controls. The reasons for hospital admissions were categorized according to ICD chapters (Appendix G), and based on the recorded primary and secondary diagnoses. A hospitalization was considered as MS-related if an MS code (ICD9: 340 or ICD10: G35) was recorded as the primary or secondary diagnosis.

Statistical Analyses

We conducted four distinct analyses. First, we determined the annual hospitalization rates for both the MS and matched control cohorts over the study period (1997-2016). We then examined predictors of all-cause hospitalizations in both cohorts. In a subgroup of MS cases and matched controls who had at least one hospitalization during the study period, we further examined the impact of an MS diagnosis on reasons for hospital admissions. Finally, we examined predictors of MS-related hospitalizations in a subgroup of the MS cohort who were hospitalized during the study period.

Descriptive variables were reported as means (standard deviations [SD]) or frequencies (percent), as appropriate. Hospitalization rates for both the MS and matched control cohorts were age- and sex-standardized to the 2006 Canadian census (closest to study midpoint) and reported per 100 persons.

To identify predictors of hospitalization, we used negative binomial regression fitted with generalized estimating equations[16] with an exchangeable correlation structure. To account for varying study observation periods for each subject, the log of person-years (length of time that a subject was in the study) was used as an offset in the model. A matched cohort design does not require a matched analysis; however, because study participants had different follow-up times, covariate adjustment for matching variables is recommended.[17] Potential predictors that were tested in the models include: sex, age determined at July 1 of each observation year (<40 years, 40-59 years, ≥60), median household income at index date estimated by linking first three digits of postal code to Canadian census data (reported as quintiles), calendar year (1997-2001, 2002-2006, 2007-2011, 2012-2016), hospitalization in the year before the index date (yes/no), and comorbidity status in the year before the index date. Comorbidity status was estimated using hospital and physician claims to determine the modified Charlson Comorbidity Index (hemiplegia and paraplegia claims were excluded, as they may be secondary to MS).[18] First-order interactions were tested, and an interaction between cohort (MS vs. matched controls) and age was present. Therefore, separate models were built for each cohort. Adjusted rate ratios (aRR) with 95% confidence intervals were reported for the MS and matched control cohorts.

To test the association between a diagnosis of MS (yes/no) and hospitalization for each specific ICD chapter (yes/no) (Appendix G) we used binary logistic regression models fitted with GEE with an exchangeable correlation matrix. Models were adjusted for sex, age, median household income, calendar year, comorbidity status, and prior hospitalizations, as described above.

Predictors of MS-specific hospitalizations were also examined using binary logistic regression models fitted with GEE with an exchangeable correlation matrix. We tested the association between an MS-specific hospitalization (yes/no) and the variables described above. All logistic regression results were reported as adjusted odds ratios (aOR) with 95% confidence intervals.

This study was approved by the University of Saskatchewan's Biomedical Research Ethics Board. Data was accessed at the Saskatchewan Health Quality Council under data sharing agreements with the Saskatchewan Ministry of Health and eHealth Saskatchewan. Statistical analyses were performed with SAS 9.4 (SAS Institute Inc., Cary, NC).

4.4 RESULTS

We identified 4,878 MS cases, and 23,662 matched controls, and followed them for an average of 11.7 (SD 6.5) and 11.5 (SD 6.5) years, respectively. The two groups were well matched demographically (Table 4.1). A total of 11,744 inpatient hospitalizations were identified in the MS cohort, and 32, 541 in the matched control cohort. Approximately 66% of the MS cohort had at least one hospitalization during the study period compared to 44% of the matched cohort ($p<0.0001$). The mean length of inpatient stay in the MS cohort was longer than in the matched cohort (11.2 (SD 41.8) days compared to 8.6 (SD 14.0) days; $p<0.0001$) (Table 4.1).

The age- and sex- standardized hospitalization rate in the MS cohort decreased by approximately 49% from 25.9 per 100 persons (95% CI: 20.48-31.35) in 1997 to 15.3 per 100

persons (95% CI: 11.95-18.70) in 2016. The age- and sex-standardized hospitalization rate decreased by approximately 32% in the matched control cohort from 13.6 per 100 persons (95% CI: 11.57-15.57) in 1997 to 9.20 per 100 persons (95% CI: 8.07-10.33) in 2016 (Figure 4.1). The decrease in hospitalization rate was greater in subjects under the age of 40 years in both cohorts. The observed gap in hospitalization rates between the MS and the matched general population cohorts decreased with increasing age (Table 4.2).

Higher comorbidity burden, older age, and prior hospital admissions were associated with an increased rate of all-cause hospitalizations in the MS and matched control cohorts (Table 3). Males were more likely to be hospitalized compared to females in the MS cohort (aRR: 1.20; 95% CI: 1.07 – 1.34); there was no association between sex and all-cause hospitalizations in the matched cohort (Table 4.3).

The subgroup who had at least one hospitalization during the study period included 3,195 MS cases and 10,320 matched controls. A significant association between an MS diagnosis (compared to no MS) and the reason for hospitalization was observed for several of the ICD chapters. MS was associated with increased odds of a hospitalization for diseases of the sense organs, infectious and parasitic diseases, diseases of the skin and subcutaneous tissue, and diseases of the genitourinary and nervous systems. A diagnosis of MS was associated with decreased odds of hospitalization due to neoplasms, diseases of the circulatory system, endocrine, nutritional and metabolic diseases and mental health and behavioural disorders (Table 4.4).

In those MS cases who had a least one hospitalization during the study period (n=3,195) the odds of having an MS-specific hospitalization (compared to a non-MS specific hospitalization) were higher in males than females (aOR: 1.34; 95% CI 1.15 – 1.55). In contrast to observations related to all-cause hospitalizations, the risk for an MS-related hospitalization decreased with increased age, and there was no association with comorbidity burden or prior hospitalizations (Table 4.3).

4.5 DISCUSSION

This population-based study examined hospitalizations over two decades in Saskatchewan, Canada. Hospitalization rates decreased in both the MS and matched general population cohorts, although subjects with MS still had a higher rate of hospitalizations and longer inpatient stays than the general population. Higher comorbidity burden, older age, and previous hospitalizations increased the rate of all-cause hospitalizations in both cohorts, while the risk for an MS-related hospitalization was increased in males and subjects who were younger. Reasons for admission differed between the MS and matched cohorts.

Although we observed a more profound decrease in hospitalization rates in the MS cohort, they remained higher than those in the general population. This is similar to findings from a population-based study from Manitoba that reported hospitalizations declined by 75% in the MS population compared to 41% in the general population over the period 1984 to 2011, but were higher in the MS cohort.[10] The decline in MS-specific hospitalization rates may be due to shifting some treatment of relapses to the outpatient setting,[19] and changes in ascertainment of MS that could have led to detection of milder cases of MS.[20,21] Furthermore,

the introduction of more effective disease-modifying therapies has resulted in milder and less frequent relapses,[22-24] and potentially better disease management.

Comorbidity burden was found to increase the risk of all-cause hospitalizations in both cohorts. This has been reported previously in MS and other chronic diseases such as heart failure and chronic obstructive lung disease.[25-27] Interestingly, comorbidity was not associated with MS-specific hospitalizations, consistent with findings from another Canadian study.[25] This seems counterintuitive as MS-related hospitalizations are often due to relapses at least early in the disease course, and high comorbidity burden has been shown to increase the risk of relapses.[28] However, it has been suggested that individuals with MS and a high comorbidity burden have more frequent contacts with the healthcare system and therefore may receive better MS care, resulting in fewer relapses or disease-related complications requiring hospitalization.[25]

Our findings demonstrated that hospitalizations related to MS decline as subjects age, similar to what has been reported by Marrie *et al*.[25] Assuming that many of the MS-related hospitalizations are due to relapses, these findings are not surprising, given that the natural history studies of MS have shown that disease activity decreases with age.[29] We also noted that as subjects aged, the gap in hospitalization rates (i.e. rate ratios) between the MS and general population controls narrowed, especially in the more recent years. This is likely due to a combination of decreased disease activity, change in MS disease management over the last several years, and increasing illness in the general population with age. Similar to existing literature,[8] we found that males were more likely to be hospitalized for MS compared to

females. This finding was not unexpected, given that males diagnosed with MS typically have a worse prognosis and higher disability than females.[30,31]

We specifically examined the association between a diagnosis of MS and the most responsible reason(s) for admission. We found individuals with MS were more likely to be hospitalized for infections than subjects without MS. These findings are comparable to results from a population-based study in British Columbia that examined infection-related healthcare utilization in the MS and matched-general populations.[32] Individuals with MS had 2-3 times more hospitalizations for pneumonia, urinary tract infections, and skin infections, and more than twice as many hospitalizations for gastroenteritis and sepsis.[32] We also observed an increased odds for admissions due to diseases of the respiratory system. This appeared to be due to higher rates of pneumonia, which is similar to previous findings.[10,32,33]

An increase in the rate of hospitalizations related to diseases of the sense organs was observed. This finding is not unexpected as this ICD chapter contains the diagnoses optic neuritis and benign paroxysmal vertigo, both of which are common in the MS population.[34,35]

Hospital admissions due to neoplasms were lower in our MS cohort compared to the matched cohort. The relationship between cancer and multiple sclerosis is complicated and the literature is conflicting. Studies have reported a higher risk of cancer associated with immunosuppressant drug use in the MS population,[36,37] yet the overall risk of cancer in MS is lower than the general population.[38] With the exception of an increased incidence of brain and genitourinary neoplasms, which could be the result of surveillance bias from increased MRI use and urology consults, recurrent urinary tract infections and chronic catheterizations, which are

all common in the MS population,[39,40] the general incidence of cancer has been reported to be lower in subjects with MS than those in the general population.[41,38] This may be due to competing risk, rather than any kind of protective effect, as cancer incidence increases with age,[41-43] and individuals with MS die earlier than those in the general population.[44] Another possible explanation for reduced cancer incidence in MS may be diagnostic neglect, as reported in a study from British Columbia that found evidence that certain cancers are being diagnosed at later stages in the MS population compared to the general population.[38]

Interestingly, despite a high prevalence of vascular comorbidity such as ischemic heart disease, hypertension, hyperlipidemia and diabetes in the MS population,[45,46] we observed a lower rate of hospitalizations due to diseases of the circulatory system and endocrine, nutritional and metabolic diseases. Although potential misclassification or categorization of complications rather than the underlying disease could be a possible explanation, these findings may support a recent Canadian study that identified underdiagnosis and undertreatment of cardiac disease in the MS population.[47] That population-based study compared management of acute myocardial infarction in the MS population and a matched general population cohort, and found subjects with MS were less likely to undergo diagnostic and therapeutic management for acute myocardial infarction such as cardiac catheterization, revascularization, or fill a guideline-recommended medication.[47]

Similarly, subjects with MS in our study were less likely to be hospitalized for mental and behavioural disorders, despite high rates of depression and anxiety in the MS population[48] that exceed the general population rates by 2-3 fold.[49] The high rates of depression in MS are attributed to the emotional stress related to the disabling and progressive nature of the

disease, in addition to the direct results of inflammation and neurodegeneration.[50,51] Mental health disorders, such as anxiety and depression, may be underdiagnosed and undertreated.[52] Identifying depression may be complicated because of the difficulty in differentiating between symptoms of MS, a true depressive episode,[52,53] or a potential adverse effect related to disease-modifying therapy.[41,54]

Several limitations in our study should be considered. As with any observational study, we were unable to identify, or adjust for, all potential confounders. We did not have access to clinical data such as MS phenotype, relapses, disability levels, or lifestyle factors that might affect hospitalization risk. However, we utilized 20 years of population-based data using matched controls from the general population, and we were able to consider relevant factors such as household income, comorbidity, and prior healthcare utilization. We did not consider the impact of disease-modifying treatments (DMT) on hospitalizations in the MS cohort. The literature is conflicting with respect to the impact of DMTs on hospitalizations,[22-24,55] and accurately determining DMT exposure and related-outcomes would require a different approach from the current study. Finally, we were not able to determine the specific reasons for the MS-related hospitalizations. We, like others,[25,56-60] assumed the majority were relapse-related, although this may not always have been the case.

Hospitalizations in the Saskatchewan MS population have decreased over the last two decades. As expected, age, comorbidity, and prior hospital admissions were predictors of all-cause hospitalizations. Conversely, MS-related hospitalizations decreased as subjects aged, and there was no association with comorbidity. Rates of hospitalizations related to circulatory diseases, and mood and behavioural disorders were significantly lower in the MS cohort

compared to the general population. These results may support the suggestion that certain comorbidities in the MS population are potentially underdiagnosed and undertreated, although further research is needed to confirm this. They also highlight that reasons for hospitalizations can differ by age, and that clinicians should consider this when managing patients to try to reduce hospitalizations in the MS population.

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Table 4.1 Characteristics of the Saskatchewan MS and matched general population control cohorts

Characteristics	MS Cohort (n=4,878)	Matched Cohort (n=23,662)	p-value
Female, n (%)	3,349 (68.7)	16,128 (68.2)	0.50
Age at index date (years), mean (SD)	44.81 (14.4)	44.73 (14.6)	0.75
Residence at index date, n (%)			0.96
Urban (population ≥1000)[a]	3,361 (68.9)	16,291 (68.9)	
Rural (population <1000)[a]	1,502 (30.8)	7,294 (30.8)	
Missing	15 (0.3)	77 (0.3)	
Modified Charlson score[b] at index date, n (%)			<0.0001
0	3,963 (81.2)	20,190 (85.3)	
1	538 (11.0)	2,025 (8.6)	
≥2	377 (7.7)	1,447 (6.1)	
Modified Charlson score[b] at end date, n (%)			<0.0001
0	3,494 (71.6)	19,305 (81.6)	
1	526 (10.8)	1,818 (7.7)	
≥2	858 (17.6)	2,539 (10.7)	
Median household income at index date, n (%)			0.88
Quintile 1 (lowest)	933 (19.1)	4,455 (18.8)	
Quintile 2	928 (19.0)	4,576 (19.3)	
Quintile 3	889 (18.2)	4,300 (18.2)	
Quintile 4	992 (20.3)	4,676 (19.8)	
Quintile 5 (highest)	912 (18.7)	4,556 (19.3)	
Missing	225 (4.6)	1,099 (4.6)	
≥1 hospitalization in year prior to index date, n (%)	447 (9.2)	1,549 (6.6)	<0.0001

Follow up (years), mean (SD)	11.7 (6.5)	11.5 (6.5)	0.88
Subjects with at least one hospitalization (all-cause) during the study period			
Total number of hospitalizations	**MS Cohort**	**Matched Cohort**	
Total number of hospitalizations	11,744	32,541	
n (%)	3,195 (65.5)	10,320 (43.6)	<0.0001
Length of stay (days), mean (SD)	11.2 (41.8)	8.6 (14.0)	<0.0001
Female, n (%)	2,211 (68.2)	7,113 (68.9)	0.769
Age at first admission during study period (years), mean (SD)	50.6 (15.2)	55.3 (16.0)	<0.0001
≥1 hospitalization in year prior to index date, n (%)	356 (11.1)	978 (9.5)	0.006
Subjects with at least one MS-related hospitalization during the study period			
Total number of hospitalizations	3,471		
n (%)	1,603 (32.9)		
Length of stay (days), mean (SD)	11.2 (44.8)		
Female, n (%)	1,041 (66.6)		
Age at first admission during the study period (years), mean (SD)	50.1(14.5)		
≥1 hospitalization in year prior to index date, n (%)	167 (10.4)		

a. Based on Statistics Canada definition (https://www150.statcan.gc.ca/n1/pub/11-630-x/11-630-x2015004-eng.htm#def1)

b. Modified Charlson Comorbidity Index excludes hemiplegia and paraplegia claims, as they may be secondary to MS

Table 4.2 Age-specific crude hospitalization rates of the Saskatchewan MS and matched general population control cohorts in 1997, 2006, and 2016

	MS Cohort			Matched Cohort			MS: Matched Controls
Age (years)	**Total Number of Hospitalizations**	**n**	**Rate (95% CI)**	**Total Number of Hospitalizations**	**n**	**Rate (95% CI)**	**Rate Ratio (95% CI)**
1997							
<40	106	471	0.23 (0.19-0.26)	249	2263	0.11 (0.10-0.12)	2.04 (1.09-2.97)
40-59	200	828	0.24 (0.21-0.27)	343	3806	0.09 (0.08-0.10)	2.68 (1.29-3.63)
≥60	151	408	0.37 (0.32-0.42)	519	1951	0.27 (0.25-0.39)	1.39 (0.96-2.62)
2006							
<40	87	653	0.13 (0.11-0.16)	204	3240	0.06 (0.04-0.07)	2.12 (1.08-2.94)
40-59	311	1758	0.18 (0.16-0.19)	575	8258	0.07 (0.06-0.08)	2.54 (1.31-3.69)
≥60	211	741	0.28 (0.25-0.32)	762	3592	0.20 (0.19-0.21)	1.34 (0.97-2.65)
2016							
<40	67	613	0.11 (0.08-0.13)	145	3060	0.047 (0.04-0.05)	2.30 (1.08-2.94)
40-59	254	1806	0.14 (0.12-0.16)	618	8795	0.07 (0.06-0.08)	2.00 (1.17-3.21)
≥60	298	1288	0.23 (0.21-0.25)	1205	6124	0.20 (0.19-0.21)	1.17 (0.95-2.58)

Table 4.3 Predictors of hospitalization in the Saskatchewan MS and matched general population control cohorts

	Matched Control Cohort (all hospitalizations) n=23,662	**MS Cohort (all hospitalizations) n=**4,878	**MS Cohort (MS-specific hospitalizations) n=**3,195
Variable	**Rate Ratio (95% CI)**	**Rate Ratio (95% CI)**	**Odds Ratio (95% CI)**
Sex			
Female	Reference	Reference	Reference
Male	1.00 (0.95-1.07)	**1.20 (1.07-1.34)**	**1.34 (1.15-1.55)**
Age[a] (years)			
<40	Reference	Reference	Reference
40-59	1.00 (0.94-1.06)	1.02 (0.92-1.12)	**0.59 (0.49-0.71)**
≥60	**2.13 (1.98-2.29)**	**1.67 (1.48-1.88)**	**0.36 (0.30-0.44)**
Comorbidity (Modified Charlson Score)[b]			
0	Reference	Reference	Reference
1	**1.75 (1.58-1.93)**	**1.21 (1.03-1.43)**	0.98 (0.78-1.24)
≥2	**2.73 (2.48-3.00)**	**2.21 (1.84-2.65)**	1.04 (0.80-1.36)
Median household income at index date			
Quintile 1 (lowest)	Reference	Reference	Reference
Quintile 2	**0.89 (0.81-0.97)**	0.87 (0.73-1.03)	0.87 (0.69-1.10)
Quintile 3	**0.81 (0.74-0.89)**	0.90 (0.76-1.07)	0.89 (0.71-1.12)
Quintile 4	**0.77 (0.70-0.85)**	0.95 (0.80-1.13)	0.80 (0.64-1.00)
Quintile 5 (highest)	**0.71 (0.65-0.78)**	0.93 (0.78-1.12)	0.99 (0.79-1.24)
Missing	0.98 (0.85-1.12)	0.97 (0.76-1.24)	1.07 (0.74-1.53)

	Matched Control Cohort (all hospitalizations) n=23,662	**MS Cohort (all hospitalizations) n=**4,878	**MS Cohort (MS-specific hospitalizations) n=**3,195
Variable	**Rate Ratio (95% CI)**	**Rate Ratio (95% CI)**	**Odds Ratio (95% CI)**
Hospitalization in Year Prior to Index Date			
No	Reference	Reference	Reference
Yes	**3.65 (3.33-4.01)**	**4.11 (3.46-4.87)**	0.92 (0.72-1.17)
Calendar Year			
2010-2016	Reference	Reference	Reference
2007-2011	0.95 (0.91-1.00)	**0.91 (0.85-0.96)**	1.08 (0.94-1.24**)**
2002-2006	**1.10 (1.04-1.16)**	1.01 (0.94-1.09)	**1.44 (1.24-1.67)**
1997-2001	**1.54 (1.46-1.64)**	**1.26 (1.15-1.37)**	**2.08 (1.77-2.44)**

a: calculated on July 1 of each observation year
b: Modified Charlson Comorbidity Index excludes hemiplegia and paraplegia claims, as they may be secondary to MS

Table 4.4 Association between multiple sclerosis and reason for hospital admissions in the Saskatchewan MS cohort

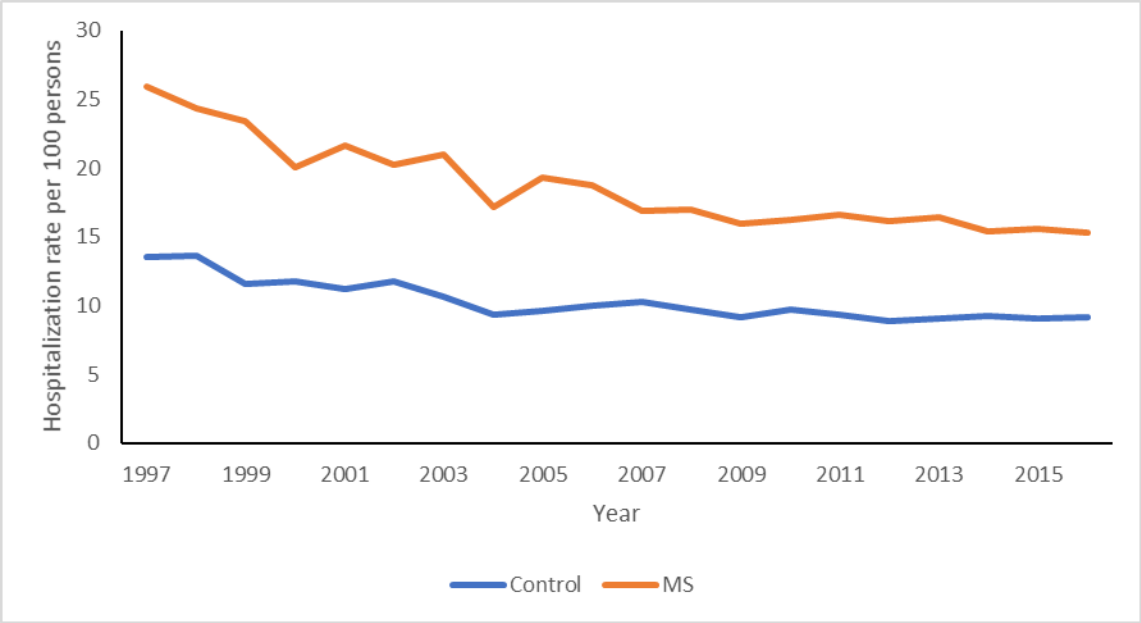
Number of hospitalizations	Odds Ratio[a] (95% CI)	Most frequently reported diagnoses in MS population (listed most common to least common)
Diseases of blood and blood-forming organs		
MS (no) n=947 MS (yes) n=255	Reference **0.77 (0.61 – 0.97)**	Anemia unspecified, anemia in neoplastic disease, neutropenia, iron deficiency anemia
Diseases of the circulatory system		
MS (no) n=8059 MS (yes) n=1560	Reference **0.50 (0.46 – 0.56)**	Benign hypertension, congestive heart failure, atherosclerotic heart disease, unstable angina, acute myocardial infarction, atrial fibrillation
Diseases of the digestive system		
MS (no) n=2449 MS (yes) n=726	Reference **0.81 (0.70-0.92)**	Calculus of gallbladder with other cholecystitis, non-infective gastroenteritis and colitis, intestinal obstruction
Endocrine, nutritional and metabolic diseases		
MS (no) n=4489 MS (yes) n=1085	Reference **0.69 (0.61-0.78)**	Type 2 diabetes with no complications, dehydration, Type 2 diabetes with circulatory complications
Diseases of the genitourinary system		
MS (no) n=4681 MS (yes) n=2239	Reference **1.18 (1.07-1.29)**	Urinary tract infection, excessive menstruation, acute renal failure, calculus of ureter, tubular interstitial nephritis, calculus of kidney
Certain Infectious and parasitic diseases		
MS (no) n=1563 MS (yes) n=878	Reference **1.58 (1.38-1.81)**	Gastroenteritis and colitis of unspecified origin, E. Coli causing disease, sepsis, enterocolitis to Clostridium difficile
Mental and behavioral disorders		
MS (no) n=3513 MS (yes) n=802	Reference **0.66 (0.56-0.78)**	Depressive episode, mental and behavior disorders due to use of alcohol (dependence syndrome), adjustment disorders (stress), anxiety disorder

Number of hospitalizations	Odds Ratio[a] (95% CI)	Most frequently reported diagnoses in MS population (listed most common to least common)
Diseases of the musculoskeletal system and connective tissue		
MS (no) n=3508 MS (yes) n=1031	Reference **0.73 (0.65-0.82)**	Gonarthrosis, coxarthrosis (osteoarthritis of hip), lumbar and other intervertebral disease disorders,
Diseases of the nervous system		
MS (no) n=1384 MS (yes) n=4637	Reference **14.61 (13.10-16.31)**	Multiple sclerosis, nerve root and plexus compressions in intervertebral disc disorders, transient cerebral ischemic attack
Diseases of the respiratory system		
MS (no) n=4783 MS (yes) n=1693	Reference **1.58 (1.32-1.89)**	Pneumonia, COPD with acute exacerbation, COPD with acute lower respiratory infection, bronchopneumonia, COPD unspecified
Diseases of the sense organs		
MS (no) n=454 MS (yes) n=278	Reference **2.00 (1.61-2.49)**	Retinal detachment, Meniere's disease, optic neuritis, labyrinthitis, benign paroxysmal vertigo
Diseases of the skin and subcutaneous tissue		
MS (no) n=816 MS (yes) n=465	Reference **1.56 (1.29-1.89)**	Cellulitis of lower limb, cellulitis and abscess of leg, decubitus ulcer and pressure area unspecified, cellulitis of upper limb
Neoplasms		
MS (no) n=4693 MS (yes) n=860	Reference **0.49 (0.43-0.55)**	Leiomyoma of uterus, anemia in neoplastic disease, malignant neoplasm of bronchus or lung, malignant neoplasm of prostate

Logistic regression models adjusted for age (determined at July 1 of each observation year), sex, median household income at index date, comorbidity at index date, calendar year, and hospitalization prior to index date

ICD: International Classification of Disease, COPD: chronic obstructive pulmonary disease

Figure 4.1 Age and sex-standardized hospitalization rate (per 100 persons) between 1997 and 2016 in multiple sclerosis (MS) cohort and general population matched control cohort


Hospitalization rate per 100 persons
30
25
20
15
10
5
0
1997
1999
2001
2003
2005
2007
2009
2011
2013
2015
Year
Control
MS

Appendix E. Disease modifying drugs available in Canada during the study period

DIN	Drug (brand name)
02169649	interferon beta 1b (Betaseron) 0.3 mg/vial
02269201	interferon beta 1a (Avonex) 30mcg/0.5 ml
02237319	interferon beta 1a (Rebif) 22 mcg/0.5 ml
02237320	interferon beta 1a (Rebif) 44mcg/0.5 ml
02318253	interferon beta 1a (Rebif) 66 mcg/1.5 ml
02318261	interferon beta 1a (Rebif) 132 mcg/1.5 ml
02337819	interferon beta 1b (Extavia) 0.3 mg/ml
02245619	glatiramer acetate (Copaxone) 20 mg/1 ml
02404508	dimethyl fumarate (Tecfidera)120 mg
02420201	dimethyl fumarate (Tecfidera) 240 mg
02416328	teriflunomide (Aubagio) 14 mg
02286386	natalizumab (Tysabri) 300 mg/15ml
02365480	fingolimod (Gilenya) 0.5 mg
02418320	alemtuzumab (Lemtrada) 12mg/1.2ml

DIN: drug identification number

Appendix F. ICD codes associated with multiple sclerosis and demyelinating diseases

ICD CODE (ICD-9/ICD-10-CA)	Disease
(340/G35)	Multiple sclerosis
(341.0/G36.0)	Neuromyelitis optica
(G36)	Acute disseminated demyelination
(341.9/G37.8)	Demyelinating disease of unspecified origin
(323/G36.9)	Acute disseminated encephalomyelitis
(323.82/G37)	Acute transverse myelitis
(377.3/H46)	Optic neuritis

ICD: International Classification of Diseases

Appendix G. International Classification of Diseases chapters

Diagnostic Codes	Title/Disease
ICD-9: 001 – 139 ICD-10: A00 – B99	Certain infectious and parasitic diseases
ICD-9: 140 – 239 ICD-10: C00 – D492	Neoplasms
ICD-9: 280– 289 ICD-10: D50 – D89	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism
ICD-9: 240 – 279 ICD-10: E00 – E89	Endocrine, nutritional and metabolic diseases
ICD-9: 290 – 319 ICD-10: F01 – F99	Mental and behavioral disorders
ICD-9: 320 – 359 ICD-10: G00 – G99	Diseases of the nervous system
ICD-9: 360 – 389 ICD-10: H00-H95	Diseases of the sense organs
ICD-9: 390 – 459 ICD-10: I00 – I99	Diseases of the circulatory system
ICD-9: 460 – 519 ICD-10: J00 – J99	Diseases of the respiratory system
ICD-9: 520 – 579 ICD-10: K00 – K95	Diseases of the digestive system
ICD-9: 680 – 709 ICD-10: L00 – L99	Diseases of the skin and subcutaneous tissues
ICD-9: 710 – 739 ICD-10: M00 – M99	Diseases of the musculoskeletal system and connective tissue

ICD-9: 580 – 629 ICD-10: N00 – N99	Diseases of the genitourinary system

5 Impact of comorbidity on hospitalizations in individuals newly diagnosed with multiple sclerosis: a longitudinal population-based study

LAS, CE and RAM designed the study. LAS conducted data analyses. LAS and CE drafted the manuscript. LAS, CE, RAM, DB and KK were involved in the interpretation of data and critically revising the manuscript.

5.1 ABSTRACT

Background: It has been suggested that comorbidity in subjects with multiple sclerosis (MS) increases the risk of hospitalizations, although few studies have examined this, and rarely in an incident population.

Methods: Incident MS cases were identified retrospectively from administrative data using a validated definition (≥3 hospital, physician or drug claims for MS); the date of the first claim for MS or a demyelinating condition was considered the index date. All hospitalizations occurring after the index were included in the analyses. Comorbidity was defined in 3 ways: any comorbidity (yes/no); a total count of comorbidity (0, 1, or ≥2); and by individual comorbidities. The impact of comorbidity on all-cause hospitalizations was examined with negative binomial regression models fitted with generalized estimating questions (GEE). In subjects with at least one hospitalization during the follow-up period, we examined associations between comorbidity and MS-related hospitalizations logistic using regression models fitted with GEE.

Results: Subjects with comorbidity had a higher rate of all-cause hospitalizations compared to those without any comorbidity (aRR 1.72; 95% CI: 1.48-1.99); comorbidity did not increase the odds of having an MS-specific hospitalization (aOR 0.76; 95% CI: 0.59-0.99). Individual comorbidities including diabetes, ischemic heart disease, chronic lung disease, epilepsy, and mood disorders increased the rate of all-cause hospitalizations, but had little impact on MS-related hospitalizations. A longer disease duration was associated with decreased all-cause and MS-specific admissions.

Conclusion: Comorbidity increased the rate of all-cause, but not MS-specific, hospital admissions. Hospitalization rates were higher during the earlier stages of MS. Therefore, managing comorbidity in the MS population, especially early in the disease course, will likely have the biggest impact on reducing hospital admissions.

5.2 INTRODUCTION

Multiple sclerosis (MS) is a chronic neurologic disease that creates a substantial burden on the individual, the healthcare system, and society, due to its relatively early age of onset and progressive nature.[1] Healthcare utilization in the MS population exceeds utilization in the general population by almost 2-fold;[1,2] this increased utilization has been observed as early as 5 years before a diagnosis of MS.[3,4]

Comorbidities are common in the MS population and they can impact an individual's disease course and prognosis, be associated with longer diagnostic delays and greater disability at diagnosis,[5] more progressive disease,[6-8] and increased risk of mortality.[9] It has also been suggested that comorbidity may increase the risk of hospitalization,[10] yet few studies have evaluated this potential association. Even fewer studies have used an incident population which allows for examination of this association during the early, and more active, phase of the disease. Hospitalizations are the largest driver of healthcare costs in Canada.[11] As such, it is important to identify and better understand potentially modifiable risk factors for hospitalizations, especially in higher users, such as the MS population.

The purpose of this population-based study was to examine the association between comorbidity and hospitalization rates in an incident MS cohort in Saskatchewan, Canada.

5.3 METHODS

Data source

This retrospective cohort study used health administrative data from Saskatchewan, Canada. The population of Saskatchewan is just under 1.2 million,[12] and all residents are entitled to provincial health care benefits with the exception of those covered federally (members of the Canadian Forces, Royal Canadian Mounted Police, and federal inmates).[13] The government of Saskatchewan maintains linkable electronic databases that include the Discharge Abstract Database, the physician services database, the prescription drug database, as well as registration and demographic information.

The Discharge Abstract Database captures up to 25 diagnoses and procedures that occur during a hospitalization with the primary diagnosis indicating the most responsible reason for admission. International Classification of Diseases (ICD) codes were used to record diagnoses. In the Discharge Abstract Database, ICD-9 were used until 2002 and ICD-10-CA were used thereafter.[14] The physician database records a single diagnosis using three-digit ICD-9 codes, and the prescription drug database provides information on all prescription medications dispensed in an outpatient setting.

Study cohort

We identified all subjects with MS between January 1, 1996 and December 31, 2017 using a previously validated case definition requiring ≥3 claims for either hospital (ICD-9: 340,

ICD-10-CA: G35), physician (ICD-9: 340) or an MS-specific disease-modifying drug (Appendix H).[15] The first date of any medical contact for MS or a demyelinating condition (Appendix I) was considered as the date of "diagnosis",[16] and designated as the index date. To be included in the incident cohort, subjects must have had at least 5 years of continuous health coverage in Saskatchewan prior to their index date and have no claims for MS or a demyelinating condition during this time. Subjects were followed from their index date until the earliest of death, loss of beneficiary status, or study end (December 31, 2017).

Outcomes

All hospitalizations, except those related to childbirth (ICD-9: V27, ICD-10-CA: Z37), that occurred between January 1, 2001 (to allow the minimum 5-year run-in for identifying incident cases) and December 31, 2017 were extracted from the Discharge Abstract Database. However, only hospitalizations that occurred after the subject's index date were included in the analyses. Hospitalizations occurring within one day of a previous discharge were collapsed into a single event to prevent double counting.

Exposure (Comorbidity)

We identified eight individual comorbidities to examine: hypertension, diabetes, hyperlipidemia, ischemic heart disease, chronic lung disease, migraine, epilepsy, and mood and anxiety disorders. These comorbidities were chosen based on their prevalence in, or relevance to, MS, and in response to recommendations from the International Workshop on Comorbidity in Multiple Sclerosis.[7,17,18] All comorbidities were identified using previously validated case

definitions for administrative data (Appendix J, Appendix K).[19-22] Comorbidity status was determined at the index date using data from one year prior to the index date, and then updated annually (as of January 1 of each observation year) throughout the subject's follow-up period. Comorbidity was categorized and examined in 3 ways: any comorbidity (yes/no); a total count of comorbidity (0, 1, or ≥2); and, by individual comorbidities (presence or absence of each comorbidity). Because the comorbidities evaluated are primarily chronic conditions, once a comorbidity was identified it was considered prevalent for the duration of the follow-up. Depression, anxiety, and bipolar disorder were combined into a single category (mood and anxiety disorders) as ICD-9 claims in the physician database only contained three digits so differentiating between these conditions was not possible.[20]

Statistical Analysis

Descriptive statistics were reported as means with standard deviations (SD) for continuous variables, or frequencies (percent) for categorical variables. The age- and sex-standardized hospitalization rate was calculated for each year. Rates were age- and sex-standardized to the 2011 census (census closest to midpoint) via the direct method and reported per 100 persons. Poisson regression models adjusted for calendar year (continuous variable) were used to examine the changes in rates over time.

To evaluate the impact of comorbidity on all-cause hospitalizations, negative binomial regression fitted with generalized estimating equations and an exchangeable correlation structure were used. To account for varying study times for each subject, the log of person-

years (length of time that a subject was in the study) was used as an offset in the model. We also adjusted for the following covariates: age (calculated annually on July 1 of the observation year and categorized as <40, 40 -59, and ≥60 years), sex, socioeconomic status (SES) at index date estimated by linking the first three digits of a subject's postal code to Canadian census data to establish median household income (reported in quintiles), and disease duration (years). Disease duration was estimated by the calculating the number of years between observation year and index (i.e. "diagnosis") year. A moderate correlation between disease duration and calendar year (Spearman's correlation coefficient = 0.48) was observed, so we initially fit separate models stratified by calendar time. However, as the direction and significance of association of comorbidity was similar across the strata, we opted to remove calendar year as a variable and use a single model for easier interpretation. No other statistically or clinically significant interactions were identified. Results are reported as adjusted rate ratios (aRR) with 95% confidence intervals.

In the subcohort of subjects with at least one hospitalization during the follow-up period, we used logistic regression models fitted with GEE with an exchangeable correlation structure to examine associations between comorbidity and hospitalizations specifically related to MS (yes/no). All covariates were included as described above, and comorbidity was defined in the same three ways: any comorbidity (yes/no); a total count of comorbidity (0, 1, or ≥2); and, by individual comorbidities. A hospitalization was considered MS-related if an MS code

(ICD-9: 340 or ICD-10-CA: G35) was recorded as the primary or secondary diagnosis. Results were reported as adjusted odds ratios (aOR) with 95% confidence intervals.

This study was approved by the University of Saskatchewan's Biomedical Research Ethics Board. Data was accessed at the Saskatchewan Health Quality Council under data sharing agreements with the Saskatchewan Ministry of Health and eHealth Saskatchewan. Statistical analyses were performed with SAS 9.4 (SAS Institute Inc., Cary, NC).

5.4 RESULTS

Between January 1st, 2001 and December 31st, 2017, we identified 2,275 individuals newly diagnosed with MS, and followed them for a mean of 8.7 (SD 4.9) years. During the study period, a total of 3,312 hospitalizations, occurring in 52% of the MS cohort were identified. The mean age at index date was 43.1 (SD 14.3) years, and 68% of the cohort was female. Over half of the cohort had at least one existing comorbidity at their index date, the most common of which were mood and anxiety disorders (26.6%), hypertension (16.9%), migraine (14.6%), and chronic lung disease (13.5%) (Table 5.1).

The age and sex standardized all-cause hospitalization and non-MS hospitalization rates did not change significantly over the study period. A decreasing trend was observed for MS-related hospitalizations (-0.050; 95% CI:-0.096 to -0.003, p=0.04), and the rate of 7.2 per 100

persons (95% CI: 3.66 – 10.73) in 2001 decreased to 3.0 per 100 persons (95% CI: 2.2 – 3.7) in 2017 (Figure 5.1).

The presence of any comorbidity increased the rate of all-cause hospitalization (aRR 1.72; 95% CI: 1.48-1.99) (Table 5. 2), and the number of comorbidities increased the rate of hospitalization in a dose-response manner (Supplemental - Table 5.1). Each individual comorbidity was associated with increased all-cause hospitalizations rates, except for hyperlipidemia (aRR 0.85; 95% CI: 0.72 – 1.02) (Table 5.3). When examining the impact of comorbidities on MS-specific admissions in individuals with at least one hospitalization during their study period, the presence of any comorbidity did not increase the odds of having an MS-specific hospitalization (aOR 0.76; 95% CI: 0.59 – 0.99) (Table 5. 4). Overall, individual comorbidities were not associated with MS-specific hospitalization rates with the exception of hypertension which decreased the odds of an MS-related hospitalization by 33% (aOR 0.67; 95% CI: 0.51 – 0.88) (Table 5.5)**.**

The rate of all-cause hospitalizations increased with age; hospitalization rates increased by more than double in subjects over the age of 60 years compared to those under the age of 40 years (aRR 2.51; 95% CI: 2.07 – 3.04) (Table 5.2). Conversely, MS-related hospitalizations were more likely to occur in younger subjects, and rates decreased consistently with increasing age (Table 5.4, Table 5.5). A longer disease duration was associated with lower hospitalization rates for both all-cause (aRR 0.93; 95% CI: 0.91 – 0.94, Table 5.2) and MS-specific (aRR 0.85: 95% CI: 0.83 – 0.88, Table 5.4) admissions. The protective effect of disease duration was seen

even in models stratified by age (data not shown). A hospitalization prior to the index date was significantly associated with an increased rate of all-cause hospitalizations, but not MS-specific hospitalizations (Table 5.2, Table 5.4).

5.5 DISCUSSION

In this retrospective study of 2,275 individuals with incident MS, 54% of subjects had at least one comorbidity at the time of their MS "diagnosis". We observed a slight decrease in MS-related hospitalizations, but relatively stable rates for all-cause hospitalizations. We found that the presence of comorbidity increased the rate of all-cause hospitalizations but did not increase the rate of MS-related admissions. Similarly, individual comorbidities were associated with increased all-cause hospitalization rates, but few significantly impacted MS-specific hospitalizations. The rate of all-cause hospitalizations increased with age, whereas the odds of an MS-specific hospitalization decreased with age. Both all-cause and MS-specific hospitalizations decreased with a longer MS disease duration.

Our findings are consistent with a population-based study from Manitoba where the presence of comorbidity increased the risk of all-cause hospitalization but did not impact MS-related hospitalizations.[10] Also similar to our findings, the study found that specific comorbidities including hypertension, diabetes, heart disease, mental health disorders, and chronic lung disease increased the rate of all-cause hospitalizations.[10] We observed a dose-

response relationship with comorbidity burden in that subjects with more comorbidities had higher hospitalization rates compared to subjects with fewer or no comorbidity. This is consistent with findings from the British Columbia MS clinic where a high comorbidity burden (3 or more) was found to increase the risk of hospitalization more than three-fold compared to those with no comorbidity.[23] It is not clear why comorbidity did not increase the risk of MS-related hospitalizations given that comorbidities are associated with an increase in relapse rates and disability progression.[5,7,8,17] However, it has been suggested that the increased healthcare contacts for managing comorbidities may result in better MS care as well.[10] Another possibility is the potential pleiotropic effects of certain medications commonly used to treat comorbid conditions, such as statins and metformin, which have been suggested to have beneficial effects in MS.[24-27] Further research into the impact of concurrent medications for comorbidities in MS is warranted.

We evaluated the impact of individual comorbidities on both all-cause and MS-specific hospitalizations. Given the high prevalence of comorbid conditions like diabetes, hypertension, ischemic heart disease, mood disorders, and chronic lung disease in MS,[19,22,28-30] we expected to see the higher rates of all-hospitalizations associated with these conditions. Our study also found epilepsy increased the risk of all-cause hospitalizations. Findings from a Canadian population-based study reported that epilepsy was associated with higher levels of disability in the MS population,[7] which has been associated with increased healthcare utilization.[31] Interestingly, hypertension was associated with a lower rate of MS-related hospitalization,

which is contrary to what has been reported in the literature. In an American study from 2016, individuals with MS and hypertension had poorer health outcomes and more disability than individuals without hypertension.[6] This difference might be due to examining outcomes during different stages of MS; the American study used a prevalent cohort while ours was an incident cohort which examined outcomes early in the disease. Another possible explanation is that individuals with hypertension are strongly encouraged to adopt healthier lifestyles.[32] Smoking, inactivity, and high salt consumption have been associated with an increase in relapse activity and disability in MS,[33-35] thus health behavior management, could have had an impact on mitigating MS disease activity requiring hospitalization.

The rate of all-cause hospitalizations increased with age. This is not surprising given that older individuals in general are more likely to be hospitalized than those who are younger.[36] Conversely, the rate of MS-specific hospitalizations decreased with age. We also observed decreasing rates of hospitalizations (both all-cause and MS specific) with increasing duration of MS. A decrease in MS-specific admissions with age and longer disease duration is understandable, given the natural progression of MS. Many MS-specific admissions are related to relapses, and as the disease progresses, the rate of relapses typically decline.[37] A hospitalization in the year prior to the index (or "diagnosis") date was associated with a higher rate of all-cause hospitalization in our study. In general, previous hospitalizations have been shown to predict subsequent hospitalizations[38] and can also be a measure of disease severity.[39]

Our study has several limitations that should be considered. As with all observational studies, we were not able to identify or adjust for all possible confounders. We did not have access to clinical data such as MS phenotype, relapse rates, progression scores, laboratory values, or lifestyle factors that may affect hospitalization rates (e.g. smoking). Therefore, we were unable to determine MS disease status or the level of control of the comorbid conditions. However we did utilize population-based data from a province with one of the highest rates of MS worldwide.[15] We were not able to determine the specific reason for the MS-related admissions and made the assumption that the majority were related to relapses. This assumption is similar to what others have made.[10,40-44] We only identified eight comorbidities; however, we did identify the most prevalent comorbidities reported in MS populations using validated case definitions, and followed the recent recommendations of the International Working Group on Comorbidity in MS. Because we utilized an incident cohort, we only had access to 16 years of data. This may not be long enough to truly examine outcomes in a chronic condition like MS that can span over many decades. Nevertheless, we did have an average of 8 years of follow-up and are one of the only studies to examine the impact of comorbidities on hospitalizations in an incident population. The use of an incident cohort also allowed us to consider the impact of disease duration in our analyses.

Our population-based study confirmed that comorbidity is prevalent in the Saskatchewan MS population, with more than half having a comorbid condition at the time of diagnosis. Comorbidity increases the rate of all-cause hospitalizations, but appears to have little

impact on MS-related hospital admissions. We also observed increased hospitalization rates during the earlier stages of MS, when the disease is typically more active. These findings highlight the importance of recognizing and managing comorbidity in the MS population, especially early in the disease course, as this will likely have the biggest impact on reducing hospital admissions.

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Table 5. 1 Characteristics of the Saskatchewan MS incident cohort

Characteristics	n=2,275
Female, n (%)	1,545 (67.9)
Age at index date (years), mean (SD)	43.13 (14.3)
Socioeconomic status at index date, n (%)	
Quintile 1 (lowest)	367 (16.2)
Quintile 2	447 (19.7)
Quintile 3	426 (18.8)
Quintile 4	482 (21.2)
Quintile 5 (highest)	436 (19.2)
Missing	117 (5.0)
Index year	
2001-2004	717 (31.5)
2005-2008	577 (25.4)
2009-2012	476 (20.9)
2013-2017	505 (22.2)
≥1 hospitalization in year prior to index date, n (%)	282 (12.4)
Any comorbidity at index date, n (%)	1274 (54.8)
Number of comorbidities at index date, n (%)	

0	1028 (45.2)
1	659 (29.0)
≥2	588 (25.9)
Individual comorbidity at index date, n (%)	
Hypertension	385 (16.9)
Diabetes	130 (5.7)
Hyperlipidemia	222 (9.8)
Ischemic heart disease	127 (5.6)
Mood and anxiety disorder	605 (26.6)
Chronic lung disease	308 (13.5)
Migraine	332 (14.6)
Epilepsy	55 (2.4)
Individual comorbidity at end date, n (%)	
Hypertension	712 (31.3)
Diabetes	272 (12.0)
Hyperlipidemia	404 (17.8)
Ischemic heart disease	246 (10.8)
Mood and anxiety disorder	1022 (45.0)
Chronic lung disease	410 (18.0)
Migraine	529 (23.3)
Epilepsy	108 (4.8)

Follow-up (years) from index, mean (SD)	8.69 (4.9)

Table 5. 2 The association of any comorbidity and all-cause hospitalization rate in the Saskatchewan incident MS cohort

	n=2,275
Variable	**Rate Ratio (95% CI)**
Sex	
Female	Reference
Male	1.17 (0.99-1.38)
Age (years)[a]	
<40	Reference
40-59	1.20 (0.94-1.54)
≥60	**2.51 (2.07-3.04)**
Disease duration (years)	**0.93 (0.91-0.94)**
Comorbidity (any)[b]	
No	Reference
Yes	**1.72 (1.48-1.99)**
Socioeconomic status at index date	
Quintile 1 (lowest)	Reference
Quintile 2	**0.67 (0.53-0.84)**
Quintile 3	**0.68 (0.52-0.88)**
Quintile 4	**0.65 (0.46-0.76)**
Quintile 5 (highest)	**0.59 (0.46-0.76)**
Missing	0.78 (0.50-1.22)

	n=2,275
Variable	**Rate Ratio (95% CI)**
Hospitalization in year prior to index date	
No	Reference
Yes	**2.72 (2.20-3.36)**

a: calculated annually on July 1 for each observation year; b: estimated annually on January 1 for each observation year

Table 5. 3 The association of individual comorbidities and all-cause hospitalization rate in the Saskatchewan incident MS cohort

	n=2,275
Variable	**Rate Ratio (95% CI)**
Sex	
Female	Reference
Male	**1.19 (1.01-1.39)**
Age (years)[a]	
<40	Reference
40-59	1.16 (1.00-1.35)
≥60	**2.12 (1.71-2.62)**
Disease duration (years)	**0.92 (0.90-0.93)**
Socioeconomic status at index date	
Quintile 1 (lowest)	Reference
Quintile 2	**0.72 (0.57-0.90)**
Quintile 3	**0.70 (0.55-0.90)**
Quintile 4	**0.72 (0.58-0.90)**
Quintile 5 (highest)	**0.65 (0.51-0.83)**
Missing	0.78 (0.53-1.14)
Hospitalization in year prior to index date	
No	Reference
Yes	**2.24 (1.80-2.80)**

	n=2,275
Variable	**Rate Ratio (95% CI)**
Comorbidity[b] (Reference category = individual comorbidity not present)	
Hypertension	**1.33 (1.13-1.58)**
Diabetes	**1.89 (1.53-2.34)**
Hyperlipidemia	0.85 (0.72-1.02)
Ischemic heart disease	**1.45 (1.10-1.92)**
Mood and anxiety disorder	**1.52 (1.32-1.75)**
Chronic lung disease	**1.43 (1.19-1.71)**
Migraine	1.09 (0.89-1.32)
Epilepsy	**1.56 (1.02-2.39)**

a: calculated annually on July 1 for each observation year; b: estimated annually on January 1 for each observation year

Table 5. 4 The association of any comorbidity on MS-related hospitalization (yes/no) in subjects with at least one hospitalization

	n=1,180
Variable	**Odds Ratio (95% CI)**
Sex	
Female	Reference
Male	**1.74 (1.36-2.23)**
Age (years)[a]	
<40	Reference
40-59	**0.67 (0.52-0.88)**
≥60	**0.47 (0.34-0.66)**
Disease duration (years)	**0.85 (0.83-0.88)**
Comorbidity (any)[b]	
No	Reference
Yes	**0.76 (0.59-0.99)**
Socioeconomic status at index date	
Quintile 1 (lowest)	Reference
Quintile 2	1.17 (0.82-1.67)
Quintile 3	1.15 (0.79-1.68)
Quintile 4	1.21 (0.84-1.74)
Quintile 5 (highest)	0.88 (0.59-1.31)
Missing	2.07 (1.14-3.76)

	n=1,180
Variable	**Odds Ratio (95% CI)**
Hospitalization in year prior to index date	
No	Reference
Yes	0.76 (0.57-1.03)

a: calculated annually on July 1 for each observation year; b: estimated annually on January 1 for each observation year

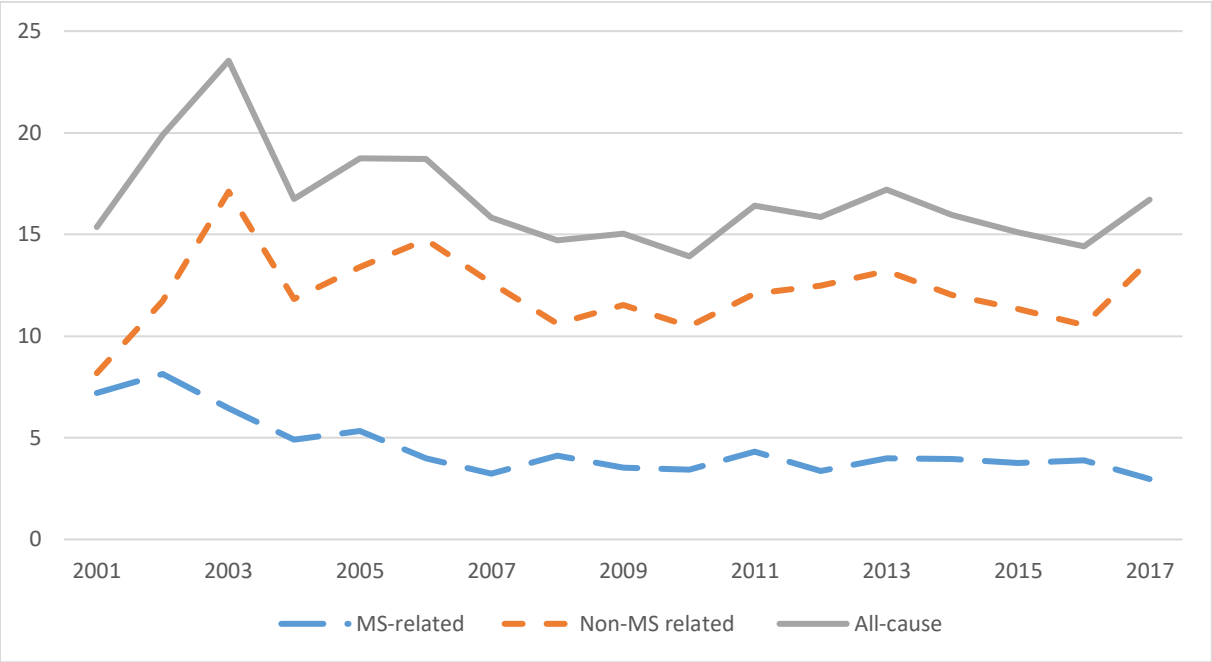
Table 5. 5 The association of individual comorbidities on MS-related hospitalizations (yes/no) in subjects with at least one hospitalization

	n=1,180
Variable	**Odds Ratio (95% CI)**
Sex	
Female	Reference
Male	**1.71 (1.32-2.21)**
Age (years)[a]	
<40	Reference
40-59	**0.70 (0.53-0.92)**
≥60	**0.52 (0.37-0.74)**
Disease duration (years)	**0.86 (0.83-0.89)**
Socioeconomic status at index date	
Quintile 1 (lowest)	Reference
Quintile 2	1.19 (0.83-1.71)
Quintile 3	1.18 (0.81-1.73)
Quintile 4	1.19 (0.82-1.73)
Quintile 5 (highest)	0.87 (0.58-1.30)
Missing	2.02 (1.13-3.62)
Hospitalization in year prior to index date	
No	Reference
Yes	0.80 (0.60-1.09)

	n=1,180
Variable	**Odds Ratio (95% CI)**
Comorbidity[b] (Reference category = individual comorbidity not present)	
Hypertension	**0.67 (0.51-0.88)**
Diabetes	1.14 (0.84-1.57)
Hyperlipidemia	1.04 (0.77-1.42)
Ischemic heart disease	0.88 (0.61-1.28)
Mood and anxiety disorder	0.86 (0.67-1.09)
Chronic lung disease	1.03 (0.78-1.37)
Migraine	0.83 (0.60-1.13)
Epilepsy	0.67 (0.36-1.23)

a: calculated annually on July 1 for each observation year; b: estimated annually on January 1 for each observation year

Figure 5. 1 Annual age- and sex- standardized hospitalization rates per 100 persons (2001-2017)



All-cause hospitalization -0.0142; 95% CI: -0.0379 to 0.0090, p-value = 0.2427

MS-specific hospitalization -0.0498; 95% CI: -0.0963 to -0.0032, p-value = 0.0362

Non-MS specific hospitalization -0.0021; 95% CI: -0.029 to 0.0265, p-value = 0.9299

Appendix H. Disease modifying drugs available in Canada during the study period

DIN	Drug (Brand name)
02169649	interferon beta 1b (Betaseron) 0.3 mg/vial
02269201	interferon beta 1a (Avonex) 30mcg/0.5 ml
02237319	interferon beta 1a (Rebif) 22 mcg/0.5 ml
02237320	interferon beta 1a (Rebif) 44mcg/0.5 ml
02318253	interferon beta 1a (Rebif) 66 mcg/1.5 ml
02318261	interferon beta 1a (Rebif) 132 mcg/1.5 ml
02337819	interferon beta 1b (Extavia) 0.3 mg/ml
02245619	glatiramer acetate (Copaxone) 20 mg/1 ml
02404508	dimethyl fumarate (Tecfidera)120 mg
02420201	dimethyl fumarate (Tecfidera) 240 mg
02416328	teriflunomide (Aubagio) 14 mg
02286386	natalizumab (Tysabri) 300 mg/15ml
02365480	fingolimod (Gilenya) 0.5 mg
02418320	alemtuzumab (Lemtrada) 12mg/1.2ml

DIN: drug identification number

Appendix I. ICD codes associated with multiple sclerosis and demyelinating diseases

ICD CODE (ICD-9/ICD-10-CA)	DISEASE
(340/G35)	Multiple sclerosis
(341.0/G36.0)	Neuromyelitis optica
(G36)	Acute disseminated demyelination
(341.9/G37.8)	Demyelinating disease of unspecified origin
(323/G36.9)	Acute disseminated encephalomyelitis
(323.82/G37)	Acute transverse myelitis
(377.3/H46)	Optic neuritis

ICD: International Classification of Diseases

Appendix J. Administrative case definitions for identifying study comorbidities

Comorbidity	Case definition	Years of data required	ICD-9 codes	ICD-10 codes
Hypertension[a]	≥ 1H or ≥ 2P	2	401–405	I10–I13, I15
Diabetes[a]	≥ 1H or ≥ 2P	5	250	E10–E14
Dyslipidemia[a]	≥ 1H or ≥ 2P or ≥ 2 Rx	5	272	E780, E782, E784, E785
Mood and anxiety disorders[b]	≥1 H or ≥5P OR (≥1P AND ≥4 Rx)	2	300.0, 300.2, 296.0, 296.1, 296.04, 296.14, 296.4, 296.44, 296.5, 296.54, 296.6, 296.7, 296.8, 296.2, 296.3, 298.0, 300.4, 311	F40, F41, F31, F32, F33, F34
Chronic lung disease[c]	≥ 1H or ≥ 2P or ≥ 2 Rx	5	493, 491, 492, 496	J45, J46, J40, J42, J43, J44
Epilepsy[c]	≥ 1H or (≥ 1P and ≥2 Rx)	3	345	G40, G41
Migraine[c]	≥ 2H or ≥ 2P or ≥ 2 Rx	2	345, 625.4	G43
Ischemic heart disease[d]	≥ 1H or ≥ 2P	5	410-415	I20-I25

H: hospitalization; P: physician claims; Rx: drug claims

[a] Marrie, Ruth Ann, et al. Rising prevalence of vascular comorbidities in multiple sclerosis: validation of administrative definitions for diabetes, hypertension, and hyperlipidemia. *Multiple Sclerosis Journal* (2012): 1310-1319.

[b] Marrie, Ruth Ann, et al. Mental comorbidity and multiple sclerosis: validating administrative data to support population-based surveillance. *BMC neurology* (2013): 16.

[c] Marrie, Ruth Ann, et al. The utility of administrative data for surveillance of comorbidity in multiple sclerosis: a validation study. *Neuroepidemiology* (2013): 85-92.

[d] Marrie, Ruth Ann, et al. Prevalence and incidence of ischemic heart disease in multiple sclerosis: a population-based validation study. *Multiple sclerosis and related disorders* (2013): 355-361.

Appendix K. ATC codes used for identifying study comorbidities

Comorbidity	ATC Code
Hyperlipidemia[a]	C10 (lipid modifying agents)
Mood disorders[b]	Antidepressants, anticonvulsants/ mood stabilizers, anxiolytics including N06AA01, N06AA02, N06AA04, N06AA11, N06AA12, N06AA17, N06AA21, N06AB03, N06AB04, N06AB05, N06AB06, N06AB08, N06AB10, N06AF03, N06AF04, N06AG02, N06AX06, N06AX11, N06AX16, N06AX21, N06AX23, N05AB12, N05AB06, N05AN01, N03AF01, N03AG01, N03AX09
Chronic lung disease[c]	RO3 (Oral and inhaled beta agonists, Inhaled corticosteroids, Leukotriene inhibitors, Xanthine derivatives, Ipratropium bromide, Mast cell stabilizers)
Epilepsy[c]	N03AA02 (phenobarbital) N03AA03 (primidone) N03AB02 (phenytoin) N03AD01 (ethosuximide) N03AF01 (carbamazepine) N03AF02 (oxcarbamazepine) N03AG01 (valproic acid) N03AG04 (vigabatrin) N03AX09 (lamotrigine)

Comorbidity	ATC Code
	N03AX12 (gabapentin) N03AX15 (pregabalin) N03AX14 (levetiracetam) N05BA09 (clobazam)
Migraine[c]	N02CA (ergot alkaloids) N02CC (triptans) N02CX (other anti-migraine preps)

ATC: Anatomic therapeutic chemical classification system

[a] Marrie, Ruth Ann, et al. Rising prevalence of vascular comorbidities in multiple sclerosis: validation of administrative definitions for diabetes, hypertension, and hyperlipidemia. *Multiple Sclerosis Journal* (2012): 1310-1319.

[b] Marrie, Ruth Ann, et al. Mental comorbidity and multiple sclerosis: validating administrative data to support population-based surveillance. *BMC neurology* (2013): 16.

[c] Marrie, Ruth Ann, et al. The utility of administrative data for surveillance of comorbidity in multiple sclerosis: a validation study. *Neuroepidemiology* (2013): 85-92.

[d] Marrie, Ruth Ann, et al. Prevalence and incidence of ischemic heart disease in multiple sclerosis: a population-based validation study. *Multiple sclerosis and related disorders* (2013): 355-361.

Supplemental Table 5. 1 The association of comorbidity count and all-cause hospitalization rate in the Saskatchewan incident MS cohort

	n=2,275
Variable	**Rate Ratio (95% CI)**
Sex	
Female	Reference
Male	**1.22 (1.04-1.44)**
Age (years)[a]	
<40	Reference
40-59	1.15 (0.99-1.34)
≥60	**2.16 (1.78-2.63)**
Disease duration (years)	**0.92 (0.91-0.93)**
Socioeconomic status at index date	
Quintile 1 (lowest)	Reference
Quintile 2	**0.68 (0.54-0.86)**
Quintile 3	**0.67 (0.52-0.86)**
Quintile 4	**0.69 (0.55-0.86)**
Quintile 5 (highest)	**0.62 (0.48-0.79)**
Missing	0.79 (0.51-1.21)
Hospitalization in year prior to index date	
No	Reference
Yes	**2.51 (2.01-3.12)**

	n=2,275
Variable	**Rate Ratio (95% CI)**
Comorbidity count[b]	
0	Reference
1	**1.33 (1.13-1.57)**
≥2	**2.38 (1.99-2.84)**

a: calculated annually on July 1 for each observation year; b: estimated annually on January 1 for each observation year

Supplemental Table 5. 2 The association of comorbidity count on MS-related hospitalization (yes/no) in subjects with at least one hospitalization

	n=1180
Variable	**Odds Ratio (95% CI)**
Sex	
Female	Reference
Male	**1.70 (1.32-2.17)**
Age (years)[a]	
<40	Reference
40-59	**0.71 (0.54-0.92)**
≥60	**0.52 (0.37-0.72)**
Disease duration (years)	**0.86 (0.83-0.88)**
Socioeconomic status at index date	
Quintile 1 (lowest)	Reference
Quintile 2	1.15 (0.81-1.64)
Quintile 3	1.17 (0.80-1.70)
Quintile 4	1.17 (0.81-1.69)
Quintile 5 (highest)	0.86 (0.57-1.28)
Missing	2.04 (1.13-3.69)
Hospitalization in year prior to index date	
No	Reference
Yes	0.80 (0.59-1.09)

	n=1180
Variable	**Odds Ratio (95% CI)**
Comorbidity count[b]	
0	Reference
1	0.89 (0.67-1.19)
≥2	**0.65 (0.48-0.86)**

a: calculated annually on July 1 for each observation year; b: estimated annually on January 1 for each observation year

6 CONCLUSION

Canada has one of the highest rates of MS worldwide.[1] Saskatchewan was thought to have one of the highest rates of MS in Canada,[2,3] but prior to this work, a province-wide examination of incidence and prevalence had never been completed. MS has a complicated influence on the healthcare system in general and our research identifies opportunities to decrease the burden on the healthcare system. We first validated a case definition of MS using population-based health administrative data, and then applied the definition to estimate annual incidence and prevalence rates from 1996 to 2013. Our findings confirmed that Saskatchewan has one of the highest rates of MS nation- and world-wide,[4] and provide more supporting evidence to understand risk factors associated with MS such as the role of the geographic factor.

The validation of a case definition for MS also allowed for accurate identification of the Saskatchewan MS cohort from administrative data which can be used for further research. Recognizing the strain that MS places on the healthcare system,[5,6] we utilized this cohort to examine healthcare utilization patterns related to disease-modifying therapies, physician services, and hospitalizations – the first time this has ever been studied in Saskatchewan.

In 2018 , the government of Saskatchewan spent almost 17 million dollars on disease modifying therapies.[7] While their use has dramatically changed the treatment of MS, these costly medications also have the potential to cause severe and sometimes fatal side-effects.[8-10] DMT use has been justified by clinical trial evidence demonstrating reduced severity and

frequency of relapses.[11-13] However, real-world evidence showing an impact of DMTs on disease progression and/or health care costs is limited. In an effort to understand the impact DMTs have on healthcare utilization and to help guide policy decisions, we evaluated their impact on hospitalizations and physician visits at the population level. Studying the impact at the population level rather than at the individual level allowed us real world evaluation of the impact of DMT use in a contemporary health care system context. Over the past two decades, increasing DMT use in Saskatchewan was not associated with major reductions in the hospitalization rate among patients with MS. Further, rates of physician visits remained unchanged despite wider DMT utilization. However, it is therefore possible that any increase related to DMT prescribing and monitoring may be offset by a reduction in physician services in other areas, such as relapse management. Precise reasons for the apparent inconsistency between clinical trial benefits of DMT agents and our real-world analysis are not clear. Certainly, our results cannot rule out the possibility that DMTs have benefited the MS population in Saskatchewan. However, it is reasonable to expect that investment in DMTs should ultimately decrease the demand for acute services. Future studies assessing the impact of DMTs at the individual level and on other aspects of healthcare utilization are needed to evaluate their impact, especially with the recent introduction of more effective DMTs.

The high rates of hospitalizations observed in the MS population over the past 20 years represent the ongoing burden MS is placing on the healthcare system. Our comparison of hospitalization rates between the MS and general population to identify predictors of

hospitalization enabled us to better detect individuals at risk of future hospitalizations. We observed higher rates of hospitalizations with a higher comorbidity burden. We also observed that as subjects aged, the type of hospitalizations changed. Furthermore, the gap in hospitalization rates (i.e. rate ratios) between the MS and general population controls was highest among subjects less than 40 and narrowed with age, as the rate of hospitalizations in the MS population approached the rate in the general population in subjects aged 60 and above. These findings highlight areas for potential improvement in MS care and prevention of future hospitalizations, such as focusing efforts towards younger or newly diagnosed individuals with MS and addressing modifiable factors such as comorbidity. We also found that individuals with MS were more likely to be admitted for certain diseases such as diseases of the sense organs, skin and subcutaneous tissue, genitourinary system, and infectious diseases, while they were less likely to be admitted for mental health disorders, neoplasms, and cardiovascular disease. While this was expected for many of these conditions, we were surprised to see fewer admissions due to cardiovascular disease and mental health disorder given their high prevalence in MS.[14,15] Possible disparities in care between the MS and general population could be attributed to the differences in admissions observed.[16]

Our further evaluation of individual comorbidities in an incident MS cohort allowed us to better understand the impact of comorbidity during the early more active phase of the disease. We found that comorbidity increased the rate of all-cause hospitalizations in a dose-response manner, but did not impact MS-related admissions. An increase in all-cause

hospitalizations was expected and has been observed in MS and other chronic diseases,[17-19] but the lack of impact of comorbidities on MS-specific hospitalizations was unexpected, given how comorbidities increase relapse rates and disability progression.[20-23] Perhaps, the increase in contacts with outpatient healthcare providers to better manage comorbid conditions also led to better MS management. Furthermore, we observed a general decrease in hospitalizations with an increase in disease duration. This highlights the importance of diagnosing and managing comorbidities, especially during early stages of the disease, in efforts to decrease the total burden of MS on the healthcare system.

In conclusion, province-wide estimates of MS incidence and prevalence in Saskatchewan are critical for supporting government agencies to make decisions and/or policies for improving MS care in the province.[24] Saskatchewan has one of the highest rates of MS nation- and worldwide and future research evaluating why Saskatchewan has such high rates can help with a better understanding of the etiology of MS. The burden it is placing on the healthcare system is significant and is only expected to rise. The introduction of DMTs has dramatically changed the management of MS but future research is needed to help maximize its impact in real world settings. Individual characteristics such as age, sex, stage of disease, as well as comorbid conditions can impact rates and reasons for hospitalizations. Identifying predictors of hospitalizations can help guide collaborative efforts to prevent future hospitalizations and inform resource allocation decision.

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