













Original Article

Healthcare Cost of Multiple Sclerosis and in Relation to Disability Level in Alberta

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ABSTRACT: Background: We aimed to (1) report updated estimates of direct healthcare costs for people living with MS (pwMS), (2) contrast costs to a control population and (3) explore differences between disability levels among pwMS. **Methods:** Administrative data were used to identify adult pwMS (MS cohort) and without (control cohort) in Alberta, Canada; disability level (based on the Expanded Disability Status Scale) among pwMS was estimated. One- and two-part generalized linear models with gamma distribution were used to estimate the incremental direct healthcare cost (2021 \$CDN) of MS during a 1-year observation period. **Results:** Adjusting for confounders, the total healthcare cost ratio was higher in the MS cohort ($n = 13,089$) versus control ($n = 150,080$) (5.24 [95% CI: 5.08, 5.41]) with a predicted incremental cost of \$15,016 (95% CI: \$14,497, \$15,535) per person-year. Among the MS cohort, total predicted direct healthcare costs were higher with greater disability, \$14,430 (95% CI: \$13,980, \$14,880) to \$58,697 (\$51,514, \$65,879) per person-year in mild and severe disability, respectively. The primary health resource cost component shifted from disease-modifying therapies in mild disability to supportive care in moderate and severe disability. **Conclusion:** Adult pwMS had greater direct healthcare costs than those without. Extrapolating to the population level (where 14,485 adult pwMS were identified in the study), it is estimated that \$218 million per year in healthcare costs may be attributable to MS in Alberta. The significantly larger economic impact associated with greater disability underscores the importance of preventing or delaying disease progression and functional impairment in MS.

RÉSUMÉ : Coûts des soins de santé en Alberta pour la sclérose en plaques et relation avec le niveau d'invalidité. Contexte : Notre objectif était (1) de présenter des estimations actualisées des coûts directs des soins de santé pour les personnes vivant avec la sclérose en plaques (SP) ; (2) de comparer ces coûts à ceux d'une population témoin ; (3) d'explorer les différences entre les niveaux d'invalidité chez les patients atteints de SP. **Méthodes :** Des données administratives ont été utilisées pour identifier les adultes atteints de SP (cohorte SP) et non atteints (cohorte témoin) en Alberta (Canada). Leur niveau d'invalidité a été estimé au moyen de l'échelle Expanded Disability Status Scale (EDSS). Des modèles linéaires généralisés en une et deux parties avec une distribution gamma ont été par ailleurs utilisés pour estimer les coûts directs supplémentaires des soins de santé (en dollars canadiens de 2021) en ce qui regarde la SP, et ce, pendant une période d'observation d'un an. **Résultats :** Après ajustement pour les facteurs de confusion, le ratio des coûts totaux des soins de santé était plus élevé dans la cohorte SP ($n = 13\ 089$) que dans le groupe témoin ($n = 150\ 080$) (5,24 [IC 95 % : 5,08-5,41]) avec un coût supplémentaire prédit de 15 016 \$ (IC 95 % : 14 497 \$-15 535 \$) par année-personne. Dans la cohorte SP, les coûts directs totaux prédits des soins de santé étaient plus élevés avec une plus grande invalidité, ce qui représentait respectivement 14 430 \$ (IC 95 % : 13 980 \$-14 880 \$) à 58 697 \$ (51 514 \$-65 879 \$) par année-personne dans des cas d'invalidité légère et sévère. La principale composante du coût des ressources de santé est passée des thérapies modificatrices de la maladie en cas d'invalidité légère aux soins de soutien en cas d'invalidité modérée et grave. **Conclusion :** Les coûts directs des soins de santé sont plus élevés chez les adultes atteints de SP que chez ceux qui ne le sont pas. En extrapolant cette observation à l'échelle de la population et en tenant compte que 14 485 adultes atteints de SP ont été identifiés dans cette étude, on peut estimer que 218 millions de dollars en coûts de santé peuvent être attribués par année à la SP en Alberta. L'impact économique significativement plus important associé à une plus grande invalidité souligne du coup l'importance de prévenir ou de retarder la progression de la maladie ainsi que la déficience fonctionnelle liée à la SP.

Keywords: Administrative data; healthcare cost; neurological disorder; real world; retrospective

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Highlights

- Multiple sclerosis (MS) imposed an additional annual healthcare cost of \$15,016 per person compared with controls.
- \$218 million/year in healthcare costs may be attributable to MS in Alberta.
- The larger economic impact associated with greater disability among those living with MS underscores the importance of preventing/delaying disease progression in MS.

Introduction

Multiple sclerosis (MS) is a chronic disorder of the central nervous system. This disorder typically begins between the ages of 20 and 50 years, primarily affecting females, and is lifelong.¹ MS is the most common nontraumatic disabling neurological condition among working-age adults in Canada.² The prevalence of MS in Canada is one of the highest in the world, with the province of Alberta reported to have a particularly large population living with MS (310 cases per 100,000 population).^{3–5} The most common form of MS is relapsing-remitting, in which individuals experience periods of neurological disability followed by complete or partial recovery over weeks to months.⁶ Some features of MS that negatively impact the physical and psychosocial well-being of people living with MS (pwMS) and increase healthcare resource utilization and associated costs include the frequency and severity of relapses and disability level.^{7–9}

PwMS require complex care management involving pharmacological and nonpharmacological interventions to control symptoms, delay disease progression or accumulation of disability and manage comorbid conditions that are commonly present.¹⁰ Consequently, pwMS utilize more healthcare services compared with those without MS, and advancing disease severity is associated with additional utilization and associated costs.^{11,12} Relatively few studies have been conducted on the healthcare cost of MS in Canada;^{11,13–18} even fewer have been conducted in the past decade,^{11,17} during which numerous disease-modifying therapies (DMTs) have been introduced. DMTs are the current pharmacological standard of care for pwMS based on evidence that these treatments reduce the frequency and severity of relapses and may reduce disability over the long term.^{19–21} A contemporaneous estimate of the healthcare cost of MS is needed to support decision and policymakers and prioritize resources. The objectives of this study were to estimate the incremental direct healthcare cost of MS among adults and according to disability level among pwMS in Alberta, Canada.

Methods

Ethics approval was received from the University of Alberta Research Ethics Board (Pro00116074) and the University of Calgary Conjoint Health Research Ethics Board (pSite-21-0031). No study participants were placed at risk, and a waiver of consent was applied. Data custodian approvals were received from Alberta Health and Alberta Health Services for the use of administrative health data for this study. This study was reported according to the Reporting of Studies Conducted Using Observational Routinely Collected Health Data guidelines.²²

Study design

This retrospective, observational, population-based cohort study was conducted using administrative health data from Alberta

between April 1, 1993, and March 31, 2021. Adult residents of Alberta living with and without MS on April 1, 2019 (index date), were included. Data back to April 1, 1993, were used for determining cohort selection and baseline characteristics, and a 1-year post-index observation period was used for determining outcomes (April 1, 2019, to March 31, 2020).

Data sources

Canadian provinces provide publicly funded health care for all residents. In Alberta, the fourth most populous Canadian province (4.4 million people in 2019/2020),²³ health care is administered under the Alberta Health Care Insurance Plan (AHCIP), of which over 99% of Albertans participate.²⁴ A person-level data extract from the Discharge Abstract Database (DAD), National Ambulatory Care Reporting System (NACRS), Practitioner Claims (data available from January 1, 1994, onward), Alberta Continuing Care Information System (ACCIS), National Rehabilitation Reporting System (NRS), Pharmaceutical Information Network (PIN) and Vital Statistics was linked to the Population Registry using a unique individual identifier (Personal Health Number) and then deidentified and provided to the researchers by the data custodians. DAD and NACRS include demographic, administrative, diagnostic, procedural and resource intensity weight information on people discharged from hospital (DAD), emergency department (ED) and facility-based ambulatory care clinics (NACRS). Diagnostic fields for each visit include the most responsible diagnosis and room for up to 24 (DAD) and 9 (NACRS) secondary International Classification of Disease – version 10 – Canadian Enhancement (ICD-10-CA) codes. Physician visits were obtained from the Practitioner Claims database that includes patient, provider and service information such as demographics, physician specialty, date of service, amount paid to the service provider (on fee-for-service, alternative payment plan physician billing and shadow billing) and health service and diagnostic codes; up to three ICD – version 9 – Clinical Modification (ICD-9-CM; Alberta specific) diagnostic codes can be used per visit. ACCIS contains information on long-term care and professional community home care; elements include demographics, admission and discharge information and resource utilization groupers. NRS contains data on adult inpatient rehabilitation facilities and programs. The PIN contains information on all dispensed prescription medications from community pharmacies (including both retail and specialty). Vital statistics contains information on all events related to an individual's entrance and departure from life. The Provincial Registry contains demographic information for all Albertans with AHCIP coverage; elements include migration in and out of the province and birth and death indicators. Records that were duplicates or contained an invalid Personal Health Number were discarded. Variables were checked for missing data and inconsistencies; inconsistent data were corrected using data logic or information majority.

Cohort selection

The MS cohort included those who (1) met a validated case definition for MS, defined as having ≥ 1 hospitalization (from April 1, 1993, onward) or ≥ 5 ambulatory care visits (from April 1, 1998, onward) and/or physician visits (from January 1, 1994, onward) with a recorded code for MS (ICD-10-CA G35, ICD-9-CM 340) located in any diagnostic field within a 2-year period between April 1, 1993, and March 31, 2021 (multiple outpatient

visits by an individual within the same day were considered as one visit for case definition purposes);²⁵ (2) had an MS incident date, defined as the first healthcare encounter with a recorded diagnostic code for MS or a related demyelinating disease of the central nervous system with none occurring ≥ 5 years beforehand (see Supplementary Table 1), occurring before the index date; (3) were aged ≥ 18 years and alive on the index date; and (4) had AHCIP coverage for ≥ 2 years before the index date and ≥ 1 year after the index date or until death whichever occurred first.

The case definition used in this study to identify pwMS was validated in Canada using electronic medical records linked to administrative data and resulted in high sensitivity (84%), specificity (100%) and positive predictive value (86%).²⁵ This algorithm provided the shortest time interval (i.e., 2 years) to achieve $> 80\%$ for both sensitivity and positive predictive value compared with the other tested options (e.g., ≥ 1 hospitalization or 1–10 claims within 1–20 years) and can accurately identify pwMS using administrative data.²⁵

The control cohort (adult residents of Alberta not living with MS) included randomly selected individuals from those who (1) were alive and aged ≥ 18 years on the index date; (2) did not have a hospitalization (from April 1, 1993, onward), ambulatory care visit (from April 1, 1998, onward) and/or physician visit that contained an MS code between April 1, 1993, and March 31, 2021; (3) did not have a DMT dispensation between April 1, 2008 (date from which data were available in PIN) and March 31, 2021; and (4) had AHCIP coverage for ≥ 5 years before the index date and ≥ 1 year after the index date or until death whichever occurred first.

Study measures

Sociodemographic characteristics recorded on the index date included age, sex, urban/rural residence (based on postal code) and Pampalon material deprivation index (includes education, employment status and average income); this index was derived from the Alberta general population at the dissemination area level that was linkable to postal code and presented based on quintiles from most well-off (quintile 1) to most deprived (quintile 5).²⁶ Clinical characteristics included the Charlson Comorbidity Index and specific MS-related comorbidities;^{27,28} the number of years living with MS (time between the MS incident date and the index date) and disability level were reported among the MS cohort. A Charlson Comorbidity Index score was determined during the 2-year pre-index period that was based on ICD-10-CA and ICD-9-CM codes of 17 different specific medical conditions weighted according to their potential for influencing mortality (Supplementary Table 2).^{29,30} MS-related comorbidities included anxiety,³¹ cardiovascular disease (atrial fibrillation, chronic heart failure, coronary artery disease, peripheral artery disease and stroke),^{32–36} chronic obstructive pulmonary disease (COPD),³⁷ depression,³⁸ diabetes³⁹ and hypertension;³⁵ each participant was classified with respect to the presence or absence of these conditions as measured during the 2-year period before the index date (Supplementary Table 3). A validated algorithm was used to estimate Expanded Disability Status Scale (EDSS) scores using age, specific healthcare service use (home care, long-term care and inpatient rehabilitation) and health conditions (visual disturbance, other paralytic syndromes and spasticity; Supplementary Table 4).^{40,41} Disability level was defined in this study as mild (EDSS ≤ 3.5), moderate (EDSS 4–6.5) and severe (EDSS ≥ 7).

During the 1-year post-index observation period, healthcare resource utilization and costs were determined for acute care (hospitalizations, ED visits), outpatient care (ambulatory care, physician visits), supportive care (long-term care admissions, home care services) and pharmacy dispensed prescription medications (overall and subgrouped into DMTs [Supplementary Table 5] and all others). Acute and ambulatory care costs were derived by multiplying the associated resource intensity weight with the Canadian Institute for Health Information (CIHI) standardized cost for Alberta in 2019/2020.⁴² Resource intensity weight is a measure to estimate healthcare resource use and represents the relative value of resources that a given patient, contingent on diagnostic case-mix, would be expected to consume relative to a standard patient; CIHI provides standardized average costs incurred through the direct care of a standardized patient.⁴³ Physician visit costs were based on the actual amount paid. Time residing in long-term care (e.g., nursing homes, auxiliary hospitals) was measured and cost estimated based on the average daily cost (\$230.36 per day; from Alberta Health) of all such facilities in Alberta.⁴⁴ The total hours of home care encounters were measured, and the provider type was identified; estimated costs were based on the hourly wage of service providers in Alberta.⁴⁵ Drug costs were calculated using the drug product identification number and quantity dispensed, combined with the drug list price (from Alberta Blue Cross); a 3% per unit markup and a \$12.15 dispensing fee were included.^{46,47} Costs were reported in 2021 Canadian dollars (\$CDN).⁴⁸

Statistical analyses

Descriptive statistics were reported as counts and percentages, means with standard deviations (SD) or medians with interquartile ranges (IQR), where appropriate. One- and two-part generalized linear models (GLM) were employed to examine cost differences. Function and distribution were determined based on results from several tests (Pearson correlation test, Pregibon link test, modified Hosmer and Lemeshow test, modified Park's test). When minimal or absent zero cost values were present, a one-part GLM model with a gamma distribution and log-link function was used, producing cost ratios. When cost outcomes had prevalent zero values, a two-part GLM approach was adopted.⁴⁹ The first part involved logistic regression to predict the odds of observing a nonzero cost (corresponding to the odds of having a cost occurrence), yielding odds ratios that quantify relative differences in odds of nonzero cost. The second part, conditional on a nonzero cost, involved a GLM with a gamma distribution and log-link function to predict the positive costs, producing cost ratios. Incremental cost (the incurred additional cost of pwMS compared to controls) was presented by cost ratios (accompanied by odds ratio in two-part models) and the difference between predicted costs using an average marginal effect approach.⁵⁰ The potential confounders of sociodemographic characteristics (age, sex, urban/rural residence and socioeconomic status) were included in the MS versus control model; sociodemographic characteristics and the number of years living with MS were included in the disability level model among pwMS. The healthcare cost attributable to MS in Alberta was estimated by multiplying the per person-year incremental cost of MS by the number of pwMS identified in this study. Analyses were performed using SAS 9.4 software (SAS Institute Inc., Cary, NC, USA) and Stata 18 (StataCorp LLC, College Station, TX, USA).

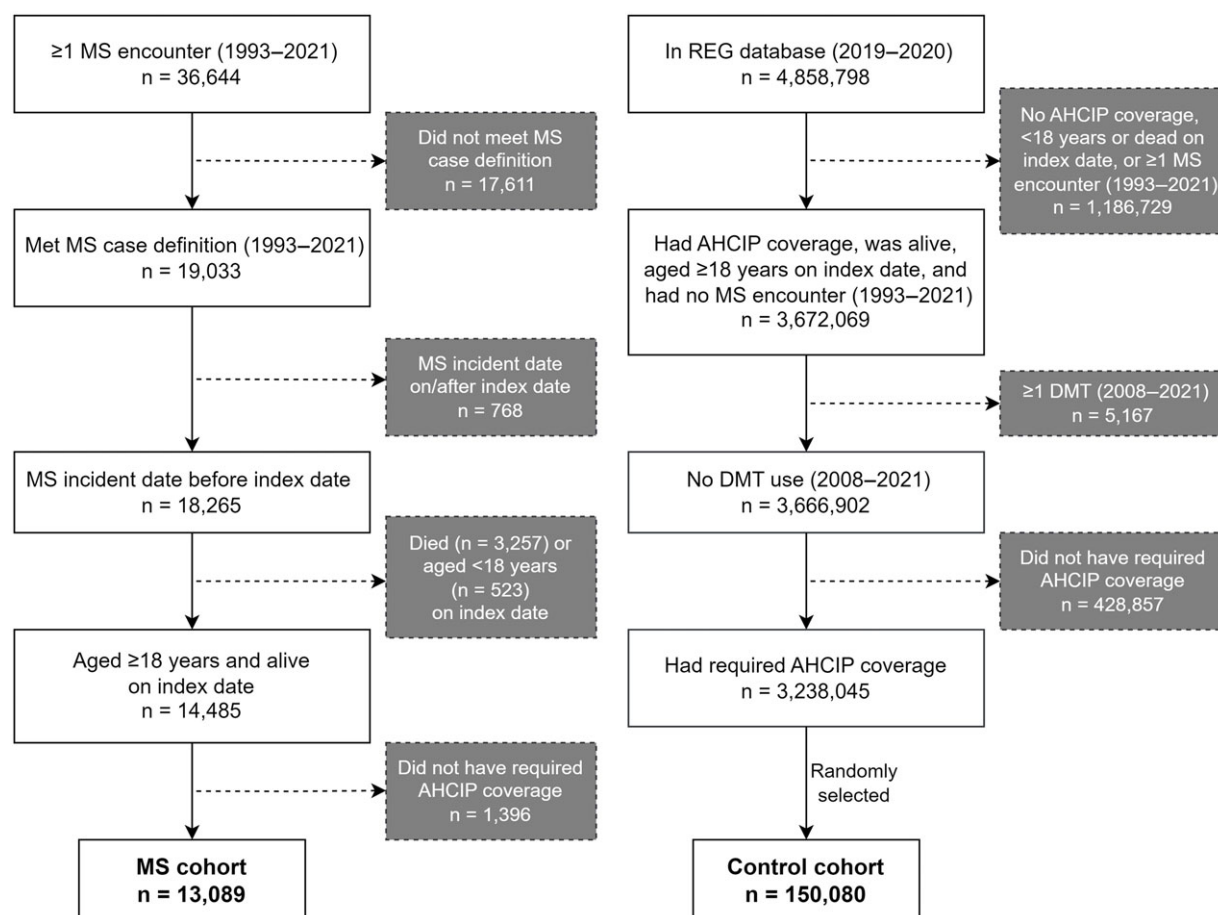


Figure 1. MS and control cohort selection. AHCIP = Alberta health care insurance plan; DMT = disease-modifying therapy; MS = multiple sclerosis; REG = the Provincial Registry.

Results

Cohort selection

A total of 14,485 pwMS were identified on the index date, and 13,089 met the criteria for the MS cohort (Figure 1; Supplementary Figure 1 shows data linkages). Among the 3,238,045 individuals who met the criteria for the control cohort, approximately 11 were randomly selected for each individual within the MS cohort ($n = 150,080$); privacy compliance guidelines of the data custodians informed the number of controls.⁵¹

Baseline characteristics

The MS cohort was older (53 [SD < 1] vs. 47 [SD < 1] years), predominantly female (71.7% vs. 49.6%), and experienced a higher overall burden of disease (Charlson Comorbidity Index score: 0.5 [SD 1.2] vs. 0.3 [SD 1.0]) than the control cohort (Table 1). The MS cohort was more likely to have hypertension (17.2% vs. 15.4%), depression (16.9% vs. 8.0%), anxiety (10.2% vs. 6.4%), cardiovascular disease (6.3% vs. 4.8%) and COPD (4.6% vs. 3.0%) compared with the control cohort (Table 1). Within the MS cohort, 24.6%, 35.7% and 39.7% had been living with MS for ≤ 5 years, 6–15 years and > 15 years, respectively (Table 1). Regarding disability status, 66.9% ($n = 8,751$) of the MS cohort had mild disability (EDSS ≤ 3.5 ; none had a score 0–1.5), 29.0% ($n = 3,794$) had moderate disability (EDSS 4–6.5) and 4.2% ($n = 544$) had severe

disability (EDSS ≥ 7) (Table 1). Age, the overall burden of disease, the proportion living with specific MS-related comorbidities and the number of years living with MS were greater in those with more severe disability (vs. less disability) (Table 1).

Healthcare resource utilization

The MS cohort had a higher proportion with ≥ 1 hospitalization (11.6% vs. 6.2%), ED visit (32.7% vs. 22.7%), ambulatory care visit (72.1% vs. 27.1%), physician visit (95.2% vs. 79.7%), long-term care admission (3.8% vs. 0.1%) and home care encounters (16.9% vs. 3.4%) compared with the control cohort over the 1-year post-index observation period (Table 2). A greater proportion of the MS cohort also received ≥ 1 prescription medication dispensation (89.1% [29.8% received a DMT] vs. 67.7%) during the 1-year post-index observation period (Table 2).

Within the MS cohort, the proportion of those who had ≥ 1 hospitalization, ED visit, physician visit, long-term care admission and home care encounter was numerically greater among those with greater disability; those with moderate disability had a lower proportion with ambulatory care visits (68.6%) than those with lower or higher disability (73.5% each; Table 2). Among the different types of physicians, the proportion of those who visited primary care physicians and other types of physicians was greater, and those who visited neurologists were lower, among those with more severe disability (compared with those who had less

Table 1. Baseline characteristics

	Control cohort		MS cohort		
	(n = 150,080)	Overall (n = 13,089)	Mild EDSS ≤ 3.5 (n = 8,751)	Moderate EDSS 4–6.5 (n = 3,794)	Severe EDSS ≥ 7 (n = 544)
Age, years (mean, SD)	47 (<1)	53 (<1)	47 (10)	66 (10)	71 (12)
Sex, n (%)					
Male	75,578 (50.4%)	3,707 (28.3%)	2,356 (26.9%)	1,166 (30.7%)	185 (34.0%)
Female	74,502 (49.6%)	9,382 (71.7%)	6,395 (73.1%)	2,628 (69.3%)	359 (66.0%)
Region of residence (n, %)					
Urban	128,965 (85.9%)	11,137 (85.1%)	7,548 (86.3%)	3,137 (82.7%)	452 (83.1%)
Rural	21,115 (14.1%)	1,952 (14.9%)	1,203 (13.8%)	657 (17.3%)	92 (16.9%)
Material deprivation index, n (%)					
1 (most well-off)	27,552 (18.4%)	2,386 (18.2%)	1,624 (18.6%)	674 (17.8%)	88 (16.2%)
2	27,018 (18.0%)	2,467 (18.9%)	1,741 (19.9%)	639 (16.8%)	87 (16.0%)
3	28,060 (18.7%)	2,499 (19.1%)	1,720 (19.7%)	691 (18.2%)	88 (16.2%)
4	30,510 (20.3%)	2,686 (20.5%)	1,795 (20.5%)	782 (20.6%)	109 (20.0%)
5 (most deprived)	30,118 (20.1%)	2,313 (17.7%)	1,517 (17.3%)	698 (18.4%)	98 (18.0%)
Missing	6,822 (4.6%)	738 (5.6%)	354 (4.1%)	310 (8.2%)	74 (13.6%)
Charlson Comorbidity Score mean (SD)	0.3 (1.0)	0.5 (1.2)	0.3 (0.8)	0.8 (1.5)	1.8 (2.2)
MS-related comorbidities, n (%)					
Hypertension	23,172 (15.4%)	2,253 (17.2%)	942 (10.8%)	1,113 (29.3%)	198 (36.4%)
Depression	11,982 (8.0%)	2,214 (16.9%)	1,458 (16.7%)	623 (16.4%)	133 (24.5%)
Anxiety	9,610 (6.4%)	1,336 (10.2%)	984 (11.2%)	296 (7.8%)	56 (10.3%)
Diabetes	11,027 (7.4%)	1,019 (7.8%)	416 (4.8%)	482 (12.7%)	121 (22.2%)
Cardiovascular disease	7,136 (4.8%)	819 (6.3%)	293 (3.4%)	410 (10.8%)	116 (21.3%)
COPD	4,490 (3.0%)	601 (4.6%)	210 (2.4%)	321 (8.5%)	70 (12.9%)
Years since MS diagnosis (n, %)					
0–1	---	1,015 (7.8%)	877 (10.0%)	121 (3.2%)	17 (3.1%)
2–5	---	2,204 (16.8%)	1,809 (20.7%)	364 (9.6%)	31 (5.7%)
6–10	---	2,381 (18.2%)	1,958 (22.4%)	373 (9.8%)	50 (9.2%)
11–15	---	2,291 (17.5%)	1,622 (18.5%)	605 (16.0%)	64 (11.8%)
>15	---	5,198 (39.7%)	2,485 (28.4%)	2,331 (61.4%)	382 (70.2%)

COPD = chronic obstructive pulmonary disease; MS = multiple sclerosis; SD = standard deviation.

Table 2. Healthcare resource utilization during the 1-year post-index observation period

	Control cohort		MS cohort		
	(n = 150,080)	Overall (n = 13,089)	Mild EDSS ≤ 3.5 (n = 8,751)	Moderate EDSS 4–6.5 (n = 3,794)	Severe EDSS ≥ 7 (n = 544)
Among the total cohort, those who had ≥ 1 visit, n (%)					
Among those with ≥ 1 visit, median (IQR)					
Hospitalizations, n (%) median (IQR)	9,306 (6.2%)1 (1–1)	1,518 (11.6%)1 (1–1)	629 (7.2%)1 (1–1)	678 (17.9%)1 (1–2)	211 (38.8%)1 (1–2)
Length of stay, days median (IQR)	3 (2–9)	6 (2–17)	3 (1–8)	8 (3–22)	11 (5–29)
ED visits, n (%) median (IQR)	34,058 (22.7%)1 (1–2)	4,274 (32.7%)1 (1–3)	2,583 (29.5%)1 (1–2)	1,396 (10.4%)1 (1–3)	295 (54.2%)2 (1–3)
Ambulatory care visits, n (%) median (IQR)	40,630 (27.1%)2 (1–4)	9,435 (72.1%)4 (2–8)	6,433 (73.5%)4 (2–8)	2,602 (68.6%)4 (2–8)	400 (73.5%)3 (2–8)
Physician visits, n (%) median (IQR)	119,686 (79.7%)7 (3–13)	12,466 (95.2%)11 (6–20)	8,279 (94.6%)5 (3–10)	3,648 (96.2%)8 (4–15)	539 (99.1%)26 (13–52)
Primary care physician visits, n (%) median (IQR)	115,268 (76.8%)4 (2–8)	11,925 (91.1%)6 (3–12)	7,831 (89.5%)5 (3–10)	3,561 (93.9%)8 (4–17)	533 (98.0%)17 (7–40)
Neurologist visits, n (%) median (IQR)	3,819 (2.5%)1 (1–2)	7,682 (58.7%)1 (1–2)	5,856 (66.9%)1 (1–2)	1,631 (43.0%)1 (1–2)	195 (35.8%)1 (1–2)
Other physician types, n (%) median (IQR)	87,565 (58.3%)3 (2–7)	10,129 (77.4%)4 (2–8)	6,474 (74.0%)4 (2–7)	3,185 (83.9%)5 (2–11)	470 (86.4%)7 (3–14)
Long-term care admissions, n (%) median (IQR)	168 (0.11%)1 (1–1)	500 (3.8%)1 (1–1)	96 (1.1%)1 (1–1)	302 (8.0%)1 (1–1)	102 (18.8%)1 (1–1)
Length of stay, days (365 max) median (IQR)	365 (365–365)	365 (311–365)	365 (365–365)	365 (365–365)	255 (81–365)
Home care encounters, n (%) median (IQR)	5,152 (3.4%) 7 (3–15)	2,213 (16.9%)7 (4–17)	558 (6.4%)6 (3–11)	1,196 (31.5%)4 (2–7)	459 (84.4%)9 (4–21)
Length of encounter, hours median (IQR)	13 (3–74)	24 (4–319)	8 (3–55)	34 (5–388)	123 (9–762)
Medication dispensations, n (%) median (IQR)	101,684 (67.7%)8 (3–18)	11,670 (89.1%)18 (9–37)	7,746 (88.5%)15 (8–28)	3,413 (90.0%)25 (12–58)	511 (93.9%)63 (24–151)
DMT dispensations, n (%)	NA	3,896 (29.8%)	3,467 (39.6%)	413 (10.9%)	16 (2.9%)
Number of drug types, median (IQR)	4 (2–6)	6 (3–9)	5 (3–8)	7 (4–11)	10 (7–14)

DMT = disease-modifying therapy; ED = emergency department; IQR = interquartile range; max = maximum.

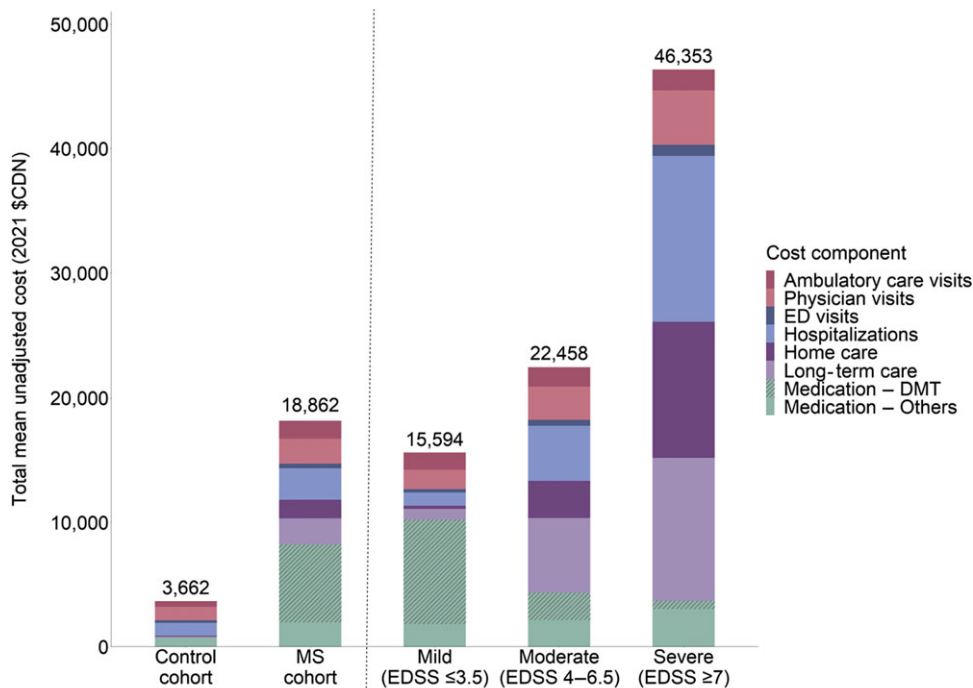


Figure 2. Total mean unadjusted healthcare cost presented overall and by cost components. CDN = Canadian; DMT = disease-modifying therapy; ED = emergency department; EDSS = expanded disability status scale; MS = multiple sclerosis.

disability) (Table 2). The proportion who received ≥ 1 DMT was greater in those with mild disability (39.6%) and lower in those with moderate (10.9%) and severe (2.9%) disability (Table 2).

Healthcare cost of multiple sclerosis

The total mean unadjusted healthcare cost of the MS cohort was \$18,862 per person-year and \$3,662 for the control cohort (Figure 2). Medication (43.5%) comprised the largest cost component of the total healthcare cost among the MS cohort, and physician visits (29.5%) and hospitalizations (28.4%) were the largest components among the control cohort (Figure 2). After adjusting for confounding sociodemographic factors (age, sex, urban/rural residence and socioeconomic status), total healthcare costs were 5.2 times higher (cost ratio: 5.24 [95% CI: 5.08, 5.41]) in the MS cohort versus the control cohort, with MS having a predicted incremental cost of \$15,016 (95% CI: \$14,497, \$15,535) per person-year; the average adjusted annual per-person cost of MS was \$18,555 (95% CI: \$18,036, \$19,073) versus \$3,539 (95% CI: \$3,478, \$3,600) in the control cohort (Table 3).

Within the MS cohort, the total mean unadjusted annual healthcare cost of those with mild disability was \$15,594, moderate disability was \$22,458 and severe disability was \$46,353 (Figure 2). Medication (65.3% of total cost, of which DMTs encompassed 82.0%) comprised the largest cost component of those with mild disability; supportive care (long-term care and home care) was the largest cost component among those with moderate (40.1%) and severe disability (48.3%) (Figure 2). After adjusting for confounding sociodemographic factors and years living with MS, total healthcare costs were 1.8 times higher (cost ratio: 1.75 [95% CI: 1.62, 1.89]) for those with moderate disability and 4.1 times higher (cost ratio: 4.07 [95% CI: 3.56, 4.64]) for those with severe disability compared with mild disability (Table 4). The average adjusted annual per-person cost of pwMS with mild disability was \$14,430 (95% CI: \$13,980, \$14,880) versus \$25,261 (95% CI: \$23,711, \$26,810) for moderate disability and \$58,697 (95% CI: \$51,514,

\$65,879) for severe disability (Table 4). Acute care (hospitalizations, ED), supportive care (long-term care, home care) and outpatient care (ambulatory care, physician visits) contributed to the higher cost in those with greater disability, with supportive care being the primary driver; the cost of DMTs was lower in those with greater disability compared with those with mild or moderate disability (Table 4).

Discussion

In this retrospective, observational, population-based cohort study of adults living with and without MS in Alberta, the incremental direct healthcare cost of MS and cost by disability level among pwMS was determined between April 1, 2019, and March 31, 2020, using administrative health data (reported in 2021 \$CDN). The annual cost of MS was found to be more than five times higher than those not living with MS, with a predicted incremental cost of \$15,016 per person-year. Extrapolating this cost to the population level, where 14,485 adults were identified as living with MS on the index date in this study (Figure 1), it is estimated that \$218 million per year in healthcare costs were attributable to MS in Alberta during the observation period. This study also characterized the large economic burden associated with disability among pwMS, with total predicted direct healthcare costs greater by more than fourfold from \$14,430 to \$58,697 per person-year among pwMS with mild and severe disability, respectively; the primary cost component shifted from DMTs in mild disability to supportive care in moderate and severe disability. Collectively, this study provides insights into the healthcare costs associated with MS and the distribution of cost by levels of disability, highlighting the importance of preventing or delaying disability progression as an economic priority, in addition to being clinically significant and enhancing the health-related quality of life for pwMS.

Although Canada has one of the highest prevalence of MS in the world, relatively few studies have been conducted on the healthcare cost of MS in the country;^{11,13–18} even fewer have been conducted in

Table 3. Total healthcare cost comparisons between the multiple sclerosis cohort and the control cohort

Study cohorts	Unadjusted			Adjusted				
	Total cost (\$CDN)	95% CI	Total cost (\$CDN)	95% CI	Cost ratio	95% CI	Incremental cost (\$CDN)	95% CI
Multiple sclerosis	18,396	17,907	18,886	18,036	19,073	5.24	15,016	14,497
Control (reference)	3,577	3,514	3,640	3,478	3,600	—	—	—
<i>Among those with multiple sclerosis</i>								
Disease level								
Mild (EDSS ≤ 3.5; reference)	15,439	15,027	15,850	13,980	14,880	—	—	—
Moderate (EDSS 4–6.5)	21,684	20,504	22,863	23,711	26,810	1.75	10,831	9,104
Severe (EDSS ≥ 7)	46,871	41,671	52,070	51,514	65,879	4.07	44,267	36,979

Individuals with a missing Pampalon material deprivation index were not included. Potential confounders that were adjusted for included age, sex, residence and socioeconomic status (multiple sclerosis cohort vs. control cohort), along with the number of years living with multiple sclerosis (moderate and severe vs. mild disability). Incremental costs (the incurred additional cost in pwMS compared to controls) were estimated using an average marginal effect approach based on predicted costs from generalized linear models with a log-link function and gamma distribution.

CDN = Canadian; CI = confidence interval; EDSS = expanded disability status scale.

the past decade to capture the numerous DMTs and current pharmacological standard of care with this therapy.⁵² Among the more recent studies, Amankwah *et al.* (2017) applied a micro-simulation model and found that the total direct healthcare cost, which included hospitalizations, physician services, prescription drugs and provincially funded supportive services (long-term and home care) and assistive devices, was estimated to be approximately \$16,800 per person-year for pwMS aged 20 years and older (2011 CDN).¹¹ The total direct healthcare cost of pwMS was similar to the current study when inflated to 2021 dollars (i.e., \$18,782 CDN).⁴⁸ Recently, Khakban *et al.* (2023) conducted a retrospective population-based cohort study using administrative health data among 17,071 pwMS and 85,355 matched controls to determine the incremental healthcare cost of MS in British Columbia.¹⁷ Based on inpatient, outpatient (ED and physician visits) and medication costs, the total excess cost of MS was estimated at \$6,881 per person-year (2020 CDN).¹⁷ The total incremental healthcare cost of MS estimated in the current study was more than twice as much, at \$15,016 per person-year; this difference may be due to the more comprehensive capture of healthcare resources in this study, including ambulatory care, long-term care and home care. Of mention, the proportional contribution of medication and healthcare resources to the total direct healthcare cost of MS in the USA is similar to the current study but greater in terms of cost itself (e.g., \$88,487 per person-year [2019 USD]).^{53,54}

The extensive literature on the cost of illness in MS has shown that disability is a well-documented key driver of healthcare costs among pwMS; a significant increase in the total cost of MS, both direct and indirect, occurs with increasing disability from mild to severe, as measured by the EDSS.^{12,55} This escalation in cost is coupled with shifts in the distribution of the economic burden of MS.^{8,12,55} However, large population-based studies using rigorous comparisons are very limited. Most studies use samples with relatively small numbers of participants and rely on self-reports of healthcare resource utilization, and recruitment occurs most often from specialized outpatient MS tertiary clinics, which introduces selection bias toward those with less severe disability and those more likely to use a DMT.⁵⁶ Recognizing these limitations, studies conducted in a contemporaneous era consistently report DMTs as the main cost component at milder disability levels and supportive care or inpatient care as the primary cost driver at more severe disability levels. For example, Fogarty *et al.* (2014) recruited 214 pwMS from a specialized MS clinic and determined direct healthcare costs of inpatient, outpatient, medication, supportive care (long-term and home care), tests and assistive devices at different disease severity levels in Ireland.⁵⁷ The authors found that all cost categories were greater in those with severe disability ($n = 27$) compared with mild disability ($n = 114$), with the exception of medication and tests that were lower; the largest cost component of those with severe disability was supportive care followed by inpatient care.⁵⁷ Among 799 pwMS recruited from specialized MS and neurology clinics in Belgium (where almost half of the individuals received a DMT during the observation period), DMTs comprised 80% of the total direct healthcare cost in mild disability and 4% in severe disability; the cost of inpatient care was tenfold greater among those with severe disability compared with mild disability.⁵⁸ Findings from the current study are consistent with previous reports; total direct healthcare costs were significantly greater at more severe disability levels, and the primary cost component shifted from DMTs in mild disability to supportive care in moderate and severe disability.

Table 4. Healthcare cost comparisons of acute care, supportive care, outpatient care and prescription medications between disease severity levels within the multiple sclerosis cohort

	Odds ratio of encounter* (nonzeros)			Cost ratio			Incremental cost (\$CDN)		
	Point estimate	95% CI		Point estimate	95% CI		Point estimate	95% CI	
Mild (EDSS ≤ 3.5; reference)	—	—	—	—	—	—	—	—	—
Moderate (EDSS 4–6.5)	1.71	1.53	1.92	2.50	2.01	3.12	3,425	2,557	4,293
Severe (EDSS ≥ 7)	3.65	2.96	4.51	4.35	2.94	6.45	10,720	6,279	15,162
Mild (EDSS ≤ 3.5; reference)	—	—	—	—	—	—	—	—	—
Moderate (EDSS 4–6.5)	8.08	6.94	9.39	1.71	1.42	2.06	6,911	5,903	7,920
Severe (EDSS ≥ 7)	119.2	85.5	166.1	1.97	1.53	2.52	20,254	16,000	24,508
<i>Outpatient care (ambulatory care visits, physician visits)</i>									
Mild (EDSS ≤ 3.5; reference)	—	—	—	—	—	—	—	—	—
Moderate (EDSS 4–6.5)	NA	NA	NA	1.55	1.42	1.68	1,583	1,240	1,927
Severe (EDSS ≥ 7)	NA	NA	NA	2.25	1.95	2.59	3,604	2,728	4,480
<i>Prescription medication</i>									
<i>Overall</i>									
Mild (EDSS ≤ 3.5; reference)	—	—	—	—	—	—	—	—	—
Moderate (EDSS 4–6.5)	NA	NA	NA	0.71	0.65	0.77	–2,589	–3,163	–2,015
Severe (EDSS ≥ 7)	NA	NA	NA	0.71	0.61	0.83	–2,551	–3,532	–1,570
<i>Disease-modifying therapy</i>									
Mild (EDSS ≤ 3.5; reference)	—	—	—	—	—	—	—	—	—
Moderate (EDSS 4–6.5)	0.41	0.35	0.47	1.01	0.95	1.06	–3,298	–3,815	–2,781
Severe (EDSS ≥ 7)	0.12	0.07	0.21	1.03	0.81	1.30	–5,742	–6,539	–4,945
<i>Other prescription medications</i>									
Mild (EDSS ≤ 3.5; reference)	—	—	—	—	—	—	—	—	—
Moderate (EDSS 4–6.5)	NA	NA	NA	1.50	1.31	1.72	836	528	1,145
Severe (EDSS ≥ 7)	NA	NA	NA	2.40	2.00	2.88	2,321	1,644	2,998
<i>Total cost</i>									
Mild (EDSS ≤ 3.5; reference)	—	—	—	—	—	—	—	—	—
Moderate (EDSS 4–6.5)	NA	NA	NA	1.75	1.62	1.89	10,831	9,104	12,557
Severe (EDSS ≥ 7)	NA	NA	NA	4.07	3.56	4.64	44,267	36,979	51,554

* Estimated by gamma hurdle models (acute care, supportive care and disease-modifying costs) or a generalized linear model with log link and gamma distribution (outpatient care, overall and 'other' prescription medications and total costs). Incremental cost was the incurred additional cost of people living with multiple sclerosis compared to controls. CDN = Canadian; CI = confidence interval, EDSS = expanded disability status scale; NA = not applicable.

In the current study, the observed higher and lower DMT use and cost in those with mild and more severe disability, respectively, are in alignment with recommendations from the Canadian MS Working Group that state all individuals with relapsing-remitting MS should be encouraged to start treatment with a DMT soon after diagnosis (when disability is likely to be mild), and stopping a DMT can be considered among pwMS who are older than 60 years of age with prolonged stable disease.^{52,59} Older individuals appear to have an increased risk of infection and other adverse effects that may be due to age-related immunosenescence and therapy-induced alterations to the immune system, as well as a higher burden of comorbidities.⁶⁰ In this study, we found that those with mild disability had been living with MS for fewer years than those who had moderate and severe disability who in turn were older had a higher overall burden of disease and a greater proportion living

with comorbidities. Other potential reasons for the observed lower DMT use among those with severe disability in this study may be attributed to a lesser perceived benefit given the already great amount of accrued disability, which is irreversible, and that provincial public coverage plans generally limit DMT coverage to those with an EDSS < 7.0. Recent studies have shown that early initiation of DMTs, particularly highly effective antibody-mediated therapies, reduces the frequency and severity of relapses and reduces disability, with the potential to lessen healthcare costs over the long term.^{19–21,61} Further research is needed to delineate the cost-effectiveness of MS treatments aimed at delaying the progression of MS and reducing the frequency of relapses.⁶²

Important strengths of this study are the large population-based design and high-quality source of administrative health data that contains information on comprehensive healthcare resources in

Alberta. However, this study is also subject to a number of limitations that should be taken into consideration when interpreting results. Retrospective administrative claims-based studies use administrative data as opposed to medical records, and therefore, there is a potential for misclassification of the study groups or measures. To minimize the possibility of including individuals in the MS cohort who did not have the disease, a case-finding algorithm for MS was applied in the current study that was validated in Ontario and resulted in high sensitivity (84%), specificity (100%), positive predictive value (86%), negative predictive value (100%) and kappa (0.85).²⁵ Although a validated algorithm was used to estimate the level of disease severity among pwMS based on EDSS,⁴¹ informal care and assistive devices were not included in the algorithm nor captured within provincial administrative data, and therefore, it is possible that some individuals with a higher EDSS score may have been misclassified as having a lower score. While individual-level direct healthcare costs would not be affected, the total healthcare cost of mild and moderate disability would be subject to potential overestimation and underestimation of severe disability. The algorithm also tends to overestimate EDSS scores at the lower end of the range as evidenced by the model intercept that exceeded 0 (i.e., 1.27)⁴¹ and was reflected in this study (none had EDSS scores 0–1.5). The PIN database only provides information on prescription medication dispensations from community pharmacies and therefore may not represent actual medication uptake by individuals. The use of over-the-counter medications and other non-pharmacotherapy management was not captured within the administrative data; prescription medications provided in a hospital or secondary care setting were not measured in this study. This study was conducted from the perspective of the Canadian healthcare system and did not include costs borne by individuals or indirect costs such as informal care and productivity loss (of the individual and/or caregiver). Previous studies have shown that when a societal perspective is considered, costs outside the health system increasingly outweigh direct healthcare costs as disability escalates, dominating total costs in severe disability.¹²

Conclusions

This study provides insights into the direct healthcare costs associated with MS and the distribution of cost by disability status. Adults living with MS used greater healthcare resources and incurred higher incremental costs compared with those not living with MS, which may represent an additional \$218 million per year in healthcare costs related to MS and associated comorbidities in Alberta. Health economic impact was apparent by disability status, underscoring the importance of preventing or delaying disability progression in MS. The observed shift in primary cost components with disability levels can be used to inform resource allocation planning.

Supplementary material. The supplementary material for this article can be found at <https://doi.org/10.1017/cjn.2024.288>.

Data availability statement. The data that support the findings of this study are available from Alberta Health Services and Alberta Health, but restrictions apply to the availability of these data, which were used under license for the current study and so are not publicly available.

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Author contributions. KV, KM, LR and SK contributed to the study concept and design. HS, KV and SAH conducted the analyses, PUN created the tables and figures and KM prepared the draft manuscript. All authors contributed to the interpretation of the data and critical revision of the report for intellectual content. SK provided study supervision.

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Competing interests. The author(s) declared the following potential conflicts of interest with respect to the research, authorship and/or publication of this manuscript: HS, KV, HL, KM, SAH, PUN, LR, TW and SK are members of the Alberta Real World Evidence Consortium (ARWEC) and the Alberta Drug and Therapeutic Evaluation Consortium (ADTEC); these entities (comprised of individuals from the University of Alberta, University of Calgary and Institutes of Health Economics) conduct research including investigator-initiated industry-funded studies (ARWEC) and government-funded studies (ADTEC). EB, JM, PS and MK declare no competing interests. All authors of this study had complete autonomy over the content and submission of the manuscript, as well as the design and execution of the study.

References

1. The Multiple Sclerosis International Federation. *Atlas of MS*. 3rd ed. The Multiple Sclerosis International Federation (MSIF); 2020.
2. Trisolini M, Honeycutt A, Wiener J, Lesesne S. *Global Economic Impact of Multiple Sclerosis*. London, United Kingdom: Multiple Sclerosis International Federation; 2010.
3. Walton C, King R, Rechtman L, et al. Rising prevalence of multiple sclerosis worldwide: insights from the Atlas of MS. *Mult Scler J*. 2020;26:1816–21.
4. Gilmour H, Ramage-Morin PL, Wong SL. Multiple sclerosis: prevalence and impact. *Health Rep*. 2018;29:3–8.
5. Balcom EF, Smyth P, Kate M, et al. Disease-modifying therapy use and health resource utilisation associated with multiple sclerosis over time: a retrospective cohort study from Alberta, Canada. *J Neurol Sci*. 2024;458:12–2913.
6. Dutta R, Trapp BD. Relapsing and progressive forms of multiple sclerosis: insights from pathology. *Curr Opin Neurol*. 2014;27:271–8.
7. Nicholas J, Zhou H, Deshpande C. Annual cost burden by level of relapse severity in patients with multiple sclerosis. *Adv Ther*. 2021;38:758–71.
8. Patwardhan MB, Matchar DB, Samsa GP, McCrory DC, Williams RG, Li TT. Cost of multiple sclerosis by level of disability: a review of literature. *Mult Scler*. 2005;11:232–9.
9. Gil-González I, Martín-Rodríguez A, Conrad R, Pérez-San-Gregorio M. Quality of life in adults with multiple sclerosis: a systematic review. *BMJ Open*. 2020;10:e041249.
10. Marrie RA. Comorbidity in multiple sclerosis: implications for patient care. *Nat Rev Neurol*. 2017;13:375–82.
11. Amankwah N, Marrie RA, Bancej C, et al. Multiple sclerosis in Canada 2011 to 2031: results of a microsimulation modelling study of epidemiological and economic impacts. *Health Promot Chronic Dis Prev Can*. 2017;37:37–48.
12. Schrieffer D, Haase R, Ness NH, Ziemssen T. Cost of illness in multiple sclerosis by disease characteristics - a review of reviews. *Expert Rev Pharmacoecon Outcomes Res*. 2022;22:177–95.
13. Asche CV, Ho E, Chan B, Coyte PC. Economic consequences of multiple sclerosis for Canadians. *Acta Neurol Scand*. 1997;95:268–74.

14. The Canadian Burden of Illness Study Group. Burden of illness of multiple sclerosis: part I: cost of illness. *Can J Neurol Sci.* 1998;25:23–30.
15. Grima DT, Torrance GW, Francis G, Rice G, Rosner AJ, Lafortune L. Cost and health related quality of life consequences of multiple sclerosis. *Mult Scler.* 2000;6:91–8.
16. Karampampa K, Gustavsson A, Miltenburger C, Kindundu CM, Selchen DH. Treatment experience, burden, and unmet needs (TRIBUNE) in multiple sclerosis: the costs and utilities of MS patients in Canada. *J Popul Ther Clin Pharmacol.* 2012;19:e11–25.
17. Khakban A, Rodriguez Llorian E, Michaux KD, et al. Direct health care costs associated with multiple sclerosis: a population-based cohort study in British Columbia, 2001–2020. *Neurology.* 2023;100:e899–e910.
18. Canadian Institute for Health Information. *The Burden of Neurological Diseases, Disorders and Injuries in Canada.* Ottawa, ON: CIHI; 2007.
19. Harding K, Williams O, Willis M, et al. Clinical outcomes of escalation vs early intensive disease-modifying therapy in patients with multiple sclerosis. *JAMA Neurol.* 2019;76:536–41.
20. Moccia M, Palladino R, Lanzillo R, et al. Healthcare costs for treating relapsing multiple sclerosis and the risk of progression: a retrospective Italian cohort study from 2001 to 2015. *PLoS One.* 2017;12:e0169489.
21. Spelman T, Magyari M, Piehl F, et al. Treatment escalation vs immediate initiation of highly effective treatment for patients with relapsing-remitting multiple sclerosis: data From 2 Different national strategies. *JAMA Neurol.* 2021;78:1197–204.
22. Benchimol EI, Smeeth L, Guttman A, et al. The REporting of studies conducted using observational routinely-collected health data (RECORD) statement. *PLoS Med.* 2015;12:e1001885.
23. Statistics Canada. Table 17-10-0005-01 Population estimates on July 1st, by age and sex. Government of Canada. Published 2021. <https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1710000501>.
24. Jin Y, Elleho E, Sanderson M, Malo S, Haan M, Odynak D. *Comparison of Alberta Population Counts Between the AHCIIP Registry and the 2006 Census.* Edmonton, Alberta, Canada: Alberta Health and Wellness; 2009.
25. Widdifield J, Ivers NM, Young J, et al. Development and validation of an administrative data algorithm to estimate the disease burden and epidemiology of multiple sclerosis in Ontario, Canada. *Mult Scler.* 2015;21:1045–54.
26. Pampalon R, Hamel D, Gamache P, Raymond G. A deprivation index for health planning in Canada. *Chronic Dis Can.* 2009;29:178–91.
27. Magyari M, Sorensen PS. Comorbidity in multiple sclerosis. *Front Neurol.* 2020;11:851.
28. Marrie RA, Patten S, Tremlett H, et al. Chronic lung disease and multiple sclerosis: incidence, prevalence, and temporal trends. *Mult Scler Relat Disord.* 2016;8:86–92.
29. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis.* 1987;40:373–83.
30. Lix L, Smith M, Pitz M, et al. *Cancer Data Linkage in Manitoba: Expanding the Infrastructure for Research.* Winnipeg, MB: Manitoba Centre for Health Policy; 2016.
31. Marrie RA, Fisk JD, Yu BN, et al. Mental comorbidity and multiple sclerosis: validating administrative data to support population-based surveillance. *Bmc Neurol.* 2013;13:16.
32. Canadian Stroke Best Practices Stroke Quality Advisory Committee. *Quality of Stroke Care in Canada: Stroke Key Quality Indicators and Stroke Case Definitions.* Toronto, ON, Canada: Heart and Stroke Foundation of Canada; 2016.
33. Quan H, Li B, Saunders LD, et al. Assessing validity of ICD-9-CM and ICD-10 administrative data in recording clinical conditions in a unique dually coded database. *Health Serv Res.* 2008;43:1424–41.
34. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care.* 2005;43:1130–9.
35. Tonelli M, Wiebe N, Fortin M, et al. Methods for identifying 30 chronic conditions: application to administrative data. *BMC Med Inform Decis.* 2015;15:31.
36. Tu K, Mitiku T, Lee DS, Guo H, Tu JV. Validation of physician billing and hospitalization data to identify patients with ischemic heart disease using data from the electronic medical record administrative data linked database (EMRALD). *Can J Cardiol.* 2010;26:e225–8.
37. Gershon AS, Wang C, Guan J, Vasilevska-Ristovska J, Cicutto L, To T. Identifying individuals with physician diagnosed COPD in health administrative databases. *COPD.* 2009;6:388–94.
38. Doktorchik C, Patten S, Eastwood C, et al. Validation of a case definition for depression in administrative data against primary chart data as a reference standard. *BMC Psychiatry.* 2019;19:9.
39. Hux JE, Ivis F, Flintoft V, Bica A. Diabetes in Ontario: determination of prevalence and incidence using a validated administrative data algorithm. *Diabetes Care.* 2002;25:512–6.
40. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology.* 1983;33:1444–52.
41. Marrie RA, Tan Q, Ekuma O, Marriott JJ. Development and internal validation of a disability algorithm for multiple sclerosis in administrative data. *Front Neurol.* 2021;12:754144.
42. Canadian Institute for Health Information. Cost of a standard hospital stay; Available from: [https://yourhealthsystem.cihi.ca/hsp/inbrief?lang=en&_ga=2.36659107.2018561862.1586970892-168035366.1586970892#/indicators/015/cost-of-a-standard-hospital-stay/mapC1;mapLevel2;provinceC20018;trend\(C1,C20018\);](https://yourhealthsystem.cihi.ca/hsp/inbrief?lang=en&_ga=2.36659107.2018561862.1586970892-168035366.1586970892#/indicators/015/cost-of-a-standard-hospital-stay/mapC1;mapLevel2;provinceC20018;trend(C1,C20018);). Accessed April 2019
43. Canadian Institute for Health Information. *DAD Resource Intensity Weights and Expected Length of Stay (ELOS) for Case Mix Group (CMG+)* 2020. Canadian Institute for Health Information; 2020. <https://www.cihi.ca/en/resource-indicators-dad-resource-intensity-weights-and-expected-length-of-stay>.
44. Tonelli M, Wiebe N, Joannette Y, et al. Age, multimorbidity and dementia with health care costs in older people in Alberta: a population-based retrospective cohort study. *CMAJ Open.* 2022;10:E577–e88.
45. Government of Alberta. *Alberta careers, learning, and employment information.* Edmonton, AB, Canada: Government of Alberta; 2023. <https://alis.alberta.ca/>.
46. Government of Alberta. *Pharmacy services and fees.* Edmonton, AB, Canada: Government of Alberta; 2020. <https://www.alberta.ca/pharmacy-services-and-fees.aspx>.
47. Government of Canada. *Markup policies in public drug plans.* Ottawa, ON, Canada: Government of Canada; 2017/2018.
48. Statistics Canada. *The Canadian consumer price index reference paper.* Ottawa, ON: The Minister responsible for Statistics Canada; 2023.
49. Duan N, Manning WG, Morris CN, Newhouse JP. A comparison of alternative models for the demand for medical care. *J Bus Econ Stat.* 1983;1:115–26.
50. Stata. Marginal means, adjusted predictions, and marginal effects; A available from: <https://www.stata.com/features/overview/marginal-analysis/>. Accessed January, 2024
51. Alberta Health. Health data, research and standards: health research data access; Available from: <https://www.alberta.ca/health-research>. Accessed May 24, 2024
52. Freedman MS, Devonshire V, Duquette P, et al. Treatment optimization in multiple sclerosis: Canadian MS working group recommendations. *Can J Neurol Sci.* 2020;47:437–55.
53. Bebo B, Cintina I, LaRocca N, et al. The economic burden of multiple sclerosis in the United States: estimate of direct and indirect costs. *Neurology.* 2022;98:e1810–e7.
54. Schauf M, Chinthapatla H, Dimri S, Li E, Hartung DM. Economic burden of multiple sclerosis in the United States: a systematic literature review. *J Manag Care Spec Pharm.* 2023;29:1354–68.
55. Kobelt G, Thompson A, Berg J, Gannedahl M, Eriksson J. New insights into the burden and costs of multiple sclerosis in Europe. *Mult Scler.* 2017;23:1123–36.
56. McKay KA, Tremlett H, Zhu F, Kastrukoff L, Marrie RA, Kingwell E. A population-based study comparing multiple sclerosis clinic users and non-users in British Columbia, Canada. *Eur J Neurol.* 2016;23:1093–100.

57. Fogarty E, Walsh C, McGuigan C, Tubridy N, Barry M. Direct and indirect economic consequences of multiple sclerosis in Ireland. *Appl Health Econ Health Policy*. 2014;12:635–45.
58. Kobelt G. Costs and quality of life for patients with multiple sclerosis in Belgium. *Eur J Health Econ*. 2006;7 Suppl 2:24–33.
59. Rae-Grant A, Day GS, Marrie RA, et al. Practice guideline recommendations summary: disease-modifying therapies for adults with multiple sclerosis: report of the guideline development, dissemination, and implementation subcommittee of the American Academy of Neurology. *Neurology*. 2018;90:777–88.
60. Graves JS, Krysko KM, Hua LH, Absinta M, Franklin RJM, Segal BM. Ageing and multiple sclerosis. *Lancet Neurol*. 2023;22:66–77.
61. Batcheller L, Baker D. Cost of disease modifying therapies for multiple sclerosis: Is front-loading the answer? *J Neurol Sci*. 2019;404:19–28.
62. Navarro CE, Ordóñez-Callamand E, Alzate JP. Disease modifying therapies in multiple sclerosis: cost-effectiveness systematic review. *Farm Hosp*. 2020;44:68–76.