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Disease-Modifying Drugs for Multiple Sclerosis and Association With Survival

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Abstract

Background and Objectives

We examined the association between the disease-modifying drugs (DMDs) for multiple sclerosis (MS) and survival in a multiregion population-based study.

Methods

We accessed multiple administrative health databases from 4 Canadian provinces. Persons with MS were identified and followed from the most recent of the first MS or demyelinating event or January 1, 1996 (index date), until death, emigration, or December 31, 2017. Association between the first-generation and second-generation DMDs and all-cause mortality was examined using stratified Cox proportional hazard models, reported as adjusted hazard ratios (aHRs). Timing of DMD initiation was explored, with findings reported at 2, 5, or 10 years postindex date, representing very early, early, or late initiation.

Results

We identified 35,894 persons with MS; 72% were female. The mean age at index date was 44.5 years (SD = 13.6). The total person-years of follow-up while DMD-exposed was 89,180, and total person-years while unexposed was 342,217. Compared with no exposure, exposure to any DMD or to any first-generation DMD was associated with a 26% lower hazard of mortality (both aHRs 0.74; 95% CI 0.56–0.98), while any second-generation DMD exposure was associated with a 33% lower hazard (aHR 0.67; 95% CI 0.46–0.98). Earlier DMD initiation (beta-interferon or glatiramer acetate vs no exposure) was associated with a significant mortality effect ($p < 0.05$), while later initiation was not (95% CIs included 1). However, the survival advantage with earlier initiation diminished over time, no longer reaching statistical significance at 15 years postindex date.

Discussion

Our study demonstrates an association between the DMDs for MS and improved survival in the real-world setting.

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Glossary

aHR = adjusted hazard ratio; **DMD** = disease-modifying drug; ***ICD-9/10*** = *International Classification of Diseases, 9th/10th Revision*; **MS** = multiple sclerosis; **NPV** = negative predictive value.

Multiple sclerosis (MS) is a chronic immune-mediated disease affecting the CNS. Survival is negatively affected by MS, with life expectancy typically reduced by approximately 6–14 years compared with the general population.[1-4] While improvements in life expectancy have been observed in persons with MS over time, these have generally mirrored the improvements seen in the general population.[1-3]

Whether the rapid uptake and use of the disease-modifying drugs (DMDs) to treat MS has improved survival remains poorly understood. This is in part because the safety and efficacy of the DMDs for MS are typically examined in randomized clinical trials conducted over 2–3 years; a time frame insufficiently long to ascertain a potential impact on survival.[5] Although investigators of 1 clinical trial (of beta-interferon) tried to provide a longer-term estimate of the potential effects of DMD on mortality,[6] several study design–related concerns were raised.[7] Thus, while randomized clinical trials are constrained in measuring the long-term effects of DMD treatments on survival, studies using real-world data can fill this knowledge gap.[8] A recent nested case-control study showed that persons treated with beta-interferon for more than 3 years had a survival advantage over nontreated persons with MS.[9] Whether other DMDs provide similar survival advantages is unknown. Furthermore, although evidence suggests that early DMD initiation may benefit disability-related outcomes,[10-13] the long-term effects on survival remain uncertain.[9,14]

We examined the effects of DMD exposure on survival in a MS population by using linked administrative health data collected over 20 years.

Methods

Data Sources

We used a multiregion, population-based observational study design. We accessed multiple administrative health data sets from 4 provinces, comprising approximately 25% of Canada's population (British Columbia, Saskatchewan, Manitoba, and Nova Scotia).[15] Each provincial government delivers healthcare services to more than 98% of the population.[16-18] The administrative data were linked for each person within each province and included provincial health insurance registries[19]; providing demographics (sex, birthdates, residency status, place of residency [first 3-digit postal codes], and for Saskatchewan and Manitoba, death dates); physician visits; and hospitalizations,[20,21] including diagnostic codes (*International Classification of Diseases* [*ICD*]*-9/10*). Thus, all diagnostic codes were based on either a physician visit (and represent claims/billing data) or a hospitalization and were assigned at discharge based on the most likely reason(s) for that hospitalization (as determined by the attending physician[s]). Vital statistics provided death dates in British Columbia[22] and Nova Scotia, and prescription data captured information on all prescriptions filled (dates, quantity, and/or number of days supplied) at outpatient and community pharmacies in British Columbia,[23] Saskatchewan, and Manitoba. Records of DMD use in Nova Scotia including start and stop dates were provided by the Dalhousie MS Research Unit database.

Study Population

We used an algorithm to identify MS cases. The algorithm has been validated and used across multiple Canadian provinces and required ≥3 MS-specific physician visits and/or hospitalizations with an ICD-9/10 340/G35 code or a prescription filled for a MS DMD ever, in any combination.[24,25] The index date (representing the start of follow-up) was the most recent of the first MS or related demyelinating disease diagnostic code or MS DMD prescription filled (eTable 1, links.lww.com/NXI/A729); the person's 18th birthday; or January 1, 1996 (British Columbia), April 1, 1996 (Manitoba), January 1, 1997 (Saskatchewan), or January 1, 1998 (Nova Scotia). These dates represent the first date of prescription data availability within each province and the first full calendar or fiscal year that the MS DMDs became available through each provincial government's universal health insurance plan. Most persons would not have been exposed a DMD before the index date apart from a very small number of persons that may have been randomized to receive a DMD as part of a clinical trial.[25]

The study end date was the earlier of death, cancellation of health insurance plan, December 31, 2017 (British Columbia, Manitoba, and Nova Scotia), or March 31, 2018 (Saskatchewan).

One year of residency preindex date was required to determine cohort characteristics at index date. These included age, calendar year (categorized as 1996–1999, 2000–2005, 2006–2011, or 2012–2017/18), sex, socioeconomic status (measured by neighborhood income quintiles based on each person's postal code),[26] and comorbidity status (using a modified Charlson Comorbidity Index, excluding hemiplegia/paraplegia to avoid misclassifying MS-related symptoms as comorbidity).[27,28]

Outcome and Exposure

The primary outcome was all-cause mortality (i.e., death because of any cause).

Exposure to a DMD was defined as ≥6 months (180 days) of cumulative use for beta-interferon and glatiramer acetate and 3 months (90 days) of cumulative use for natalizumab,

fingolimod, dimethyl fumarate, and teriflunomide. The duration of DMD exposure was measured using the days supplied (available in British Columbia and Manitoba), the quantity dispensed (Saskatchewan), or the start and stop dates (available in Nova Scotia). Gaps in DMD supply of ≤30 days were allowed.[29] For alemtuzumab and ocrelizumab, exposure was defined after 3 months (90 days) had elapsed from the date of first prescription filled or, for Nova Scotia, from the documented start date. These exposure definitions were guided by the minimum length of time required to yield a clinical response.[9,30-32] DMD exposure status was updated over time (i.e., was treated as time-varying), and a person could reach the definition for exposure to 1 or more individual DMDs (e.g., due to switching therapy) during the study period. Once the definition for exposure was reached, a person was considered "exposed" to that DMD until that person's study end date; before that, a person was considered unexposed (i.e., had either no or very minimal exposure) to that DMD.

We assessed DMD use, primarily as exposure to any DMD (the alternative being no/minimal exposure) and then by generation: first (beta-interferon and glatiramer acetate) and second (natalizumab, fingolimod, dimethyl fumarate, teriflunomide, alemtuzumab, and ocrelizumab). Second, as an exploratory approach, the DMDs were also assessed based on 3 groups according to expected efficacy: lower (beta-interferon, glatiramer acetate, and teriflunomide), moderate (fingolimod and dimethyl fumarate), and higher (natalizumab, alemtuzumab, and ocrelizumab).[33-35] Finally, and when feasible, individual DMDs were examined, as guided by an a priori power calculation. Specifically, using a 2-tailed test with a 5% probability of a type I error, we anticipated having a minimum power of 80% to detect a hazard ratio for mortality of 0.7–0.8 for beta-interferon, glatiramer acetate, and dimethyl fumarate relative to no exposure.

Statistical Analyses

Cohort characteristics were described, using counts and proportions for categorical and means and SDs for continuous variables. Crude mortality rates per 1,000 person-years of follow-up were also reported. We examined the effects of DMD exposure on all-cause mortality using a multivariable stratified Cox proportional hazard model (stratified by calendar year at the index date, thus allowing for a different baseline hazard function for each strata and accounting for different patterns of healthcare use over time). Exposure to a DMD (any DMD, then by generation, relative presumed efficacy and individual DMD) was included as a time-varying covariate. All models were adjusted for characteristics at index date, including age, Charlson Comorbidity Index (categorical; 0, 1, 2, ≥3), sex, and socioeconomic status. Analyses were conducted separately in each province, with results combined using random-effects meta-analyses. Findings were reported as adjusted hazard ratios (aHRs) and 95% CIs.

The proportional hazards assumptions were examined by an interaction term between covariates and log(follow-up), with follow-up defined as the time from the index date to study end. Assumptions were not met for the first-generation DMDs—beta-interferon and glatiramer acetate, indicating that the hazard ratios for these varied over time. As this was worthy of further exploration, we examined the effects of the timing of first exposure (i.e., when the minimum cumulative exposure threshold was reached, as defined earlier) to each of these DMDs individually, then combined as any first-generation DMD. This was performed by including 2 interaction terms between DMD exposure status and log(time from the index date to first DMD exposure) and log(follow-up). Findings were reported by timing of first DMD exposure (at 2, 5, and 10 years postindex, representing very early, early, and late initiation) and duration of follow-up (at 2, 5, 10, and 15 years). The other covariates that did not meet the proportional hazards assumptions (i.e., age and Charlson Comorbidity Index), and their interaction terms with log(follow-up), were also included in the model.

Complementary analyses were conducted in the largest province, British Columbia, including (1) sex-specific analyses, using an interaction term between sex and DMD exposure; (2) an 'intention-to-treat' analysis, whereby DMD exposure was defined as ≥1 day; and (3) a dose-response assessment for each of the first-generation DMDs—beta-interferon and glatiramer acetate, categorized as no/minimal exposure (<6 months), shorter (6 months–3 years), and longer exposure (>3 years). Findings were reported at 3, 5, and 10 years of follow-up for beta-interferon as the hazard ratio for this varied over time (e.g., proportional hazards assumption was not met).

Statistical analyses were performed using SAS software version 9.4 and R version 4.0.2.

Standard Protocol Approvals, Registrations, and Patient Consents

This study was registered with ClinicalTrials.gov (NCT04472975), and approvals were obtained from the Research Ethics Boards at the University of British Columbia and University of Saskatchewan (harmonized ethics: #H18-00407), University of Manitoba (#HS21764), and Nova Scotia Health Authority (#1023555).

Data Availability

As we are not the data custodians, we are not authorized to make the data available. With the appropriate approvals, the data may be accessed through the Population Data British Columbia, Saskatchewan Health Quality Council, Manitoba Centre for Health Policy, and Health Data Nova Scotia of Dalhousie University.

Results

We identified 35,894 persons with MS across the 4 provinces, of whom 25,777 (72%) were female (Table 1). The mean age (SD) at the index date was 44.5 (13.6) years, and 22% (n = 7,872) had at least 1 comorbidity. Over one-quarter met the

Table 1 Characteristics of the Multiple Sclerosis Study Population From 4 Canadian Provinces (1996–2017/18)

Characteristics	Overall cohort (n = 35,894)
Sex, n (%)	
Female	25,777 (71.8)
Male	10,117 (28.2)
Age at index date, y, mean (SD)	44.5 (13.6)
Socioeconomic status,[a] n (%)	
1 (lowest income quintile)	6,429 (17.9)
2	6,916 (19.3)
3	8,074 (22.5)
4	7,384 (20.6)
5 (highest income quintile)	7,091 (19.8)
Charlson Comorbidity Index,[b] n (%)	
0	28,022 (78.1)
1	5,588 (15.6)
2	1,479 (4.1)
≥3	805 (2.2)
Calendar year at index date, n (%)	
1996–1999	16,498 (46.0)
2000–2005	7,198 (20.1)
2006–2011	6,456 (18.0)
2012–2018	5,742 (16.0)
No. of individuals exposed[c] to a DMD, during follow-up,[d] n (%)	
Any DMD	9,472 (26.4)
Any first-generation DMD[e]	8,156 (22.7)
Beta-interferon[f]	5,813 (16.2)
Glatiramer acetate	3,373 (9.4)
Any second-generation DMD[e]	3,306 (9.2)
Natalizumab	544 (1.5)
Fingolimod	682 (1.9)
Dimethyl fumarate	1,558 (4.3)
Teriflunomide	890 (2.5)
Alemtuzumab	262 (0.7)
Ocrelizumab	<6 (<0.1)
Any lower efficacy DMD (beta-interferon, glatiramer acetate, teriflunomide)	8,538 (23.8)
Any moderate efficacy DMD (fingolimod, dimethyl fumarate)	2,146 (6.0)
Any higher efficacy DMD (natalizumab, alemtuzumab, ocrelizumab)	766 (2.1)
No DMD exposure[g]	26,422 (73.6)
Person-years of follow-up: total	431,397
Person-years of follow-up after first exposure to	
Any DMD	89,180
Any first-generation DMD	86,025
Beta-interferon[f]	66,149
Glatiramer acetate	28,731
Any second-generation DMD	9,492
Natalizumab	2,780
Fingolimod	1,980
Dimethyl fumarate	3,927
Teriflunomide	1,580
Alemtuzumab	293
Ocrelizumab	<6
Any lower efficacy DMD (beta-interferon, glatiramer acetate, teriflunomide)	86,668
Any moderate efficacy DMD (fingolimod, dimethyl fumarate)	5,745
Any higher efficacy DMD (natalizumab, alemtuzumab, ocrelizumab)	3,018
No DMD exposure	342,217

Abbreviation: DMD = disease-modifying drug.
As per data privacy and access agreements, small cell sizes (<6 individuals within any group) are suppressed.
[a] Socioeconomic status closest to the index date (measured as neighborhood income quintiles based on postal code of the person's residence). If socioeconomic status was not available (n = 841), then it was assigned as quintile 3.
[b] Comorbidity was measured using the Charlson Comorbidity Index (based on physician and hospital-derived diagnoses recorded in the year preindex date, excluding hemiplegia/paraplegia).
[c] Defined as at least 6-month cumulative exposure to beta-interferon or glatiramer acetate; 3-month cumulative exposure to natalizumab, fingolimod, dimethyl fumarate, or teriflunomide; or 3 months from the date of first prescription filled for alemtuzumab and ocrelizumab.
[d] Follow-up was from the index date until the earliest of death, emigration from the province, or December 31, 2017 (British Columbia, Manitoba, and Nova Scotia), or March 31, 2018 (Saskatchewan) [study end date].
[e] Some people met the minimum cumulative exposure for >1 DMD; hence, the sum of the individual first-generation or second-generation DMDs exceeds the sum of any first-generation or second-generation DMD.
[f] All beta-interferon products were considered as one class.
[g] Defined as no exposure or less than 6-month contiguous exposure to beta-interferon and glatiramer acetate; less than 3-month contiguous exposure to natalizumab, fingolimod, dimethyl fumarate, or teriflunomide; or less than 3 months from the date of first prescription filled for alemtuzumab and ocrelizumab.

definition for minimum cumulative exposure to a DMD during follow-up and were considered exposed. The most common DMD used was beta-interferon (16%) followed by glatiramer acetate (9%). The total person-years of follow-up between the index date and study end was 89,180 while exposed to a DMD and 342,217 while unexposed.

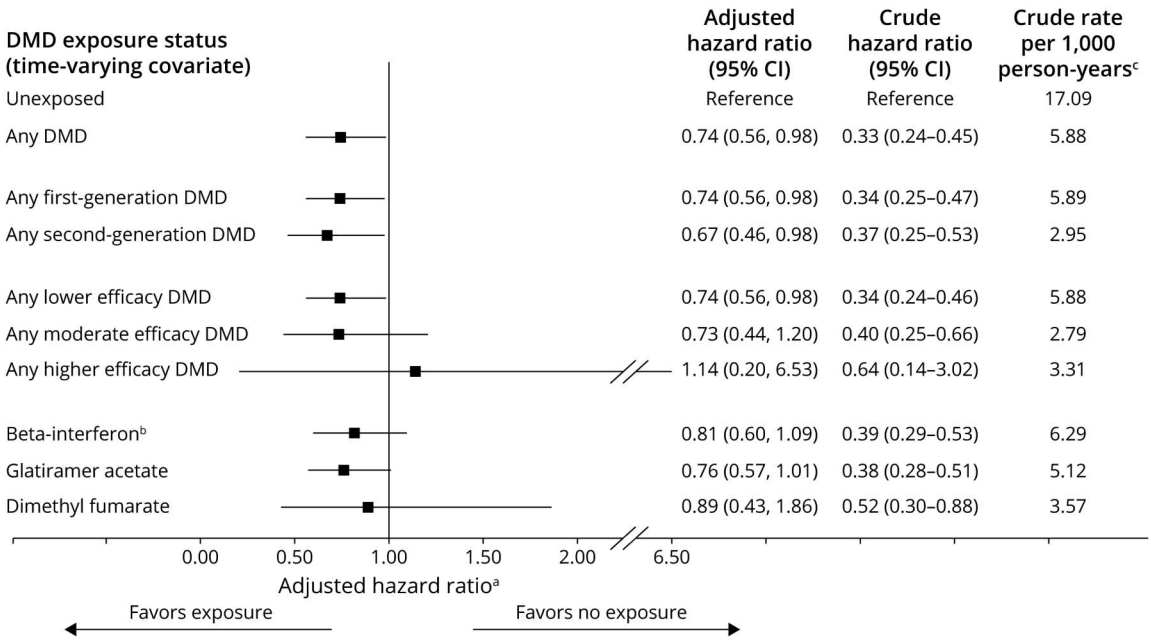
Overall, we observed 6,374 deaths because of any cause, with 524 of those who died being exposed to at least 1 DMD at any point during the study. Relative to no/minimal exposure, any DMD was associated with a 26% (aHR 0.74; 95% CI 0.56–0.98) lower hazard of mortality (Figure 1). The findings remained the same when restricted to any first-generation DMD (vs no/minimal exposure), and a 33% lower mortality was observed for the second-generation DMDs (aHR 0.67; 95% CI 0.46–0.98). Although a lower hazard of mortality was also generally observed when DMD exposure (vs no/minimal exposure) was assessed by relative efficacy (lower, moderate, or higher) or by individual DMD (beta-interferon, glatiramer acetate, and dimethyl fumarate), not all findings reached statistical significance in these smaller subgroups. The strengths of association were largely similar in these subgroups except for the higher efficacy DMDs where few deaths occurred (n = 10) resulting in wide confidence intervals. Similarly, few deaths were observed with dimethyl fumarate (n = 14), also resulting in wide confidence intervals.

When the time-varying effects of the first-generation DMDs were explored, "very early," "early," or "late" initiation, relative to no/minimal exposure, were each associated with a statistically significant lower hazard of mortality (Figure 2). However, regardless of when a first-generation DMD was started, none of the hazard ratios were statistically significant at 15 years of follow-up. A similar diminishing effect was observed when beta-interferon and glatiramer acetate were assessed separately. For example, very early initiation (i.e., first exposure at year 2 postindex date) was associated with a 62%–63% lower hazard of mortality at 2 years of follow-up (i.e., close to DMD initiation), decreasing to 44%–45% at 5 years of follow-up (i.e., 3 years after first exposure), and 24%–28% at 10 years of follow-up (i.e., 8 years after first exposure), the latter of which reached significance for glatiramer acetate only. At 15 years of follow-up, this diminished even further, to a 9%–13% lower hazard of mortality. Although 'late' initiation (i.e., first exposure at year 10 postindex date) of beta-interferon and glatiramer acetate was also associated with a lower hazard, findings did not reach significance (95% CIs included 1). Of note (and as expected), the number of people at risk of the outcome decreased over time as the duration of follow-up increased (Table 2).

Complementary Analyses

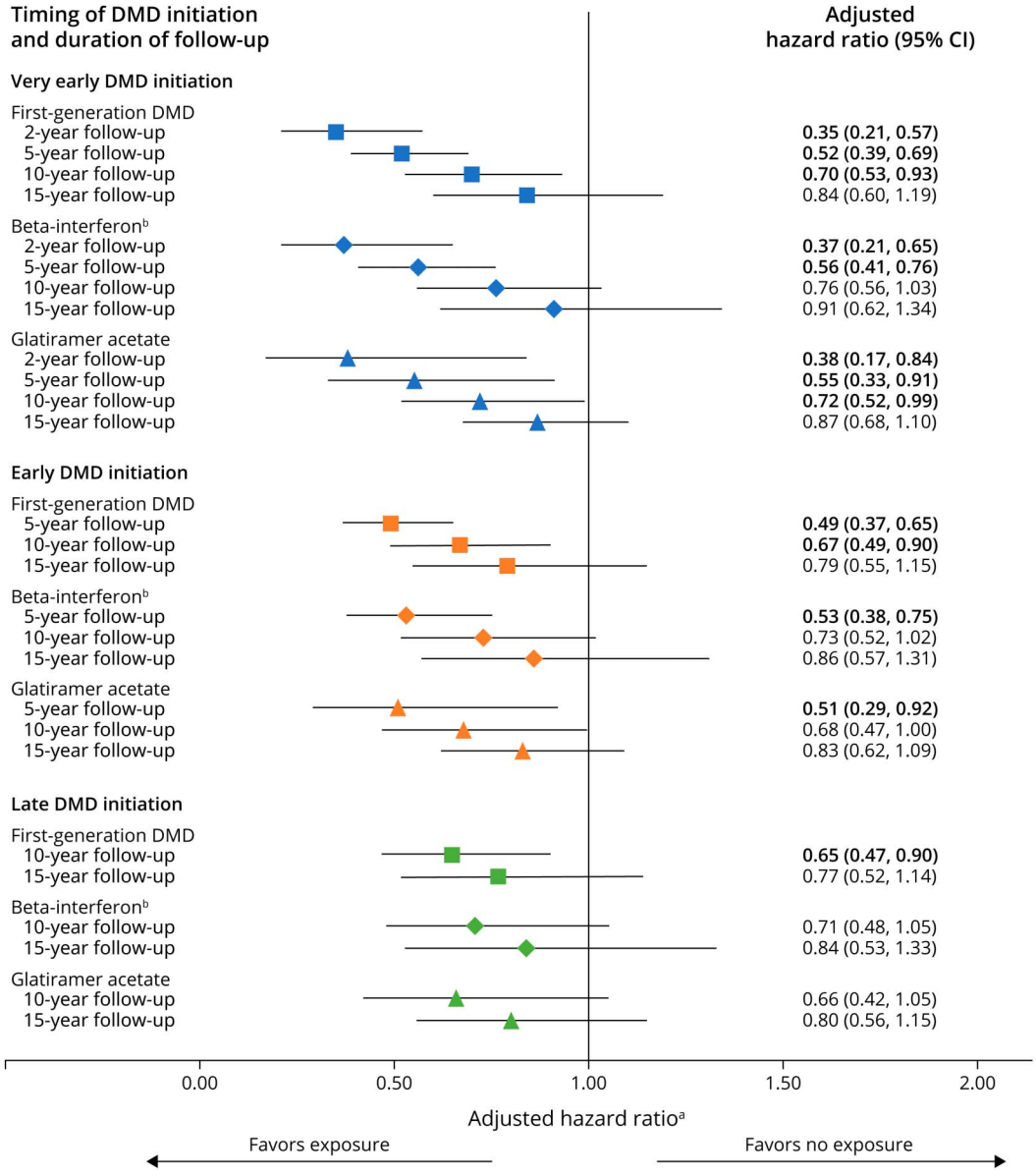
The direction of findings was similar between the sexes (Figure 3). Some hazard ratios for mortality were lower for male patients than female patients, although the p values for the interaction term between sex and DMD exposure were >0.2. Findings from the "intention-to-treat" analyses (performed in British Columbia) were also consistent with that

Figure 1 DMD Use for Multiple Sclerosis and Hazard of All-Cause Mortality



[a]Results from each of the 4 provinces were adjusted for sex, age, Charlson Comorbidity Index, and socioeconomic status at index date, and exposure to other DMDs (by generation, efficacy, or individual DMD) as a time-varying covariate, and were then combined using random-effects meta-analyses. [b]All beta-interferon products were considered as one class. [c]Person-years of follow-up for the calculation of crude rate were as per Table 1. Lower efficacy DMDs: beta-interferon, glatiramer acetate, and teriflunomide; moderate: fingolimod and dimethyl fumarate; higher: natalizumab, alemtuzumab, and ocrelizumab. DMD = disease-modifying drug.

Figure 2 The Association Between Exposure to a First-Generation DMD and All-Cause Mortality by Timing of Drug Initiation (Very Early, Early, or Late) and Duration of Follow-Up



[a]Results from each of the 4 provinces were adjusted for sex, age, Charlson Comorbidity Index, and socioeconomic status at index date, and exposure to other DMDs (by generation or individual DMD) as a time-varying covariate, and were then combined using random-effects meta-analyses. Interactions between DMD exposure and log(time from the index date to first DMD exposure) and log(follow-up) were included. Covariates that did not meet the proportional hazards assumptions (i.e., age and Charlson Comorbidity Index) and their interaction terms with log(follow-up) were also included in the model. Reference category: unexposed. [b]All beta-interferon products were considered as one class. Bold indicates $p < 0.05$. Very early, early, or late DMD initiation = minimum cumulative DMD exposure reached at year 2, 5, or 10 from the index date, respectively. Follow-up was defined as the period from the index date to study end and reported at 2, 5, 10, and 15 years of follow-up. DMD = disease-modifying drug.

province's main findings (Figure 4). The proportion of the DMD-exposed population based on the "at least 1 day" criterion in the intention-to-treat analysis was approximately 3% higher than the proportion of the DMD-exposed population included in the main analyses (which used the "minimum cumulative DMD exposure" criterion) (data not shown).

For the dose-response assessment, and relative to no/minimal exposure (<6 months), a shorter exposure to glatiramer acetate (6 months–3 years) was not associated with a lower hazard of mortality (aHR 1.07; 95% CI 0.74–1.54), and while a longer exposure (>3 years) was, by 23%, this failed to reach statistical significance (aHR 0.77; 95% CI 0.51–1.17) (Figure 5). For beta-interferon, both shorter and longer exposures (vs no/minimal exposure) were associated with a lower hazard of mortality, but this changed over time. For example, at 5 years of follow-up, shorter exposure times (ranging from 6 months to 3 years) were associated with a 42% (HR 0.58; 95% CI 0.39–0.84) lower hazard of mortality. This increased to a 78% (HR 0.22; 95% CI 0.11–0.46) lower

Table 2 Number of People Who Were Alive and Residing in the Study Regions by Timing of DMD Initiation and Duration of Follow-Up

No. of people who were alive and residing in the study regions at	Initiated first DMD between 0 and 2 y from the index date			Initiated first DMD between >2 and 5 y from the index date			Initiated first DMD between >5 and 10 y from the index date			No exposure		
	First-generation DMD	Beta-interferon	Glatiramer acetate	First-generation DMD	Beta-interferon	Glatiramer acetate	First-generation DMD	Beta-interferon	Glatiramer acetate	No exposure to any first-generation DMD	No exposure to beta-interferon	No exposure to glatiramer acetate
2 y of follow-up[a]	4,221	2,831	1,442	—	—	—	—	—	—	24,838	27,066	29,490
5 y of follow-up[a]	3,563	2,500	1,108	2,089	1,620	797	—	—	—	20,557	22,399	24,824
10 y of follow-up[a]	2,368	1,816	578	1,714	1,375	580	1,037	861	553	14,963	16,132	18,393
15 y of follow-up[a]	1,280	1,004	288	1,278	1,049	353	855	721	394	10,260	10,995	12,666

Abbreviation: DMD = disease-modifying drug.
All beta-interferon products were considered as one class.
[a] Follow-up was defined as the time from the index date (up to the study end). Overlap between the follow-up periods was permissible (e.g., persons with 10 years of follow-up would, by definition, also be represented within the 2 and 5 years of follow-up cells).

hazard with a longer exposure (>3 years). However, at year 10 of follow-up, only a longer exposure to beta-interferon was associated with a lower hazard of mortality, by 56% (HR 0.44; 95% CI 0.32–0.60), while the shorter exposure period was not.

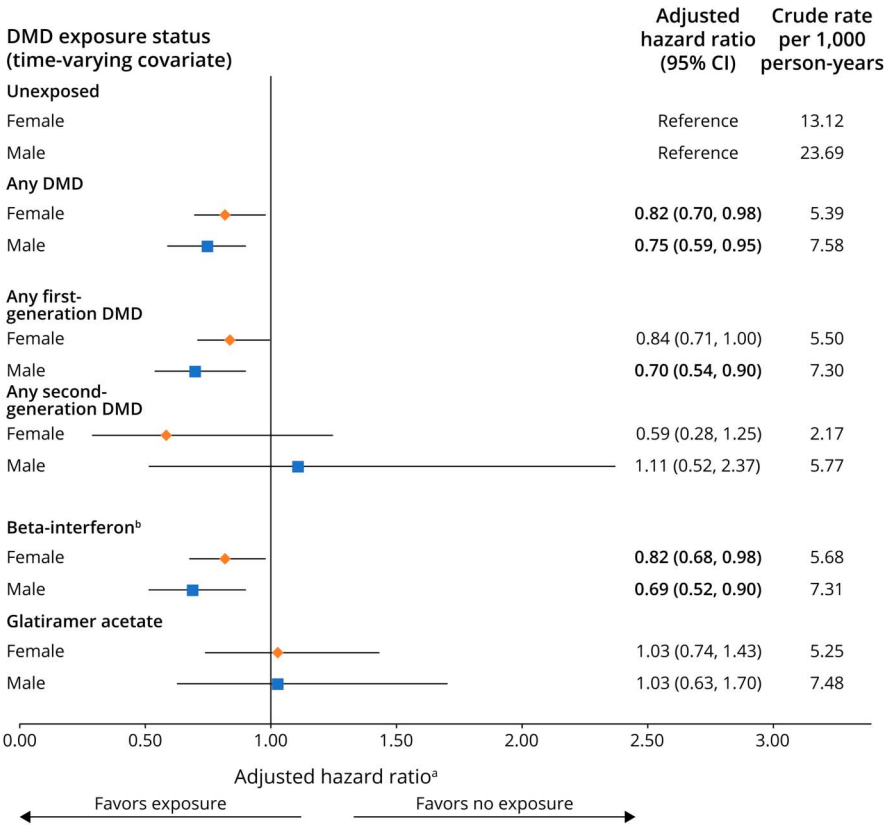
Discussion

We assessed the association between DMD exposure and survival in a multiregion population-based study using linked administrative health data collected over 20 years, including nearly 90,000 DMD-exposed person-years of follow-up. Overall, exposure to any DMD, or any first-generation or second-generation DMD, was associated with a lower hazard of mortality (by 26%–33%) relative to no exposure. When examined by individual DMD, although early initiation of a beta-interferon, or of glatiramer acetate (vs no exposure), was associated with a lower hazard of mortality, this association diminished as the time since first exposure increased. Our study provides evidence of an association between DMD exposure and improved survival in the real-world setting.

We found relatively few studies with which to compare our findings. A previous nested case-control study of nearly 6,000 persons with relapsing-remitting MS who attended an MS clinic in British Columbia, Canada, or Rennes, France, showed that exposure to beta-interferon, relative to no or minimal exposure (<6 months), was associated with a 32% lower mortality risk.[9] Furthermore, a longer exposure to beta-interferon (>3 years) was associated with a 56% lower risk of mortality.[9] Although our results concur with these prior findings, we were also able to extend them by accessing a larger study cohort, comprising more than 35,000 persons with MS. This enabled, for example, one of the first assessments of the survival benefits of the second-generation DMDs, as well as the first-generation DMD, glatiramer acetate. Another smaller population-based cohort study in Taiwan with nearly 1,150 persons with MS followed for a mean of 54.3 months reported survival benefits among persons treated with any first-generation DMD (beta-interferon or glatiramer acetate).[36] However, the introduction of "immortal time" (i.e., a time period during which the outcome could not have happened because of the exposure definition) into the study design hinders the interpretation of findings.[37] Finally, a study of 366 persons with MS previously enrolled in a clinical trial, reported a 47% reduction in mortality risk among those initially randomized to receive beta-interferon, compared with placebo.[6] However, concerns regarding the post hoc nature of the survival analyses have been raised for this study, as well as the absence of baseline information on potential confounders for all-cause mortality.[7]

The first-generation DMDs have been on the market for the longest period of time, relative to the second-generation of DMDs, which meant that we could also explore the effects of the timing of beta-interferon and glatiramer acetate initiation. We found evidence to suggest that very early or early initiation

Figure 3 DMD Use for Multiple Sclerosis and Hazard of All-Cause Mortality by Sex

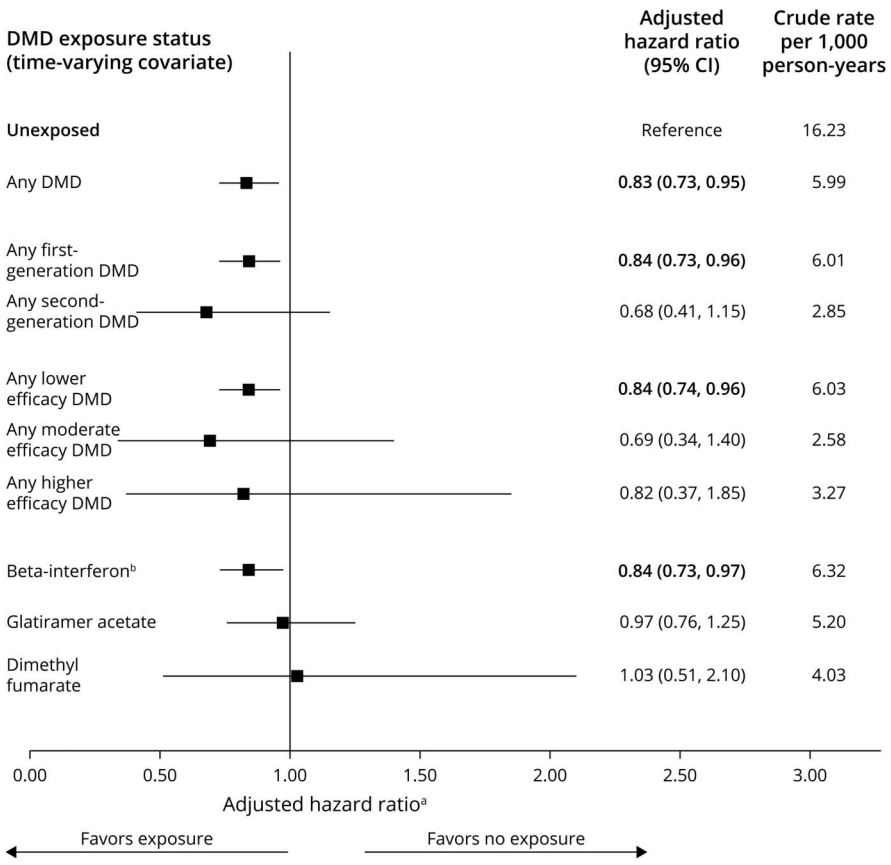


[a]Results shown are based on the largest province (British Columbia) and were adjusted for age, Charlson Comorbidity Index, and socioeconomic status at index date, and exposure to other DMDs (by generation or individual DMD) as a time-varying covariate. Hazard ratios were estimated by introducing interaction terms between sex and DMD exposure variables. Findings are not shown when a small number of deaths (<6) occurred in a subgroup, as per privacy and data access requirements (i.e., for dimethyl fumarate by sex or by the DMD efficacy groupings). [b]All beta-interferon products were considered as one class. *p* Values for the interaction term between sex and exposure to (1) any DMD = 0.50; (2) any first-generation DMD = 0.23; (3) any second-generation DMD = 0.24; (4) beta-interferon = 0.29; (5) glatiramer acetate = 0.99. Bold indicates $p < 0.05$. DMD = disease-modifying drug.

(at years 2 or 5 postindex date) of beta-interferon or glatiramer acetate was associated with a significant reduction in mortality risk, but this survival advantage diminished after a longer follow-up period. The one previous study to examine this issue was unable to determine whether initiation of beta-interferon within 5 years of MS onset was advantageous due to the modest number of persons who were early initiators.[9] Despite the emphasis on starting DMD treatment early to maximize "brain health,"[38,39] the effects of early treatment on mortality for persons with MS were previously unknown. Early initiation of a DMD has been associated with better clinical outcomes, such as lower risk of disease activity and progression, as well as a lower chance of drawing on a government-funded disability pension.[10-13] Our observation that the apparent effect of DMD treatment on mortality decreased as the duration of follow-up since first exposure to beta-interferon or glatiramer acetate increased concurs with the known clinical effects of these drugs.[38,39] Specifically, while short-term efficacy on relapse risk has been demonstrated, this seems to diminish with time,[5] and a Cochrane review concluded that the anti-inflammatory effects of beta-interferon did not prevent permanent disability once the progressive phase was established.[40] A diminishing effect of DMD treatment over time also concurs with the natural history of MS relapses which reduce in frequency as disease duration increases.[41] It is also plausible that, over time, the DMDs have less impact on survival in older persons with MS because death may occur due to accumulating frailty from other causes. However, our observation might also be partly explained by other factors, for example, over time, as more people die, the number of people at risk of the outcome will naturally decrease (resulting in a smaller sample size as the duration of follow-up increases; Table 2). Although we included calendar year at the index date in all of our models, it remains possible that other factors may have influenced our observations, such as disease duration[2,4] or changes in MS appearance or severity over time because of changes in case ascertainment, recognition, and diagnosis of MS.[42]

When we explored the association between DMD exposure and survival by relative efficacy of the drug (vs no exposure), a lower hazard of mortality was generally observed. However, only a modest number of deaths occurred among those exposed to a higher efficacy DMD, resulting in wide confidence interval. A study, published in 2021, of 1,000 DMD-treated persons with secondary progressive MS reported that high-efficacy DMDs (e.g., fingolimod, mitoxantrone, and natalizumab) were more effective than low-efficacy DMDs (beta-interferon, glatiramer acetate, and teriflunomide) in reducing relapses among persons with active disease.[43] However, no significant differences were observed between high-efficacy and low-efficacy DMDs and the risk of disability progression.

Figure 4 Exposure to at Least 1 Day of a DMD for Multiple Sclerosis and Hazard of All-Cause Mortality (Intention-to-Treat Analysis)

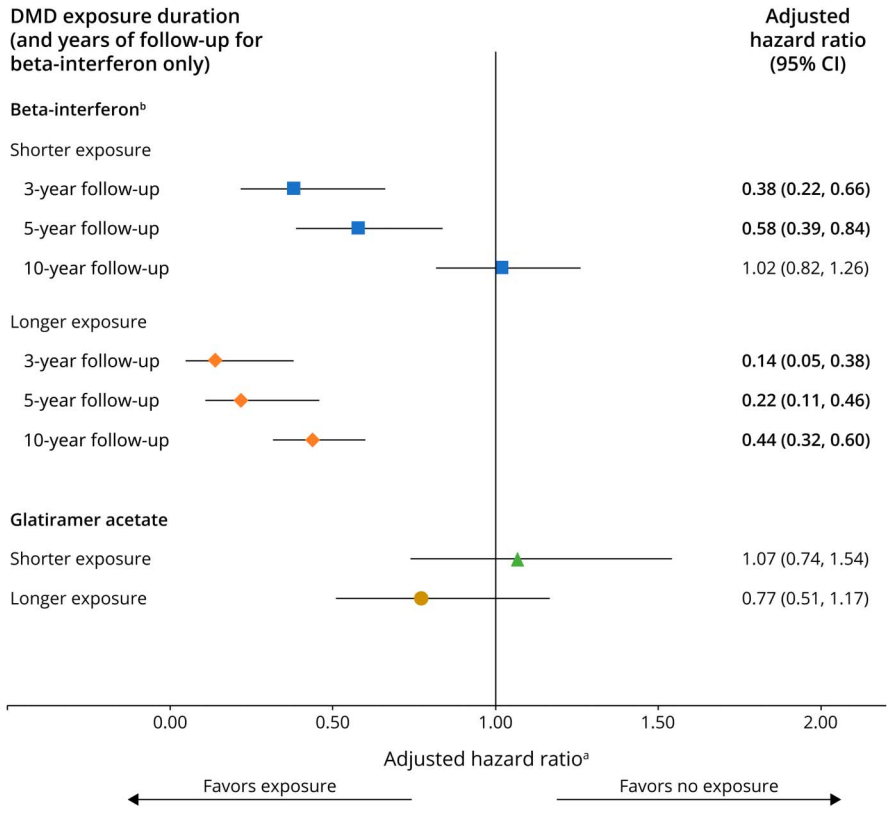


[a]Results shown are based on the largest province (British Columbia) and were adjusted for age, sex, Charlson Comorbidity Index, and socioeconomic status at index date, and exposure to other DMDs (by generation, efficacy, or individual DMD) as a time-varying covariate. [b]All beta-interferon products were considered as one class. Bold indicates $p < 0.05$. DMD = disease-modifying drug.

Studies of mortality in MS require a substantial follow-up period because MS is typically not a rapidly fatal disease.[1-3] Thus, the MS DMDs approved more recently or reserved as second-line or third-line therapies had yet to accrue sufficient time on the market or uptake in the MS population for their impact on survival to be assessed. For example, although we estimated that our sample size was sufficient to explore the mortality outcomes for dimethyl fumarate, the actual number of deaths in this subgroup was lower than anticipated. In addition, there is potential for residual confounding, as with all observational studies. However, we were able to adjust for several important characteristics including age, sex, socioeconomic status, and comorbidity in all models and used a multivariable stratified Cox proportional model (stratified by calendar year at the index date, thus accounting for different patterns of healthcare use over time). Nonetheless, we were not able to account for factors not captured in the administrative health data, such as lifestyle (e.g., alcohol intake, smoking status, and physical activity), race/ethnicity, or the MS disease duration, phenotype, or disability level. We also recognize that accurately determining an individual's MS disease duration is inherently challenging. This is especially true given the recent observations that the disease may be present 5–10 years (or more) before classical onset of MS.[44]

Owing to the nature of our data, we were not able to infer causality for the identified associations. While we cannot preclude confounding by indication, whereby individuals with more active or severe disease are more likely to start drug, this would imply that our findings are a conservative estimate of the survival benefits of DMDs. It is also possible that a person stopping a DMD because of lack of response or serious adverse event before they reached the definition of exposed would have been assigned to the "unexposed" group. Nonetheless, our complementary intention-to-treat analyses yielded findings which were consistent with the main analyses. Furthermore, although our complementary "dose-response" analyses showed an association between longer DMD exposures and survival benefit, and was adjusted for comorbidity burden, we cannot preclude "healthy user bias," whereby people who used a DMD for a longer period of time may be healthier and at lower risk of mortality. Although we did not assess these factors in detail, including DMD treatment adherence, previous studies have shown that adherence to DMD is generally quite high in the MS population.[18,45] We did not explore the specific causes of death because its distribution can be influenced by differences in coding practices, interpretation, and recording among physicians.[1] The very small event rates by various specific causes of death would also have

Figure 5 Beta-Interferon and Glatiramer Acetate for the Treatment of Multiple Sclerosis and Hazard of All-Cause Mortality: Dose-Response Assessments by Duration of Exposure



Cumulative exposure was modeled as 3 levels: no/minimal exposure (<6 months [reference category]), shorter exposure (6 months–3 years), and longer exposure (>3 years). 2,641 people reached the definition of a shorter exposure to beta-interferon, and 1,498 people reached the definition of a longer exposure. 1,239 people reached the definition of a shorter exposure to glatiramer acetate, and 536 people reached the definition of a longer exposure. [a]Results shown are based on the largest province (British Columbia) and were adjusted for age, sex, Charlson Comorbidity Index, and socioeconomic status at index date, and exposure to other individual DMDs as a time-varying covariate. Because the proportional hazards assumption for beta-interferon was not met, hazard ratios were estimated by introducing interaction terms between beta-interferon exposure and log(-follow-up), with follow-up defined as the period from the index date to study end. [b]All beta-interferon products were considered as one class. DMD = disease-modifying drug.

hindered the generation of reliable estimates.[9] The Charlson Comorbidity Index is an assessment tool designed to predict long-term mortality,[46] and we used this in our study to measure, and adjust for, comorbidity burden. This comorbidity index includes significant comorbidities that are associated with survival, such as congestive heart failure, myocardial infarction, diabetes, and vascular disease (peripheral and cerebrovascular).

Our study included a large MS population with nearly 36,000 persons and access to objectively collected linked administrative health data which minimizes selection bias. The MS population was identified using a validated case definition of MS which had been successfully applied in the Canadian provinces included in our study.[17,24,47,48] The positive predictive value was 80.5%, and the negative predictive value (NPV) was 75.5% among a population of persons with ≥1 claim for any demyelinating disease.[24] The NPV would be >99% when applied to the general population where more than 98% of individuals have no claims for demyelinating disease. Our access to comprehensive mortality data also included a sizable number of deaths captured over a long follow-up period of up to 22 years. Each provincial government delivers healthcare services to virtually all residents in each province (aside from those covered by the federal government [<2% of the population] such as the military).[16-18] Furthermore, access to provincial prescription data within a universal healthcare setting captured all prescription filled, largely unaffected by an individual's ability to pay. Thus, the proportion of persons exposed to a DMD in our study is likely to be a representative population estimate.[25] We also demonstrated a consistent effect of DMD exposure on mortality for male patients and female patients. Interestingly, some hazard ratios were lower for male patients than female patients, indicating a possible survival advantage among male patients which deserves further examination. Others have highlighted the need for more studies on the potential sex differences in response to DMD treatment.[49]

In conclusion, we found in our study that exposure to any DMD, or any first-generation or second-generation DMD was associated with a lower hazard of mortality compared with no exposure. Furthermore, earlier initiation of beta-interferon or glatiramer acetate was associated with improved survival, although the advantage diminished with longer follow-up. Although it is not feasible to examine survival in MS in the setting of a randomized controlled trial, population-based observational studies provide insights into the survival benefits offered by MS therapies in clinical practice. Our study provides real-world evidence of an association between the DMDs used to treat MS and a survival benefit. The use of all-cause mortality to study the net effects of DMD safety and

effectiveness/efficacy represents an important long-term outcome measure in persons with MS.[1] The findings provide additional insights that could inform decision-making by clinicians and people living with MS surrounding the use of the DMDs. Further work is needed to assess whether the survival benefit extends to other individual DMDs and over even more extended periods.

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Appendix Authors

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Huah Shin Ng, PhD	University of British Columbia, Vancouver, Canada	Conceptualized and designed the study, performed data analysis, interpreted the results, and drafted and revised the manuscript for intellectual content.
Feng Zhu, MSc	University of British Columbia, Vancouver, Canada	Obtained funding, conceptualized and designed the study, performed data analysis, and revised the manuscript for intellectual content.
Elaine Kingwell, PhD	University of British Columbia, Vancouver, Canada	Obtained funding, conceptualized and designed the study, and revised the manuscript for intellectual content.
Shenzhen Yao, MSc	University of Saskatchewan, Saskatoon, and Saskatchewan Health Quality Council, Canada	Performed data analysis, and revised the manuscript for intellectual content.
Okechukwu Ekuma, MSc	University of Manitoba, Winnipeg, Canada	Performed data analysis, and revised the manuscript for intellectual content.
Charity Evans, PhD	University of Saskatchewan, Saskatoon, Canada	Obtained funding and data, conceptualized and designed the study, and revised the manuscript for intellectual content.
John D. Fisk, PhD	Nova Scotia Health Authority, and Dalhousie University, Halifax, Canada	Obtained funding and data, conceptualized and designed the study, and revised the manuscript for intellectual content.

Continued

Appendix *(continued)*

Name	Location	Contribution
Ruth Ann Marrie, MD, PhD	University of Manitoba, Winnipeg, Canada	Obtained funding and data, conceptualized and designed the study, and revised the manuscript for intellectual content.
Yinshan Zhao, PhD	University of British Columbia, Vancouver, Canada	Obtained funding, conceptualized and designed the study, and revised the manuscript for intellectual content.
Helen Tremlett, PhD	University of British Columbia, Vancouver, Canada	Obtained funding and data, conceptualized and designed the study, interpreted the results, and drafted and revised the manuscript for intellectual content.

References

1. Scalfari A, Knappertz V, Cutter G, et al. Mortality in patients with multiple sclerosis. *Neurology*. 2013;81(2):184-192.
2. Kingwell E, van der Kop M, Zhao Y, et al. Relative mortality and survival in multiple sclerosis: findings from British Columbia, Canada. *J Neurol Neurosurg Psychiatry*. 2012;83(1):61-66.
3. Lunde HMB, Assmus J, Myhr KM, et al. Survival and cause of death in multiple sclerosis: a 60-year longitudinal population study. *J Neurol Neurosurg Psychiatry*. 2017; 88(8):621-625.
4. Leray E, Vukusic S, Debouverie M, et al. Excess mortality in patients with multiple sclerosis starts at 20 years from clinical onset: data from a large-scale French observational study. *PLoS One*. 2015;10(7):e0132033.
5. Tramacere I, Del Giovane C, Salanti G, et al. Immunomodulators and immunosuppressants for relapsing-remitting multiple sclerosis: a network meta-analysis. *Cochrane Database Syst Rev*. 2015;(9):CD011381. doi: 10.1002/14651858.CD14011381.pub14651852.
6. Goodin DS, Reder AT, Ebers GC, et al. Survival in MS: a randomized cohort study 21 years after the start of the pivotal IFNβ-1b trial. *Neurology*. 2012;78(17):1315-1322.
7. Gronseth GS, Ashman E. The AAN response to evidence-based medicine: promise and pitfalls. *Mult Scler*. 2012;18(7):949-950.
8. Katkade VB, Sanders KN, Zou KH. Real world data: an opportunity to supplement existing evidence for the use of long-established medicines in health care decision making. *J Multidiscip Healthc*. 2018;11:295-304.
9. Kingwell E, Leray E, Zhu F, et al. Multiple sclerosis: effect of beta interferon treatment on survival. *Brain*. 2019;142(5):1324-1333.
10. Kavaliunas A, Manouchehrinia A, Stawiarz L, et al. Importance of early treatment initiation in the clinical course of multiple sclerosis. *Mult Scler*. 2017;23(9): 1233-1240.
11. Cocco E, Sardu C, Spinicci G, et al. Influence of treatments in multiple sclerosis disability: a cohort study. *Mult Scler*. 2015;21(4):433-441.
12. Rovaris M, Comi G, Rocca MA, et al. Long-term follow-up of patients treated with glatiramer acetate: a multicentre, multinational extension of the European/Canadian double-blind, placebo-controlled, MRI-monitored trial. *Mult Scler*. 2007;13(4): 502-508.
13. Landfeldt E, Castelo-Branco A, Svedbom A, et al. The long-term impact of early treatment of multiple sclerosis on the risk of disability pension. *J Neurol*. 2018;265(3): 701-707.
14. Goodin DS, Ebers GC, Cutter G, et al. Cause of death in MS: long-term follow-up of a randomised cohort, 21 years after the start of the pivotal IFNβ-1b study. *BMJ Open*. 2012;2(6):e001972.
15. Statistics Canada. *Population Estimates, Quarterly*. Statistics Canada; 2021. Accessed July 14, 2021. www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1710000901.
16. Marrie RA, Leung S, Yu N, et al. Lower prevalence of multiple sclerosis in First Nations Canadians. *Neurol Clin Pract*. 2018;8(1):33-39.
17. Al-Sakran LH, Marrie RA, Blackburn DF, et al. Establishing the incidence and prevalence of multiple sclerosis in Saskatchewan. *Can J Neurol Sci*. 2018;45(3):295-303.
18. Evans C, Marrie RA, Yao S, et al. Medication adherence in multiple sclerosis as a potential model for other chronic diseases: a population-based cohort study. *BMJ Open*. 2021;11(2):e043930.
19. British Columbia Ministry of Health [creator]. *Consolidation File (MSP Registration & Premium Billing). V2*. Population Data BC [publisher]. Data Extract. MOH; 2017. popdata.bc.ca/data.
20. British Columbia Ministry of Health [creator]. *Medical Services Plan (MSP) Payment Information File. V2*. Population Data BC [publisher]. Data Extract. MOH; 2017. popdata.bc.ca/data.
21. Canadian Institute for Health Information [creator]. *Discharge Abstract Database (Hospital Separations). V2*. Population Data BC [publisher]. Data Extract. MOH; 2017. popdata.bc.ca/data.
22. BC Vital Statistics Agency [creator]. *Vital Statistics Deaths. V2*. Population Data BC [publisher]. Data Extract. BC Vital Statistics Agency; 2017. popdata.bc.ca/data.
23. BC Ministry of Health [creator]. *PharmaNet. V2*. BC Ministry of Health [publisher]. Data Extract. Data Stewardship Committee; 2017. popdata.bc.ca/data.
24. Marrie RA, Yu N, Blanchard J, et al. The rising prevalence and changing age distribution of multiple sclerosis in Manitoba. *Neurology*. 2010;74(6):465-471.
25. Ng HS, Zhu F, Kingwell E, et al. Characteristics of a population-based multiple sclerosis cohort treated with disease-modifying drugs in a universal healthcare setting. *Expert Rev Neurother*. 2021;21(1):131-140.
26. Canadian Institute for Health Information and Statistics Canada. *Health Indicators 2013*. CIHI; 2013. Accessed March 3, 2021. cihi.ca/sites/default/files/document/health-indicators-2013-en.pdf.
27. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol*. 1992;45(6):613-619.
28. Marrie RA, Bernstein CN, Peschken CA, et al. Intensive care unit admission in multiple sclerosis: increased incidence and increased mortality. *Neurology*. 2014; 82(23):2112-2119.
29. Andrade SE, Kahler KH, Frech F, et al. Methods for evaluation of medication adherence and persistence using automated databases. *Pharmacoepidemiol Drug Saf*. 2006;15(8):565-574.
30. Kalincik T, Kubala Havrdova E, Horakova D, et al. Comparison of fingolimod, dimethyl fumarate and teriflunomide for multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 2019;90(4):458-468.
31. Kappos L, O'Connor PW, Polman CH, et al. Clinical effects of natalizumab on multiple sclerosis appear early in treatment course. *J Neurol*. 2013;260(5):1388-1395.
32. Cohen JA, Coles AJ, Arnold DL, et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. *Lancet*. 2012;380(9856):1819-1828.
33. He A, Merkel B, Brown JWL, et al. Timing of high-efficacy therapy for multiple sclerosis: a retrospective observational cohort study. *Lancet Neurol*. 2020;19(4): 307-316.
34. Weideman AM, Tapia-Maltos MA, Johnson K, et al. Meta-analysis of the age-dependent efficacy of multiple sclerosis treatments. *Front Neurol*. 2017;8:577.
35. Giovannoni G, Hawkes C, Lechner-Scott J, et al. The COVID-19 pandemic and the use of MS disease-modifying therapies. *Mult Scler Relat Disord*. 2020;39:102073.
36. Tsai CP, Lee CT. Impact of disease-modifying therapies on the survival of patients with multiple sclerosis in Taiwan, 1997-2008. *Clin Drug Investig*. 2013;33(9):647-652.
37. Suissa S. Immortal time bias in pharmacoepidemiology. *Am J Epidemiol*. 2008;167(4): 492-499.
38. Giovannoni G, Butzkueven H, Dhib-Jalbut S, et al. Brain health: time matters in multiple sclerosis. *Mult Scler Relat Disord*. 2016;9(suppl 1):S5-S48.
39. Cerqueira JJ, Compston DAS, Geraldes R, et al. Time matters in multiple sclerosis: can early treatment and long-term follow-up ensure everyone benefits from the latest advances in multiple sclerosis? *J Neurol Neurosurg Psychiatry*. 2018;89(8):844-850.
40. La Mantia L, Vacchi L, Di Pietrantonj C, et al. Interferon beta for secondary progressive multiple sclerosis. *Cochrane Database Syst Rev*. 2012;1:CD005181. doi: 10.1002/14651858.CD14005181.pub14651853.
41. Tremlett H, Zhao Y, Rieckmann P, et al. New perspectives in the natural history of multiple sclerosis. *Neurology*. 2010;74(24):2004-2015.
42. Koch-Henriksen N, Magyari M. Apparent changes in the epidemiology and severity of multiple sclerosis. *Nat Rev Neurol*. 2021;17(11):676-688.
43. Roos I, Leray E, Casey R, et al. Effects of high and low efficacy therapy in secondary progressive multiple sclerosis. *Neurology*. 2021;97(9):e869-e880. doi: 10.1212/wnl.0000000000012354.
44. Tremlett H, Marrie RA. The multiple sclerosis prodrome: emerging evidence, challenges, and opportunities. *Mult Scler*. 2021;27(1):6-12.
45. Evans C, Marrie RA, Zhu F, et al. Adherence and persistence to drug therapies for multiple sclerosis: a population-based study. *Mult Scler Relat Disord*. 2016;8:78-85.
46. Charlson ME, Carrozzino D, Guidi J, et al. Charlson comorbidity index: a critical review of clinimetric properties. *Psychother Psychosom*. 2022;91(1):8-35.
47. Kingwell E, Zhu F, Marrie RA, et al. High incidence and increasing prevalence of multiple sclerosis in British Columbia, Canada: findings from over two decades (1991-2010). *J Neurol*. 2015;262(10):2352-2363.
48. Marrie RA, Fisk JD, Stadnyk KJ, et al. The incidence and prevalence of multiple sclerosis in Nova Scotia, Canada. *Can J Neurol Sci*. 2013;40(6):824-831.
49. Houtchens MK, Bove R. A case for gender-based approach to multiple sclerosis therapeutics. *Front Neuroendocrinol*. 2018;50:123-134.

Disease-Modifying Drugs for Multiple Sclerosis and Association With Survival

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