

# BMJ Open Association between disease-modifying therapies for multiple sclerosis and healthcare utilisation on a population level: a retrospective cohort study

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## ABSTRACT

**Objective** Disease-modifying therapy (DMT) use in multiple sclerosis (MS) has increased significantly. However, the impact of DMTs on healthcare use is limited and conflicting, and rarely examined at a population level. This study examined the association between DMTs and healthcare utilisation at the population level.

**Design** Retrospective cohort.

**Setting** Health administrative data from Saskatchewan, Canada (1997–2016).

**Participants** To test for associations at the population level, we identified two cohorts. The general population cohort included all Saskatchewan residents  $\geq 18$  years who were drug plan beneficiaries. The MS cohort included individuals  $\geq 18$  years, identified using a validated definition ( $\geq 3$  hospital, physician or drug claims for MS).

**Main outcome measures and methods** To test for an association between the total number of DMT dispensations per year and the total number of hospitalisations we used negative binomial regression fitted with generalised estimating equations (GEE); only hospitalisations that occurred after the date of MS diagnosis (date of first claim for MS or demyelinating disease) were extracted. To test for an association between the number of DMT dispensations and physician claims, negative binomial distributions with GEE were fit as above. Results were reported as rate ratios (RR), with 95% CIs, and calculated for every 1000 DMT dispensations.

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

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

## Strengths and limitations of this study

- One of the first studies to examine healthcare utilisation outcomes related to disease-modifying therapies for multiple sclerosis (MS) on a population level.
- Population-based cohort from a region with one of the highest rates of MS worldwide.
- Observational studies cannot adjust or assess all potential (unknown) confounders.
- Administrative data inherently lack some clinical information.

## INTRODUCTION

Multiple sclerosis (MS) is considered to be the leading cause of non-traumatic neurological disability in young adults,<sup>1</sup> and it is estimated that Canada has among the highest prevalence of MS worldwide.<sup>2</sup> Although the prevalence of MS is relatively low compared with other chronic diseases, the disabling and long-term nature of the disease, high healthcare utilisation and treatment costs, and lost productivity places a significant strain on the healthcare system and society.<sup>3 4</sup> In Canada, the total estimated healthcare cost per capita in 2011 was \$16 800 for adults with MS compared with \$2500 for individuals without a neurological condition; total annual costs are expected to rise from an estimated \$950 million in 2001 to \$2 billion by 2031.<sup>5 6</sup>

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

Regardless of the uncertainty surrounding the cost-effectiveness of DMTs, it is known that healthcare utilisation is higher for individuals living with MS compared with the general population.<sup>13–18</sup> The use of DMTs continues to increase as new therapies become available, and with the recommendations for treatment of early disease.<sup>8 9 11 19–22</sup>

Therefore, understanding the impact that DMTs have on healthcare utilisation at a population level will help guide health policy decisions related to issues such as the reimbursement or coverage of therapies. This study aimed to examine healthcare utilisation patterns, and to describe the association between DMTs and healthcare utilisation at the population level, using data from Saskatchewan, Canada.

## MATERIALS AND METHODS

### Data source

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

The Discharge Abstract Database records diagnoses during hospitalisations using the ninth revision of the International Classification of Diseases (ICD) codes (ICD-9) until 2002, and the ICD-10-Canadian modification (CA) onwards. Up to 25 diagnoses may be captured for each hospitalisation, with the primary diagnosis considered the one most responsible for the admission. The Physician Database records a single diagnosis using only three-digit ICD-9 codes, as well as general provider information. The Physician Database is not limited to claims for face-to-face visits, rather it reports all claims submitted for reimbursement including services such as laboratory reviews and phone consultations. Information related to outpatient medication dispensations, including the drug information number, dose, quantity and date dispensed, is captured in the Prescription Database.

### Study design

This retrospective cohort study examined exposure (DMTs) and outcomes (healthcare utilisation) on a population level, rather than individual level. To do this, we created two separate cohorts. The *general population cohort* included all Saskatchewan residents who were beneficiaries of the provincial drug plan and were  $\geq 18$  years old. The *MS cohort* included drug plan beneficiaries  $\geq 18$  years

old who were identified to have MS between 1 January 1996 and 31 December 2016, based on a previously validated algorithm requiring  $\geq 3$  hospital (ICD-9: 340, ICD-10-CA: G35), physician (ICD-9: 340) or drug claims (online supplementary appendix A) for MS.<sup>24</sup>

### Study outcomes

#### Healthcare utilisation patterns in the general population cohort

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

#### Healthcare utilisation patterns in the MS cohort

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

#### Association of DMT use on healthcare utilisation in the MS cohort

Utilisation of DMTs (online supplementary Appendix A) was measured for each year between 1997 and 2016 and reported as the total number of dispensations for *any* DMT, and the total number of individuals receiving at least one DMT dispensation. DMT use was measured on a class level, rather than reported for individual agents. Although the first DMT (interferon-beta-1b) was approved for use in Canada in 1996, it was not available through the Saskatchewan drug plan until December 1997 (online supplementary Appendix A). During the study period, the majority of DMTs prescribed were first-line agents, which include interferon-beta-1a/1b, glatiramer acetate, dimethyl fumarate and teriflunomide (online supplementary Appendix A). In Saskatchewan, prescriptions are primarily dispensed in 1-month quantities, including the DMTs that were available during the study period.

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

### Analyses

Hospitalisation rates were standardised to the Canadian 2006 census (closest census to midpoint) for age and sex via the direct method,<sup>26</sup> and reported per 100 000 population. Physician claim rates were calculated and standardised in the same manner, but reported as per person, to allow for easier interpretation. Poisson regression was used to evaluate the change in rates over time. The estimated slope of the regression line with 95% CIs was reported to describe the direction of the change.

The association between DMT use and healthcare utilisation was examined on a population level, rather than individual level. As such, individual-level covariates were not included in the models. Any subjects who died or were lost to follow-up (ie, were no longer a beneficiary of the Saskatchewan Drug Plan) would not be included in the numerators or denominators used to determine healthcare utilisation patterns; however, any data prior to being lost to follow-up were included in the analyses. Negative binomial regressions fitted with generalised estimating equations (GEE) with an exchangeable correlation matrix were used to test if an association existed between the total number of DMT dispensations per year and all-cause and MS-specific hospitalisations at the population level. Subjects were stratified by age group (18–39, 40–59, ≥60 years) and sex. The independent variable was the total number of DMT dispensations per year for each stratum; the dependent variable was either the total number of all-cause or MS-specific hospitalisations per year, and was obtained for each stratum. To account for changing population size, and to control for age and sex, the population of each stratum was included as an offset in the model. Calendar year (as a continuous variable) was also included as a covariate in the models. When the outcome was MS-specific hospitalisations, we also included the number of annual all-cause hospitalisations in the general population as a covariate to account for potential changes in hospital utilisation trends. To test for an association between the number of DMT dispensations and the average length of all-cause inpatient hospitalisations, Poisson models with GEE with an autocorrelation matrix were fit in the same manner as above. Because the length of an inpatient hospitalisation could not have a

value of zero, we subtracted 1 from the length of each hospitalisation, to allow the use of a Poisson model.<sup>26</sup> Finally, to test for an association between the number of DMT dispensations and physician claims, negative binomial distributions with GEE were fit using the same age and sex strata and offset as described for hospitalisations above, with adjustment for calendar year. Results were presented as rate ratios (RR), with 95% CIs, and calculated for every 1000 DMT dispensations.

Data were accessed at the Saskatchewan Health Quality Council under data sharing agreements with the Saskatchewan Ministry of Health and eHealth Saskatchewan. Statistical analyses were performed with SAS V.9.4 (SAS Institute). Due to the retrospective nature and design of the study it was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination of our research.

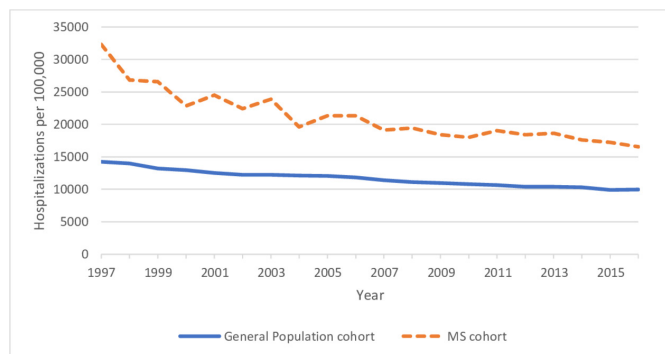
### Patient and public involvement

Patients and/or the public were not involved in the design or conduct of this study.

### RESULTS

The population of Saskatchewan in 2016 was 1 098 352, an increase of approximately 100 000 over the study period.<sup>27</sup> The incidence of MS in Saskatchewan is similar to other provinces in Canada,<sup>25 28–30</sup> and remained stable during the study period; a slight increase in prevalence was observed, with an estimated age and sex-standardised prevalence of 313.6 per 100 000 (95% CI 303.0 to 324.3) in 2013.<sup>24</sup> Between 1 January 1997 and 31 December 2016 there were 159 396 DMT dispensations in Saskatchewan, a crude increase from 27 in 1997 to 9246 in 2016 ( $p<0.0001$ ). The crude number of individuals receiving at least one DMT dispensation also increased from 23 in 1997 to 945 in 2016 ( $p<0.0001$ ).

Hospitalisation rates in both the general population cohort and the MS cohort decreased over the study period. The age and sex-standardised rate for all-cause hospitalisations in the general population cohort was 14 240 per 100 000 (95% CI 14 135 to 14 346) in 1997 and 9935 per 100 000 (95% CI 9870 to 10 000) in 2016 ( $p<0.0001$ ) (figure 1). Within the MS cohort, the age and sex-standardised rate of all-cause hospitalisations in 1997 was 32 311 per 100 000 (95% CI 27 513 to 37 109) and 16 544 per 100 000 (95% CI 14 945 to 18 144) in 2016 ( $p<0.0001$ ) (figure 1). There was a slight increase in the mean length of all-cause hospitalisation stays for the general population during the study period from 7.6 days in 1997 to 8.1 days in 2016 ( $p=0.60$ ). An increase in the mean length of stay was also observed for the MS population from 6.8 days in 1997 to 9.6 days in 2016 ( $p=0.79$ ) (figure 2); however, the trend was not significant for either cohort. The age and sex-standardised rate of MS-specific physician claims in the MS cohort decreased from 6.8 per person (95% CI 5.8 to 8.8) in 1997 to 3.5 per person (95% CI 3.2 to 3.7) in 2016 ( $p<0.10$ ). The rates for



MS cohort: Estimate: -0.0407 (95% CI: -0.0412 to -0.0402;  $p < 0.0001$ )  
 General population cohort: Estimate: -0.0185 (95% CI: -0.0192 to -0.0178;  $p < 0.0001$ )

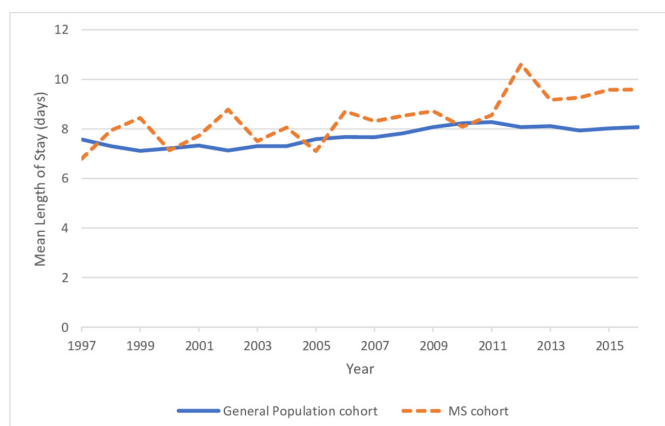
**Figure 1** Age and sex-standardised inpatient hospitalisations per 100 000 in the Saskatchewan general population cohort and MS cohort (1997–2016). MS, multiple sclerosis.

non-MS claims remained constant throughout the study period from 10.2 per person (95% CI 8.8 to 11.3) in 1997 to 10.3 per person (95% CI 9.4 to 11.2) in 2016 ( $p = 0.34$ ) (figure 3).

The number of DMT dispensations was associated with a decreased risk for both all-cause (RR=0.994; 95% CI 0.992 to 0.996,  $p < 0.0001$ ) and MS-specific (RR=0.909; 95% CI 0.880 to 0.938,  $p < 0.0001$ ) hospitalisations in the MS cohort (table 1). An association between the number of DMT dispensations and an increased length of all-cause inpatient stay was observed (RR=1.077; 95% CI 1.024 to 1.132,  $p = 0.004$ ) (table 1). Finally, the number of DMT dispensations was not associated with the number of all-cause or MS-specific physician claims in the MS cohort ( $p > 0.10$  for both) (table 1).

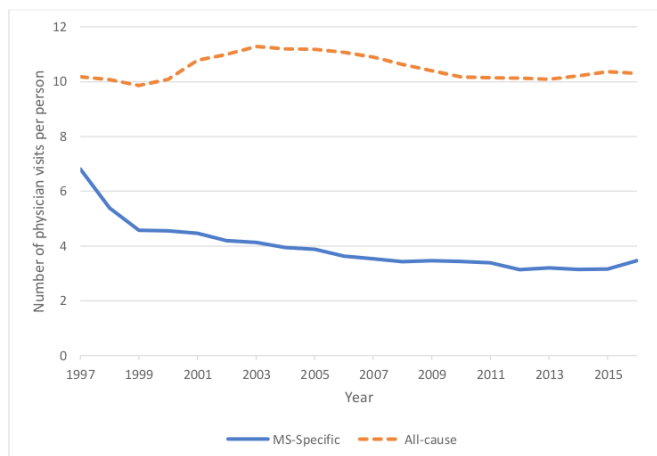
## DISCUSSION

In this retrospective population-based cohort study, we observed trends in healthcare utilisation over a 20-year period in Saskatchewan, Canada, and examined the impact of DMTs for MS on this utilisation at a population



MS cohort: Estimate: 0.0032 (95% CI: -0.0203 to 0.0267;  $p = 0.79$ )  
 General population cohort: Estimate: 0.0073 (95% CI: -0.0201 to 0.0348;  $p = 0.60$ )

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



MS-specific: Estimate: -0.0329 (95% CI: -0.0716 to 0.0058;  $p = 0.10$ )  
 All-cause: Estimate: -0.0011 (95% CI: -0.0246 to 0.0223;  $p = 0.34$ )

**Figure 3** Age and sex-standardised physician claims (all cause and MS specific) per person in the Saskatchewan MS cohort (1997–2016). MS, multiple sclerosis.

level. As DMT use increased, decreases in both all-cause and MS-specific hospitalisations were observed. Although there appeared to be an increase in the length of all-cause inpatient hospitalisations in both cohorts, the trend over the entire study period was not significant. There was no association between DMT utilisation and the number of physician claims.

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

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

Despite a reduction in hospitalisation rates, we observed a slight, although non-significant, increase in the length of inpatient stays. This is in contrast to both the Sanchirico study<sup>31</sup> and a 2018 Finnish study that described an overall decreased length of hospital stays in their MS cohorts with

**Table 1** Association between disease-modifying therapy dispensations and healthcare utilisation in the multiple sclerosis cohort in Saskatchewan

| Variable                                     | Risk ratio | 95% CI         | P value |
|--|------------|----------------|---------|
| <b>All-cause hospitalisations*</b>           |            |                |         |
| Per 1000 DMT dispensations                   | 0.994      | 0.992 to 0.996 | <0.0001 |
| Calendar year                                | 0.978      | 0.974 to 0.983 | <0.0001 |
| <b>MS-specific hospitalisations*</b>         |            |                |         |
| Per 1000 DMT dispensations                   | 0.909      | 0.880 to 0.938 | <0.0001 |
| Calendar year                                | 0.940      | 0.924 to 0.957 | <0.0001 |
| All-cause hospitalisations†                  | 1.000      | 1.000 to 1.000 | 0.090   |
| <b>All-cause mean length of stay (days)‡</b> |            |                |         |
| Per 1000 DMT dispensations                   | 1.077      | 1.024 to 1.132 | 0.004   |
| Calendar year                                | 0.999      | 0.993 to 1.005 | 0.781   |
| <b>All-cause physician claims*</b>           |            |                |         |
| Per 1000 DMT dispensations                   | 1.006      | 0.990 to 1.022 | 0.477   |
| Calendar year                                | 0.982      | 0.977 to 0.987 | <0.0001 |
| <b>MS-specific physician claims*</b>         |            |                |         |
| Per 1000 DMT dispensations                   | 0.962      | 0.910 to 1.016 | 0.165   |
| Calendar year                                | 0.954      | 0.935 to 0.975 | <0.0001 |

\*Negative binomial regression fitted with generalised estimating equation (GEE).

†Adjusted for all-cause hospitalisations in the Saskatchewan general population to account for changes in hospitalisation trends.

‡Poisson regression fitted with GEE.

DMT, disease-modifying therapy; MS, multiple sclerosis.

DMT use.<sup>34</sup> Different study populations (non-population based in the Sanchirico study) and healthcare systems and policies may be responsible for the discrepancy. For example, the mean inpatient stay was 4.2 days (SD 5.2) in the Finnish study,<sup>34</sup> but was 8.4 days (SD 0.94) in our study. Further, in Canada, a 6.9% increase in the length of inpatient hospital stays in the general population has been reported over a 15-year period from 1995–1996 to 2010–2011.<sup>35</sup> We have also previously shown an increasing length of stay in a cohort of patients with MS in British Columbia, although DMT use was not specifically evaluated in that study.<sup>13</sup> So although hospitalisation rates have decreased over time, it appears that those individuals who are hospitalised are sicker, and require more complex care.<sup>13</sup> It is also possible that some individuals with MS remain in hospital longer as they wait for placement in a long-term care facility, or are receiving inpatient rehabilitation.<sup>36</sup>

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

prescribing and monitoring may be offset by a reduction in physician services in other areas, such as relapse management.

This study has limitations that should be considered. As with all observational studies, we were unable to identify or adjust for all potential confounders. Specific to our study, Registered First Nations and recognised Inuit people in Saskatchewan have their drug costs paid for by another government agency and were excluded from the analyses as we could not accurately determine their DMT claims. The prevalence of MS in the indigenous population is low<sup>37</sup> and we do not expect their exclusion to have an impact on our results related to the association between DMT and healthcare utilisation. Some physicians in Saskatchewan receive alternate payment plans (ie, salary), rather than fee for service. Although it is required that these physicians ‘shadow bill’ for tracking purposes, some may not, and therefore not all physician service encounters may have been captured reliably. However, this number would be small and would not be expected to impact population-level results. It was not possible to examine the utilisation of other healthcare professional services, such as nurses and therapists, as these data are not systematically captured by the Saskatchewan government. We also did not have access to laboratory monitoring or MRI data, which would be important outcomes to include in future research examining the newer DMTs that require increased surveillance. We did not evaluate the effects of other factors, such as

comorbidity, concurrent medication use and adherence, which would be more appropriate for an individual-level analysis. However, in our previous work, we have shown that optimal adherence to the DMTs was 80% for the Saskatchewan MS population.<sup>38</sup> As is common with administrative data, we did not have access to important clinical factors that may affect hospitalisation rates such as type of MS<sup>13</sup> and disease severity.<sup>39</sup> However, because we were evaluating healthcare utilisation at the population level, these individual-level data were not necessary. Finally, we considered a class effect of the DMTs and therefore were not able to differentiate outcomes related to specific DMTs.

This study is novel in that it examined the association of DMTs and healthcare utilisation in an MS cohort on a population, rather than individual, level. This allowed us to examine the impact of DMT use on the healthcare system, and from a policy perspective which must balance the cost of DMTs with potential improvements in health at the health system level. This ecological approach is similar to other studies that have looked at population-level drug utilisation, interventions and outcomes in other diseases such as heart failure and diabetes.<sup>40 41</sup> Outcomes related to healthcare utilisation, and in particular hospitalisations, are of interest to payers and policymakers; hospitalisations are the largest component of healthcare resource use, and can also be surrogate measures for disease worsening.<sup>13 42</sup> Our study demonstrates that increased DMT use over two decades in Saskatchewan has been associated with a reduction in all-cause and MS-specific hospitalisations, but has not impacted the number of physician services used. Further research into areas such as cost-benefit and different treatment strategies (eg, escalation vs initial highly active therapy) would provide additional insight into the true impact of DMTs on healthcare utilisation at a population level.

**Contributors** The first author (LAS) had access to the data in the study and takes responsibility for the integrity of the data and accuracy of the data analyses. LAS, CE and RAM designed the study and CE obtained funding. LAS and CE drafted the manuscript. LAS, CE, RAM, DB and KK were involved in the interpretation of data, critically revising the manuscript, and have approved the final version to be published.

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**Disclaimer** The study sponsor had no role in the study design, data collection, data analysis, interpretation of results, writing of the manuscript or decision to submit. All inferences, opinions and conclusions drawn in this abstract are those of the authors, and do not reflect the opinions or policies of the Saskatchewan Government, the Saskatchewan Ministry of Health, or the Saskatchewan Health Quality Council.

**Competing interests** CE receives research funding from the Canadian Institutes of Health Research and the Saskatchewan Health Research Foundation. RAM receives research funding from the Canadian Institutes of Health Research, Multiple Sclerosis Society of Canada, National Multiple Sclerosis Society, Research Manitoba, the Consortium of MS Centers, Crohn's and Colitis Canada, and the Waugh Family Chair in Multiple Sclerosis. DB is the chair in Patient Adherence to Drug Therapy within the College of Pharmacy and Nutrition, University of Saskatchewan. This position was created through unrestricted financial support from AstraZeneca Canada, Merck Canada, Pfizer Canada and the Province of Saskatchewan's Ministry of Health. KK has received funding for the Saskatchewan MS Drugs Research Program from the Saskatchewan Ministry of Health. LAS declares no conflicts.

**Patient consent for publication** Not required.

**Ethics approval** This study was approved by the University of Saskatchewan's Biomedical Research Ethics Board.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** No data are available.

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