Lower prevalence of multiple sclerosis in First Nations Canadians

Ruth Ann Marrie, MD, PhD, Stella Leung, MSc, Nancy Yu, PhD, and Lawrence Elliott, MD, MSc

Neurology: Clinical Practice February 2018 vol. 8 no. 1 33-39 doi:10.1212/CPJ.0000000000000418

Correspondence

Dr. Marrie
rmarrie@hsc.mb.ca

Abstract

Background

We compared the incidence and prevalence of multiple sclerosis (MS) between First Nations (FN) and non-FN populations in Manitoba.

Methods

We applied previously validated algorithms to population-based administrative (health claims) data from Manitoba, Canada, to identify all persons with MS from 1984 to 2011. We identified FN individuals using the Municipality of Registration field held at Manitoba Health. We compared the incidence and prevalence of MS between the FN and non-FN populations using negative binomial models.

Results

From 1984 to 2011, 5,738 persons had MS, of whom 64 (1.1%) were of FN ethnicity. The average annual incidence rate per 100,000 population was 8.15 (95% confidence interval [CI] 5.98–11.1) in the FN population and 15.7 (95% CI 15.1–16.3) in the non-FN population (incidence rate ratio 0.52; 95% CI 0.38–0.71). In 1984, the crude prevalence of MS per 100,000 population was 35.8 (95% CI 14.9–86.1) in the FN population and 113.3 (95% CI 106.3–120.8) in the non-FN population. Between 1984 and 2011, the age-standardized prevalence of MS increased by 351% to 188.5 (95% CI 146.6–230.4) in the FN population. In contrast, the prevalence of MS per 100,000 general population increased by 225%–418.4% (95% CI 405.8–431.0).

Conclusions

The incidence and prevalence of MS are twofold lower in the FN population than the non-FN population. Nonetheless, the prevalence of MS in FN Manitobans is higher than in other indigenous populations outside Canada. Given reports of more rapid disability progression among FN Canadians with MS, and the rising prevalence of MS in this population, attention should be directed to the needs of this population.

Departments of Internal Medicine (RAM), Community Health Sciences (RAM, SL, NY, LE), and Medical Microbiology (LE), Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Canada.

Funding information and disclosures are provided at the end of the article. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/cp.

Manitoba Health delivers publicly funded health care to over 98% of the population, and maintains electronic databases related to health service delivery.

The incidence and prevalence of multiple sclerosis (MS) vary worldwide.^{1–3} Within regions, the risk of MS varies across racial and ethnic groups. For example, the risk of MS is substantially lower in indigenous populations in Norway and New Zealand than in the general population.^{4,5} However, a systematic review of the incidence and prevalence of MS in the Americas noted that few published studies reported findings according to racial or ethnic group.¹ In particular, little is known about the risk of MS among Canadian indigenous populations.

In 2001, one study estimated the period (1970–1996) prevalence of MS in the Manitoba First Nations (FN) population to be 56.6 per 100,000 persons over age 10 years based on cases identified through the province's 2 tertiary care centers.⁶ Subsequently, a study from Alberta, Canada, suggested that the prevalence of MS in the FN population was lower than in the general population, but rose faster between 1994 and 2002 than in the general population.⁷ Current population-based estimates of the prevalence of MS in the FN population are lacking, but are needed to plan health services.

Therefore, we compared the incidence and prevalence of MS between the FN and non-FN population in Manitoba. We hypothesized that although the incidence and prevalence of MS would be lower in the FN population than in the non-FN population, that they would be relatively high compared to other world regions, reflecting Canada's position as a high-risk region for MS.⁸

Methods

We conducted this study in the Canadian province of Manitoba using administrative data. Manitoba is located at 53.76°N and 98.81°W, with a stable population of nearly 1.3 million persons.

Administrative data

Manitoba Health delivers publicly funded health care to over 98% of the population, and maintains electronic databases related to health service delivery. For this study, we accessed de-identified versions of the health insurance registry, hospital discharge abstract database, medical services database, and Drug Program Information Network (DPIN) database. These databases are linkable using a unique personal health identification number, which is attached to all submitted health services claims.

The health insurance registry captures all individuals registered with Manitoba Health and provided information regarding dates of birth and death, sex, region of residence (postal code), and dates of insurance coverage. Hospital claims include up to 25 discharge diagnoses, coded using the ICD-9 or ICD-10 system depending on the year, as well as the dates of admission and discharge. The medical services database captures physician claims for inpatient and outpatient visits and diagnostic tests. Each claim includes the ICD-9-CM code for one physician-assigned diagnosis, as well as a tariff code for the type of service and the date of service. The DPIN database is a point of sale system that captures all prescriptions dispensed in community pharmacies including the drug identification number and date of dispensation.

Standard protocols, approvals, and consents

We obtained approval to access these databases from the Health Information Privacy Committee. The Health Research Ethics Board at the University of Manitoba approved the study, as did the Health Information Research Governance Committee, now at the First Nations Health and Social Secretariat of Manitoba, established in 2013 by the Assembly of Manitoba Chiefs, the regional organization of FN leaders in Manitoba.

First Nations

The Canadian indigenous population comprises several groups, including the Metis, Inuit, and FN. In Manitoba, these groups account for 17% of the population.⁹ The FN populations in Manitoba include 5 language and cultural groups including Cree, Ojibway, Oji-cree, Dene, and Dakota. Administrative data include a Municipality of Registration field identifying individuals as FN if they have registered as such, as designated under the Indian Act of Canada, and we used this field to classify persons identified as having MS according to our case definition as FN or non-FN.

Multiple sclerosis

We have previously developed and tested administrative case definitions for MS in Manitoba,¹⁰ then refined them in Nova Scotia.¹¹ We had previously shown that the year of diagnosis based on administrative data agreed within 3 years of diagnosis based on medical records in 74.2% of cases.¹⁰ The first case definition for MS was designed to be sensitive and required ≥ 3 claims ever, where eligible claims had an ICD-9/ICD-10 code for MS (340/G35) or include a prescription for an MS-specific disease-modifying therapy. This was the primary case definition for the present study as a more sensitive definition is most relevant for planning health services (referred to as definition 1). A more specific definition required ≥ 3 claims for individuals with ≤ 3 years of data and ≥ 7 hospital or physician claims for individuals with > 3 years of data (definition 2).

We also conducted complementary analyses using alternative case definitions to allow comparisons of our findings with those of other initiatives. We used the proposed definition for MS for the Canadian Chronic Disease Surveillance System,

which requires ≥ 1 hospital or ≥ 5 physician claims for MS in 2 years, and has a positive predictive value of 86% in a primary care population (definition 3).¹²

Incidence and prevalence

After identifying all persons with MS who met the case definition of interest at any point during the study period, we identified the first health claim for demyelinating disease (ICD-9/ICD-10 codes: MS [340/G35], other acute disseminated demyelination [G36], demyelinating disease of CNS unspecified [341.9/G37.8], acute disseminated encephalomyelitis [323/G36.9], optic neuritis [377.3/H46], acute transverse myelitis [323.82/G37]) and assigned this as the date of diagnosis. Individuals who met the case definition were classified as prevalent cases from the date of the first demyelinating disease claim (index date) until the date of death or emigration from Manitoba. To identify a case as incident, we required at least 5 years of administrative data without any claims for demyelinating disease preceding the first demyelinating disease claim. Therefore the earliest date when we could identify an incident case was 1989.

Due to the small number of incident cases in the FN population over the study period, we calculated the average annual incidence rate over the period 1989 to 2011 rather than annual incidence. We calculated annual prevalence using the mid-year population figure from the Manitoba Health Insurance Registry as the denominators. We calculated 95% confidence intervals

(CIs) for the incidence and prevalence estimates using a Poisson distribution. We age-standardized the prevalence estimates to the 2011 Canadian population using the direct method. We compared the prevalence between the FN and non-FN populations by including FN population (yes vs no) in the negative binomial regression models of age-adjusted prevalence. To determine if the temporal trends differed between the FN and non-FN populations, we included an interaction term between population and year.

Comparing study populations

We compared the characteristics of the FN and non-FN populations at the index date with respect to demographic characteristics including sex, age at the index date, and urban vs rural region of residence using χ^2 tests and Student *t* test. We also compared the populations with respect to comorbidity status at the index date. To determine comorbidity status, we selected comorbidities that could be accurately identified using administrative case definitions in the MS population,^{13–16} and were common at the time of MS diagnosis (table e-1, <http://links.lww.com/CPJ/A3>). These comorbidities were hypertension, diabetes, hyperlipidemia, heart disease, chronic lung disease, depression, and anxiety.¹⁷ We did not include comorbidities such as epilepsy or inflammatory bowel disease, which were expected to affect less than 5% of the population at MS diagnosis due to the small size of the FN population and consequent privacy concerns.

Table 1 Characteristics of multiple sclerosis cases in Manitoba at the index date

Characteristics	Prevalent		<i>p</i> Value	Incident		<i>p</i> Value
	FN (n = 64)	Non-FN (n = 5,674)		FN (n = 40)	Non-FN (n = 2,941)	
Period	1984–2011	1984–2011	—	1989–2009	1989–2009	—
Female, n (%)	40 (62.5)	4,060 (71.5)	0.068	25 (62.5)	2,170 (73.8)	0.11
Age at the index date, y, median (p25–p75)	37.5 (28.5–49.5)	42 (33–51)	0.44	39 (27–51)	39 (33–48)	0.13
Age group at the index date, y, n (%)						
15–34	29 (45.3)	1,719 (30.3)	0.0095	16 (40.0)	883 (30.0)	0.17
≥ 35	35 (54.7)	3,955 (69.7)		24 (60.0)	2,058 (70.0)	
Urban, n (%)	29 (45.3)	3,923 (69.1)	<0.0001	16 (40.0)	1,992 (67.7)	0.0002
Comorbidity at index date, n (%)						
Hypertension	8 (12.5)	627 (11.0)	0.53	7 (17.5)	442 (15.0)	0.66
Diabetes	7 (10.9)	194 (3.4)	0.0011	Suppressed	141 (4.8)	0.025
Ischemic heart disease	Suppressed	153 (2.7)	0.58	Suppressed	92 (3.1)	0.82
Hyperlipidemia	Suppressed	365 (6.4)	0.65	Suppressed	286 (9.7)	0.95
Chronic lung disease	14 (21.9)	610 (10.7)	0.0045	9 (22.5)	456 (15.5)	0.22
Depression	13 (20.3)	1,359 (23.9)	0.50	8 (20.0)	974 (33.1)	0.079
Anxiety disorder	15 (23.4)	1,366 (24.1)	0.90	11 (27.5)	1,012 (34.4)	0.36

Abbreviation: FN = First Nations.

Results

Study populations

Over the entire study period from 1984 to 2011, we identified 5,738 persons who ever met the primary case definition for MS. Of these, 64 (1.1%) were of FN ethnicity, and 71.4% were female (table 1). After we stratified by the population by FN ethnicity, the female predominance persisted in both groups, although this was less pronounced in the FN population. The FN population was less likely to live in an urban setting, and was more likely to have comorbid diabetes and chronic lung disease at the index date. Depression and anxiety were common at the index date in both populations. When we compared the incident cases of MS in the FN and non-FN populations, the findings were similar (table 1). Findings for the other 3 case definitions are shown in tables e-2 and e-3 (<http://links.lww.com/CPJ/A4>, <http://links.lww.com/CPJ/A5>).

Incidence

The average annual incidence rate per 100,000 population was 8.15 (95% CI 5.98–11.1) in the FN population and 15.7 (95% CI 15.1–16.3) in the non-FN population (incidence rate ratio [IRR] 0.52; 95% CI 0.38–0.71). In both populations, the average annual incidence rate was higher in women than men; however, this did not reach statistical significance in the FN population. Specifically, in the FN population, the incidence was 9.64 (95% CI 6.51–14.3) among women and 6.48 (95% CI 3.91–10.7) among men (IRR 1.49; 95% CI 0.78–2.82). In the non-FN population, the incidence was 22.6 (95% CI 21.7–23.6) among women and 8.42 (95% CI 7.84–9.03) among men (IRR 2.69; 95% CI 2.48–2.92).

Although the absolute incidence rates differed slightly for the other case definitions, the associations between sexes and between FN and non-FN populations were similar (data not shown).

Prevalence

Table 2 shows the age-specific prevalence of MS in 2010 in the FN population as compared to the general population of

The incidence and prevalence of MS in the FN population were twofold lower than in the non-FN population.

MS of Manitoba. In both populations, the peak age-specific prevalence was at age 55 years and older, followed by age 35–54 years. The prevalence of MS was lower in the FN population than in the non-FN population in all age groups, although this did not reach statistical significance among those aged 15–34 years.

In 1984, the crude prevalence of MS per 100,000 population was 35.8 (95% CI 14.9–86.1) in the FN population, and the age-standardized prevalence was 41.7 (95% CI 10.3–73.1). In comparison, the crude prevalence in the non-FN population was 113.3 (95% CI 106.3–120.8), and the age-standardized prevalence was 128.6 (95% CI 121.1–135.9). Between 1984 and 2011, the age-standardized prevalence of MS per 100,000 population increased by 351% to 188.5 (95% CI 146.6–230.4) in the FN population. In contrast, the prevalence of MS per 100,000 general population increased by 225%–418.4% (95% CI 405.8–431.0; figure). Findings for the alternative case definitions are shown in tables e-4 and e-5 (<http://links.lww.com/CPJ/A6>, <http://links.lww.com/CPJ/A7>) and show a similar pattern to those of the primary case definition.

In a negative binomial model adjusting for year, the prevalence of MS was 58% lower in the FN population than in the non-FN population (prevalence ratio [PR] 0.42; 95% CI 0.39–0.45). In both populations, the prevalence was 4% higher each year (PR 1.037; 95% CI 1.032–1.041). We did not identify an interaction between year and population ($\chi^2 = 0.68$, $p = 0.41$).

Discussion

Using population-based administrative data, we evaluated the incidence and prevalence of MS in the FN population in Manitoba over a more than 25-year period. The incidence and prevalence of MS in the FN population were twofold lower than in the non-FN population. Among individuals

Table 2 Prevalence with 95% confidence interval (CI) of multiple sclerosis in Manitoba per 100,000 population in 2010/2011 according to age^a

Age, y	First Nations			Non-First Nations			Both			Ratio	95% CI
	No. of cases	Prevalence	95% CI	No. of cases	Prevalence	95% CI	No. of cases	Prevalence	95% CI		
15–34	11	68.6	34.0–123.8	310	97.2	87.0–108.7	321	95.9	85.9–106.9	0.71	0.39–1.29
35–54	24	231.5	155.2–345.4	1,818	544.1	519.6–569.7	1,842	534.7	510.8–559.6	0.43	0.28–0.64
≥55 ^a	14	294.7	174.5–487.5	1,780	572.8	546.8–600.0	1,794	568.6	542.9–595.5	0.51	0.30–0.87

^a Age groups collapsed because cell sizes <5 suppressed.

Figure Age-standardized prevalence of multiple sclerosis per 100,000 population stratified by First Nations status

with MS, those of FN background were less likely to live in urban settings, and more likely to have diabetes and chronic lung disease at the index date.

In 2010, we estimated the age-standardized prevalence of MS in the Manitoba FN population to be 188.5 per 100,000 population, while the average annual incidence was 8.15 per 100,000 population. Although this prevalence was twofold lower than that observed in the general population, this prevalence estimate is high from a global perspective.⁸ In 2001, one study estimated the period (1970–1996) prevalence of MS in the Manitoba FN population to be 56.6 per 100,000 persons over age 10 years based on cases identified through the province's 2 tertiary care centers.⁶ That prior prevalence estimate is slightly lower than our estimate in the same year, but falls within the bounds of our estimate. A previous study in Alberta also used administrative data to estimate the prevalence of MS in the FN population.⁷ The case definition used was at least 1 hospitalization or 2 physician visits for MS. In 2002, the prevalence was 99.9 per 100,000 among the FN population. This estimate is higher than we observed in the same year regardless of the case definition used, but regional variation in the incidence and prevalence of MS within Canada is recognized,¹⁸ and this estimate would be expected to have higher sensitivity than our case definitions because of the smaller number of health care encounters required to meet the definition. The prevalence ratio between the FN and non-FN populations was similar to what we observed.

The reasons for the differences in incidence and prevalence of MS in these populations are unknown but may reflect differences in genetic or environmental factors or both. For example, alleles for HLA-DRB1*1501 are strongly associated with the risk of MS. In a pilot study, we previously described genetic differences between FN and non-FN

populations with MS. Specifically, HLA-DRB1*1501 alleles were less common among FN persons with MS than among non-FN persons with MS, and HLA-DRB1*1602 alleles were more common.¹⁹ Individuals of FN background often have lower socioeconomic status than those of non-FN background, and several studies have suggested that higher socioeconomic status may confer an increased risk of MS, although findings regarding this association have been inconsistent.²⁰ Diet, other health behaviors, housing conditions, exposure to infection, and vitamin D status may all differ between the FN and non-FN populations.^{21–23}

The incidence and prevalence of MS in other indigenous populations is lower than we observed, even in other world regions in which the prevalence of MS is considered to be high. In the United States Gulf War Veterans cohort, the incidence of MS was 3.1 per 100,000 in Native Americans.²⁴ In Norway, the prevalence of MS in the general population was 120.4 per 100,000 population in 1995, but no cases of MS were identified in the Sami population.²⁵ In New Zealand, a moderate prevalence region for MS, the age-standardized prevalence of MS in the general population in 2006 was 73.2 per 100,000 population.⁵ In the Maori population, the age-standardized prevalence was 20.6 per 100,000 population, 3.6-fold lower.

Due to the relatively small number of incident cases in the FN population, we were unable to evaluate temporal trends in the incidence of MS in this population. Previous studies in Manitoba and other Canadian provinces using similar methods have suggested that the incidence of MS has been stable in the general population over the last 20 years.^{10,11,26} However, studies in other jurisdictions have suggested that the incidence of MS may be rising in populations historically considered at lower risk of MS, such as the black population.

Among members of Kaiser Permanente Southern California Health Plan from 2008 to 2010, the incidence of MS was higher in African American than among white participants.²⁷ Among military veteran cohorts in the United States, the risk of MS has risen over a 60-year period among black men, black women, and other race men as compared to white men.²⁴ The reasons for these temporal changes are unknown, but the timescale of the changes implicate differential environmental factors.

Characteristics of the FN and non-FN populations with MS differed, but this appears to reflect underlying general differences between the FN and non-FN populations in Manitoba. Nearly 60% of the Manitoba FN population lives on reserves,²⁸ accounting for the lower proportion of FN persons with MS living in urban settings. The prevalence of diabetes and chronic lung disease are well-recognized to be higher in the FN population than in the non-FN population.^{29,30} Given the reported adverse effects of diabetes and chronic lung disease on outcomes in MS such as progression of ambulatory and visual disability,^{31–33} these findings suggest that the FN population with MS may be at increased risk of poor outcomes. In our prior study comparing characteristics of FN and non-FN persons with MS, the age at symptom onset was 2.5 years earlier among FN persons, and they were more likely to have motor symptoms at onset, although these differences were not statistically significant.¹⁹ In another study, indigenous Canadians with MS more rapidly accumulated disability after onset than nonindigenous Canadians.³⁴ Members of other minority ethnic groups who develop MS, such as black patients, also have been reported to experience a more aggressive disease course.³⁵ These findings may partly reflect disparities in socioeconomic status,³⁶ health care access,³⁷ the burden of health behaviors, such as smoking, and in comorbidities³⁸ known to affect outcomes.³⁵ The rising prevalence of MS in populations potentially at risk for worse outcomes warrants thoughtful attention.

Although administrative data include a field indicating FN status, this field only captures persons of FN background who are registered or reside on FN reserved regions, slightly underrepresenting the number of Manitobans who are of FN ethnicity.⁹ Therefore our findings are likely a conservative estimate of the prevalence of MS in this population. Administrative data are collected for the purpose of health system management rather than research and clinical care, therefore the diagnostic codes captured may be inaccurate. However, we used a case definition that was validated previously by medical records review. Further, our findings regarding the relative prevalence of MS in the FN population vs the general population were similar when we used alternative case definitions. Although some studies have suggested that the characteristics of MS occurring in the FN population differ from those in the general population, including a recent pilot study that we conducted comparing genetic factors across those populations,^{19,34} we were unable

to compare the clinical characteristics of MS across populations in this study. This should be the subject of future study. We also lacked information regarding other ethnicities than FN status because this is not captured in administrative data.

The incidence and prevalence of MS are twofold lower in the Manitoba FN population than the non-FN population. Nonetheless, the prevalence of MS in FN Manitobans is higher than in other indigenous populations outside Canada. Given prior reports of more rapid disability progression among FN Canadians with MS, and the rising prevalence of MS in this population, clinicians and policymakers should direct attention to the needs of this population.

Author contributions

R.A. Marrie: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, statistical analysis, study supervision, and obtaining funding. S. Leung: analysis or interpretation of data and statistical analysis. N. Yu: drafting/revising the manuscript, analysis or interpretation of data, statistical analysis, and study supervision. L. Elliott: drafting/revising the manuscript.

Acknowledgment

The results and conclusions presented are those of the authors. No official endorsement by Manitoba Health is intended or should be inferred.

Study funding

This study was funded in part by the Health Sciences Centre Foundation and Waugh Family Chair in Multiple Sclerosis.

Disclosure

R.A. Marrie serves on the editorial boards of *Neurology*[®] and *Multiple Sclerosis Journal*; and receives research support from Sanofi-Aventis, the Canadian Institutes of Health Research, Research Manitoba, Waugh Family Chair in Multiple Sclerosis, Multiple Sclerosis Society of Canada, National Multiple Sclerosis Society, Multiple Sclerosis Scientific Foundation, Consortium of Multiple Sclerosis Centers, Rx & D Health Research Foundation, and Crohn's and Colitis Canada. S. Leung and L. Elliott report no disclosures. N. Yu receives funding from the Merck Canada (research funds), Canadian Institutes of Health Research, and the National Multiple Sclerosis Society. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/cp.

Received July 12, 2017. Accepted in final form August 18, 2017.

References

1. Evans C, Beland S, Kulaga S, et al. Incidence and prevalence of multiple sclerosis in the Americas: a systematic review. *Neuroepidemiology* 2013;40:195–210.
2. Kingwell E, Marriott JJ, Jette N, et al. Incidence and prevalence of multiple sclerosis in Europe: a systematic review. *BMC Neurol* 2013;13:128.
3. Makhani N, Morrow SA, Fisk J, et al. MS incidence and prevalence in Africa, Asia, Australia and New Zealand: a systematic review. *Mult Scler Relat Disord* 2014;3:48–60.

4. Grønlie AS, Myrsvoll E, Hansen G, Grønning M, Mellgren IS. Multiple sclerosis in North Norway, and first appearance in an indigenous population. *J Neurol* 2000;247:129–133.
5. Pearson JF, Alla S, Clarke G, et al. Multiple sclerosis in New Zealand Māori. *Mult Scler J* 2014;20:1892–1895.
6. Mirsattari SM, Johnston JB, McKenna R, et al. Aboriginals with multiple sclerosis: HLA types and predominance of neuromyelitis optica. *Neurology* 2001;56:317–323.
7. Svenson LW, Warren S, Warren KG, Metz LM, Patten SB, Schopfloh DP. Prevalence of multiple sclerosis in first Nations people of Alberta. *Can J Neurol Sci* 2007;34:175–180.
8. Multiple Sclerosis International Federation. Atlas of MS 2013: Mapping Multiple Sclerosis Around the World. London: Multiple Sclerosis International Federation; 2013.
9. Chernikova E. Aboriginal Peoples: Fact Sheet for Manitoba. Ottawa: Statistics Canada; 2016.
10. Marrie RA, Yu N, Blanchard JF, Leung S, Elliott L. The rising prevalence and changing age distribution of multiple sclerosis in Manitoba. *Neurology* 2010;74:465–471.
11. Marrie RA, Fisk J, Stadnyk K, et al. The incidence and prevalence of multiple sclerosis in Nova Scotia, Canada. *Can J Neurol Sci* 2013;40:824–831.
12. 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;21:1045–1054.
13. Marrie RA, Yu B, Leung S, et al. Rising prevalence of vascular comorbidities in MS: validation of administrative definitions for diabetes, hypertension, hyperlipidemia. *Mult Scler* 2012;18:1310–1319.
14. Marrie RA, Yu BN, Leung S, et al. The utility of administrative data for surveillance of comorbidity in multiple sclerosis: a validation study. *Neuroepidemiology* 2013;40:85–92.
15. 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.
16. Marrie RA, Yu BN, Leung S, et al. Prevalence and incidence of ischemic heart disease in multiple sclerosis: a population-based validation study. *Mult Scler Relat Disord* 2013;2:355–361.
17. Marrie RA, Patten SB, Tremlett H, et al. Sex differences in comorbidity at diagnosis of multiple sclerosis: a population-based study. *Neurology* 2016;86:1279–1286.
18. Beck CA, Metz LM, Svenson LW, Patten SB. Regional variation of multiple sclerosis prevalence in Canada. *Mult Scler* 2005;11:516–519.
19. Marrie RA, Hall N, Sadovnick AD. Multiple sclerosis in First Nations Canadians: a pilot comparison study. *Mult Scler J Exp Transl Clin* 2016;2:2055217316666093.
20. Goulden R, Ibrahim T, Wolfson C. Is high socioeconomic status a risk factor for multiple sclerosis? A systematic review. *Eur J Neurol* 2015;22:899–911.
21. Reading CL, Wien F. Health Inequalities and Social Determinants of Aboriginal Peoples' Health. Prince George: National Collaborating Centre for Aboriginal Health; 2009.
22. Karunanayake CP, Albritton W, Rennie DC, et al. Ear infection and its associated risk factors in first Nations and rural school-aged Canadian children. *Int J Pediatr* 2016;2016:1523897.
23. Larcombe L, Mookherjee N, Slater J, et al. Vitamin D in a Northern Canadian first nation population: dietary intake, serum concentrations and functional gene polymorphisms. *PLoS One* 2012;7:e49872.
24. Wallin MT, Culpepper WJ, Coffman P, et al. The Gulf War era multiple sclerosis cohort: age and incidence rates by race, sex and service. *Brain* 2012;135:1778–1785.
25. Celius EG, Vandvik B. Multiple sclerosis in Oslo, Norway: prevalence on 1 January 1995 and incidence over a 25-year period. *Eur J Neurol* 2001;8:463–469.
26. Kingwell E, Zhu F, Marrie R, et al. High incidence and increasing prevalence of multiple sclerosis in British Columbia, Canada: findings from over two decades (1991–2010). *J Neurol* 2015;262:2352–2363.
27. Langer-Gould A, Brara SM, Beaber BE, Zhang JL. Incidence of multiple sclerosis in multiple racial and ethnic groups. *Neurology* 2013;80:1734–1739.
28. Indigenous and Northern Affairs Canada. First Nations in Manitoba [online]. 2016. Available at: <https://www.aadnc-aandc.gc.ca/eng/1100100020400/1100100020404>. Accessed October 1, 2016.
29. Sin DD, Wells H, Svenson LW, Man SF. Asthma and COPD among aboriginals in Alberta, Canada. *Chest* 2002;121:1841–1846.
30. Ospina MB, Voaklander DC, Stickland MK, King M, Senthilselvan A, Rowe BH. Prevalence of asthma and chronic obstructive pulmonary disease in Aboriginal and non-Aboriginal populations: a systematic review and meta-analysis of epidemiological studies. *Can Respir J* 2012;19:355–360.
31. Marrie RA, Cutter G, Tyrry T. Substantial adverse association of visual and vascular comorbidities on visual disability in multiple sclerosis. *Mult Scler* 2011;17:1464–1471.
32. Marrie RA, Rudick R, Horwitz R, et al. Vascular comorbidity is associated with more rapid disability progression in multiple sclerosis. *Neurology* 2010;74:1041–1047.
33. Conway DS, Thompson NR, Cohen JA. Influence of hypertension, diabetes, hyperlipidemia, and obstructive lung disease on multiple sclerosis disease course. *Mult Scler* 2017;23:277–285.
34. Saeedi J, Rieckmann P, Yee I, Tremlett H. Characteristics of multiple sclerosis in aboriginals living in British Columbia, Canada. *Mult Scler J* 2012;18:1239–1243.
35. McKay KA, Jahanfar S, Duggan T, Tkachuk S, Tremlett H. Factors associated with onset, relapses or progression in multiple sclerosis: a systematic review. *Neurotoxicology* 2016;61:189–212.
36. Marrie RA, Cutter G, Tyrry T, Vollmer T, Campagnolo D. Does multiple sclerosis-associated disability differ between races? *Neurology* 2006;66:1235–1240.
37. Saadi A, Himmelstein DU, Woolhandler S, Mejia NI. Racial disparities in neurologic health care access and utilization in the United States. *Neurology* 2017;88:2268–2275.
38. Marrie RA, Horwitz R, Cutter G, Tyrry T, Campagnolo D, Vollmer T. Comorbidity, socioeconomic status, and multiple sclerosis. *Mult Scler* 2008;14:1091–1098.

Subspecialty Alerts by E-mail!

Customize your online journal experience by signing up for e-mail alerts related to your subspecialty or area of interest. Access this free service by clicking on the “My Alerts” link on the home page. An extensive list of subspecialties, methods, and study design choices will be available for you to choose from—allowing you priority alerts to cutting-edge research in your field!