Sex differences in comorbidity at diagnosis of multiple sclerosis

A population-based study

OPEN

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ABSTRACT

Objective: To determine the prevalence of comorbidity in the multiple sclerosis (MS) population at the time of MS diagnosis. We also compared the prevalence of comorbidity in the MS population to that in a matched cohort from the general population.

Methods: Using population-based administrative health data from 4 Canadian provinces, we identified 23,382 incident MS cases and 116,638 age-, sex-, and geographically matched controls. We estimated the prevalence of hypertension, diabetes, hyperlipidemia, heart disease, chronic lung disease, epilepsy, fibromyalgia, inflammatory bowel disease, depression, anxiety, bipolar disorder, and schizophrenia at MS diagnosis using validated case definitions. We compared the populations using rate ratios.

Results: Of the MS cases, 16,803 (71.9%) were female. The most prevalent comorbidity was depression (19.1%). Compared to the matched population, all comorbidities except hyperlipidemia were more common in the MS population. Relative to the matched populations, the prevalence of hypertension was 16% higher for women with MS and 48% higher for men with MS, thus there was a disproportionately higher prevalence of hypertension in men with MS than women. Men with MS also had a disproportionately higher prevalence than women with MS for diabetes, epilepsy, depression, and anxiety.

Conclusions: Comorbidity is more common than expected in MS, even around the time of diagnosis. The prevalence of psychiatric comorbidity is particularly high and highlights the need for clinical attention to this issue. The observed sex-specific differences in the burden of comorbidity in MS, which differ from those in the matched population, warrant further investigation. *Neurology*® 2016;86:1279–1286

GLOSSARY

ALD = affections de longue durée; **ICD-9** = *International Classification of Diseases*–9; **ICD-10** = *International Classification of Diseases*–10; **MS** = multiple sclerosis.

In many chronic diseases, comorbidity is associated with reduced quality of life,[1] increased health care utilization, and increased mortality.[2] For example, vascular comorbidity is associated with more rapid cognitive decline in Alzheimer disease.[3] Some studies suggest that in multiple sclerosis (MS) comorbidity is associated with diagnostic delays and greater disability at MS diagnosis,[4] and increased risks of disability progression.[5] However, the epidemiology of comorbidity in MS, including sex-specific differences in the incidence or prevalence of comorbidity, remains poorly understood.[6]

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As new disease-modifying therapies for MS emerge for which risks of adverse events differ in the presence of comorbidity,[7] it becomes increasingly important to understand the frequency of

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comorbidity throughout the disease course, particularly at clinically relevant time points such as at diagnosis. Findings regarding the prevalence of comorbidity at MS diagnosis conflict.[8,9] One self-report study conducted in the United States found that comorbidity affected more than 35% of respondents at diagnosis.[9] However, a study in France that focused on persons with MS onset before age 45 years and used a national disability register found that only 3% of the MS population had a comorbidity at diagnosis.[8]

Using population-based administrative data, we aimed to determine the prevalence of comorbidity in the MS population at MS diagnosis, and whether this differed by sex. We also compared the prevalence of comorbidity in the MS population to that in a matched cohort from the general population.

METHODS **Administrative data.** We used administrative health data from 4 Canadian provinces, including British Columbia, Manitoba, Quebec, and Nova Scotia. These provinces were selected based on the feasibility of accessing the necessary administrative data, and include nearly 43% of the Canadian population (http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/demo02a-eng.htm). All Canadian provinces administer a publicly funded, universally available health care system[10] and maintain computerized records related to the provision of these services. These records include a population registry that captures dates of birth, death, and health care coverage; hospital discharge abstracts that capture dates of admission and discharge and discharge diagnoses; and physician visits that capture the date of service and diagnosis.[11–13] Due to provincial privacy regulations that prevent individual-level data from leaving the province of origin, analyses were performed in parallel at each site, then the data were aggregated by age and sex groupings.

Standard protocol approvals, registrations, and patient consents. In each province, we obtained ethics approval and provincial approval to access administrative data.

Study populations. In each province, we applied an administrative case definition for MS that had been validated and performed similarly in Manitoba and Nova Scotia.[14,15] Anyone aged ≥20 years with ≥3 hospital or physician claims for MS (ICD-9/10 codes 340/G35) during the study period was classified as having MS. To identify incident cases of MS, we used a 5-year run-in period; thus if administrative data were available in 1990, the earliest incident cases could be identified in 1995.[14,15]

We identified a cohort from the general population, matched on sex, year of birth, and region of residence (postal code or first 3 digits of postal code if unable to match on full postal code). Statistical efficiency is optimized at 4 to 6 matched controls; therefore we obtained up to 5 matches for each case after excluding anyone with any diagnostic codes (ICD-9/10) for demyelinating disease: optic neuritis (377.3/H46), acute transverse myelitis (323.82/G37), acute disseminated encephalomyelitis (323/G36.9), demyelinating disease of CNS unspecified (341.9/G37.8), other acute disseminated demyelination (G36), MS (340/G35), or neuromyelitis optica (341.0/G36.0). For each person with MS, we assigned the date of the first health claim for demyelinating disease as the date of diagnosis, and the same (index) date was assigned to matched controls.

Comorbidities. We selected several comorbidities for study that had been evaluated in earlier studies of comorbidity at diagnosis of MS,[8,9] and that our prior work had indicated could be accurately identified using administrative case definitions in the MS population.[16–19] These comorbidities were hypertension, diabetes, hyperlipidemia, heart disease, chronic lung disease, epilepsy, fibromyalgia, inflammatory bowel disease, depression, anxiety, bipolar disorder, and schizophrenia. We did not evaluate cancer because of the expected low prevalence of this condition at MS diagnosis, and due to the need to access provincial cancer registries to optimize identification of cancer. We applied the validated administrative case definitions for comorbidity to the MS and matched control populations in each province (table e-1 on the *Neurology*® Web site at Neurology.org). These definitions specified the number of years of data to be used, the ICD-9/10 codes, and the number of hospital or physician claims required to meet the case definition. For hospital claims, we used all available diagnoses. For physician claims, we had previously established that using all available diagnoses (when available) from physician claims had little influence on the performance of the case definitions,[20] and as some provinces only capture one diagnosis per physician claim, we used only the first listed diagnosis for each physician claim.

Prevalence. As the comorbidities represent chronic conditions, once a person met the case definition for a comorbidity, he or she was considered to be affected in all subsequent years while resident in the province.[21] We determined the crude prevalence of the comorbidity in the year of MS diagnosis or the index date for matched controls using the midyear population figures from the provincial population registry for denominators in the calculations. To ensure adequate cell sizes and stable estimates, we aggregated crude prevalence data across the study period. To facilitate comparisons to the study from France, which restricted its analysis to persons under age 45 years at diagnosis,[8] we present age-specific rates for persons aged 20–44, 45–59, and more than 60 years. We also present sex-specific estimates. Cell sizes <5 were suppressed as per the privacy agreements for data access. A matched analysis is not needed for a matched cohort design. Adjustment is not needed to control for confounding due to the matching variables if follow-up time is the same in both cohorts.[22] Therefore, we compared the MS and general population cohorts using rate ratios and 95% confidence intervals.[22] We report the time from comorbidity diagnosis to the index date using means and standard deviations, as we could not aggregate medians across provinces without individual level data.

Sensitivity analyses. To address the possible effect of increased health care utilization due to unrecognized symptoms of MS before MS diagnosis,[23] we repeated the analysis in individuals with an index year ≥2000 who had 10 years of administrative data before the index year. This allowed us to apply the comorbidity case definitions 5 years before the index date (as some definitions required 5 years of data to identify a comorbidity, this required 10 years of data). We report findings at the index year and at 5 years before the index year.

Analyses were performed using SAS V9.3 (SAS Institute Inc., Cary, NC).

RESULTS We identified 23,382 incident MS cases and 116,638 matched controls (table 1). Of the MS cases, 16,803 (71.9%) were female. At diagnosis, the

Table 1 Characteristics of data sources and study populations

	British Columbia	Manitoba	Quebec	Nova Scotia	Total
Data source/custodian	Population Data BC	Manitoba Health	Regie d'Assurance Maladie du Quebec	Health Data Nova Scotia	
Years	1990/1991–2008/2009[a]	1990/1991–2010/2011[a]	1990/1991–2010/2011[a]	1990/1991–2010/2011[a]	
Multiple sclerosis cases, n	6,938	2,696	11,695	2,053	23,382
Female, n (%)	5,015 (72.3)	1,976 (73.3)	8,271 (70.7)	1,541 (75.0)	16,803 (71.9)
Age at index date, y, mean (SD)	44.2 (13.1)	41.9 (12.4)	44.8 (15.4)	42.2 (12.3)	44.0 (14.1)
Age at index date, y, n (%)					
20–4	3,773 (54.4)	1,619 (60.0)	6,636 (56.7)	1,234 (60.1)	13,262 (56.7)
45–59	2,353 (33.9)	859 (31.9)	3,396 (29.0)	651 (31.7)	7,259 (31.0)
≥60	812 (11.7)	218 (8.1)	1,663 (14.3)	168 (8.2)	2,861 (12.27)
Matched controls, n	34,697	13,256	58,470	10,215	116,638
Female, n (%)	25,083 (72.3)	9,699 (73.2)	41,351 (70.7)	7,664 (75.0)	77,674 (72.3)
Age at index date, y, mean (SD)	44.0 (12.7)	41.8 (12.4)	44.8 (15.4)	42.2 (12.3)	44.0 (14.1)
Age at index date, y, n (%)					
20–44	18,774 (54.4)	7,986 (60.2)	33,178 (56.7)	6,161 (60.3)	61,172 (54.1)
45–59	11,774 (33.9)	4,226 (31.9)	16,980 (29.0)	3,234 (31.7)	33,631 (33.9)
≥60	4,049 (11.7)	1,044 (7.9)	8,312 (14.3)	820 (8.0)	13,573 (11.7)

[a] To allow 5 years run-in period actual results are presented for 1995 onward, although all stated years of data were accessed.

most prevalent comorbidity overall was depression (19.1%), followed by hypertension (15.2%) (table 2).

Among psychiatric comorbidities, prevalence varied somewhat across age groups, but without a consistent pattern (tables e-2 to e-5). Among physical comorbidities, the prevalence of diabetes, hypertension, hyperlipidemia, ischemic heart disease, chronic lung disease, and epilepsy increased with age (tables e-6 to e-13).

In both populations, depression, anxiety, and bipolar disorder were more prevalent in women than men, while schizophrenia was less common in women (table 3). Among physical comorbidities, fibromyalgia was more common in women. Inflammatory bowel disease and chronic lung disease were more common in women but this did not reach statistical significance for inflammatory bowel disease. All other comorbidities were less common in women than men.

Comparisons. Compared to the matched controls, all psychiatric comorbidities were more common in the MS population. Similarly, all physical comorbidities except hyperlipidemia were more common in the MS population at the index date (table 2). Among physical comorbidities, those for which rate ratios were 1.50 or higher included fibromyalgia, inflammatory bowel disease, epilepsy, and bipolar disorder. The mean years between comorbidity diagnosis and the index date are shown in table 4.

For some comorbidities, the strengths of the associations differed by sex or age (tables e-2 to e-13). The associations between comorbidity and population were modified by sex for hypertension, diabetes, chronic lung disease, epilepsy, depression, anxiety, bipolar disorder, and schizophrenia (table 3). Among women, the prevalence of hypertension was 16% higher in the MS than the matched population. Among men, however, the prevalence of hypertension was 48% higher in the MS than in the matched population, indicating a disproportionately higher prevalence of hypertension in men with MS than women. Findings were similar for diabetes, epilepsy, depression, and anxiety, with men again having disproportionately higher prevalence than women. With respect to chronic lung disease, the prevalence was 39% higher among women with MS than among women without MS, but only 21% higher among men with MS than men without MS. Thus there was a disproportionately higher prevalence of chronic lung disease among women with MS than men.

For diabetes, the rate ratios comparing the MS and matched populations were higher among those aged 20–44 years than among those aged ≥45 years (table e-6). We did not identify age group by population interactions for the other comorbidities.

Sensitivity analyses. The prevalence of all comorbidities was lower in both populations 5 years before MS

Table 2 Crude prevalence of comorbidity in the MS population at diagnosis compared to matched controls

Comorbidity	MS (n = 23,382), n (%)	Matches (n = 116,638), n (%)	RR (95% CI)	p Value
Hypertension	3,547 (15.2)	15,088 (12.9)	1.17 (1.13-1.21)	<0.0001
Diabetes	1,330 (5.69)	5,669 (4.86)	1.17 (1.10-1.24)	<0.0001
Ischemic heart disease	1,521 (6.50)	5,845 (5.01)	1.30 (1.23-1.37)	<0.0001
Hyperlipidemia	1,610 (6.89)	7,810 (6.70)	1.03 (0.98-1.08)	0.99
Fibromyalgia	306 (1.31)	532 (0.46)	2.87 (2.49-3.30)	<0.0001
Inflammatory bowel disease	131 (0.56)	390 (0.30)	1.68 (1.38-2.04)	<0.0001
Chronic lung disease	2,920 (12.1)	10,856 (9.14)	1.34 (1.29-1.39)	<0.0001
Epilepsy	451 (1.93)	1,034 (0.89)	2.18 (1.95-2.43)	<0.0001
Depression	4,464 (19.1)	10,936 (9.38)	2.04 (1.97-2.10)	<0.0001
Anxiety	2,594 (11.1)	8,035 (6.89)	1.61 (1.54-1.68)	<0.0001
Bipolar disorder	736 (3.15)	1,973 (1.69)	1.86 (1.71-2.02)	<0.0001
Schizophrenia	251 (1.07)	947 (0.81)	1.32 (1.15-1.52)	<0.0001

Abbreviations: CI = confidence interval; MS = multiple sclerosis; RR = rate ratio.

diagnosis (index date), but the associations between population and comorbidity were unchanged (table 5).

DISCUSSION In this population-based study of 23,382 Canadians with incident MS and 166,638 matches from the general population, we found that comorbidity was common at MS diagnosis, particularly depression. The burden of comorbidity was higher with increasing age at diagnosis, consistent with known associations of comorbidity with age in the general population.[24] The prevalence of all psychiatric comorbidities and nearly all physical comorbidities was more common in the MS population than in the matched population. The

Table 3 Sex-specific crude prevalence of comorbidity at diagnosis in the MS and matched populations

	MS population			Matched population			MS: matched	
Comorbidity, n (%)	Female (n = 16,803)	Male (n = 6,579)	Female: male ratio (95% CI)	Female (n = 83,797)	Male (n = 32,841)	Female: male ratio (95% CI)	Female: female ratio (95% CI)	Male: male ratio (95% CI)
Hypertension	2,394 (14.2)	1,413 (21.5)	0.66 (0.63-0.70)	10,320 (12.3)	4,768 (14.5)	0.85[a] (0.82-0.88)	1.16 (1.11-1.21)	1.48 (1.40-1.56)
Diabetes	812 (4.83)	518 (7.87)	0.61 (0.55-0.68)	3,690 (4.4)	1,979 (6.03)	0.73[b] (0.69-0.77)	1.10 (1.02-1.18)	1.31 (1.19-1.43)
Heart disease	843 (5.02)	678 (10.3)	0.49 (0.44-0.54)	3,140 (3.75)	2,705 (8.24)	0.45 (0.42-0.49)	1.34 (1.24-1.44)	1.25 (1.16-1.36)
Hyperlipidemia	942 (5.61)	668 (10.1)	0.55 (0.50-0.61)	4,584 (5.47)	3,225 (9.82)	0.56 (0.52-0.60)	1.02 (0.96-1.10)	1.03 (0.96-1.12)
Fibromyalgia	258 (1.54)	48 (0.73)	2.10 (1.55-2.86)	454 (0.54)	78 (0.24)	2.28 (1.79-2.90)	2.83 (2.43-3.30)	3.07 (2.15-4.40)
Inflammatory bowel disease	99 (0.59)	32 (0.49)	1.21 (0.81-1.80)	32 (0.49)	93 (0.28)	1.25 (0.99-1.58)	1.66 (1.32-2.09)	1.72 (1.15-2.56)
Chronic lung disease	2,269 (13.5)	651 (9.90)	1.36 (1.26-1.48)	8,160 (9.74)	2,696 (8.21)	1.19[c] (1.14-1.24)	1.39 (1.33-1.45)	1.21 (1.11-1.31)
Epilepsy	331 (1.97)	170 (2.58)	0.76 (0.64-0.92)	735 (0.88)	299 (0.91)	0.96[d] (0.84-1.10)	2.25 (1.97-2.55)	2.84 (2.36-3.42)
Depression	2,869 (17.1)	695 (10.6)	1.62 (1.50-1.75)	9,025 (10.8)	1,911 (5.82)	1.85[e] (1.76-1.94)	1.59 (1.53-1.65)	1.82 (1.67-1.97)
Anxiety	2,060 (12.3)	534 (8.12)	1.51 (1.46-1.56)	6,535 (7.80)	1,500 (4.57)	1.71[f] (1.53-1.90)	1.57 (1.50-1.65)	1.78 (1.62-1.95)
Bipolar	591 (3.52)	176 (2.69)	1.31 (1.11-1.55)	1,582 (1.89)	391 (1.19)	1.58 (1.42-1.77)	1.86 (1.70-2.40)	2.25 (1.88-2.68)
Schizophrenia	151 (0.90)	100 (1.52)	0.59 (0.53-0.65)	634 (0.76)	313 (0.95)	0.79[g] (0.69-0.91)	1.19 (1.00-1.42)	1.59 (1.28-1.99)

Abbreviations: CI = confidence interval; MS = multiple sclerosis.
[a] χ^2 for interaction between population and sex = 50.4, $p < 0.0001$.
[b] χ^2 for interaction between population and sex = 8.18, $p = 0.004$.
[c] χ^2 for interaction between population and sex = 9.03, $p = 0.003$.
[d] χ^2 for interaction between population and sex = 4.07, $p = 0.04$.
[e] χ^2 for interaction between population and sex = 8.33, $p = 0.004$.
[f] χ^2 for interaction between population and sex = 5.07, $p = 0.02$.
[g] χ^2 for interaction between population and sex = 4.06, $p = 0.04$.

Table 4 Mean (SD) delay between comorbidity diagnosis and the index date in the multiple sclerosis (MS) and matched populations

Comorbidity	MS population	Matched population	*p* Value
Hypertension	6.11 (4.43)	6.21 (4.38)	0.22
Diabetes	6.41 (4.84)	6.48 (4.37)	0.57
Heart disease	5.94 (4.71)	6.33 (4.30)	0.002
Hyperlipidemia	5.81 (4.52)	5.65 (4.36)	0.18
Fibromyalgia	4.56 (3.56)	5.57 (3.97)	0.0003
Inflammatory bowel disease	5.31 (2.62)	6.45 (4.03)	0.0026
Chronic lung disease	7.12 (4.46)	6.90 (4.55)	0.002
Epilepsy	6.22 (4.21)	6.65 (4.06)	0.0006
Depression	6.20 (4.14)	6.24 (4.12)	0.61
Anxiety	5.34 (3.98)	6.06 (4.05)	0.0001
Bipolar	5.61 (4.22)	5.83 (4.06)	0.21
Schizophrenia	6.42 (4.66)	7.09 (4.52)	0.32

highest rate ratios observed for physical comorbidities were seen for fibromyalgia, inflammatory bowel disease, and epilepsy.

Prior work regarding the prevalence of comorbidity at MS diagnosis has been limited. Unlike our findings, a French study based on registrations for 30 chronic long-term illnesses (affections de longue durée [ALD]) suggested that only 3% of the MS population had comorbid conditions at the time of MS diagnosis.[8] However, that study was restricted to persons aged ≤45 years, and to conditions that were notified to the ALD. Therefore, several of the comorbidities we studied were not captured, and other comorbidities, such as hypertension and chronic lung disease, had to be severe in the French study, likely underestimating their prevalence. Even among individuals with an age at MS diagnosis <45 years, we found that nearly 14% had depression, 11% had chronic lung disease, and 5% had hypertension. More in keeping with our findings are the results of a study of 8,983 American participants in the North American Research Committee on Multiple Sclerosis registry.[9] That study used a self-report questionnaire rather than prospectively collected administrative data, and found that comorbidity was common at diagnosis, with psychiatric comorbidities affecting 18% and vascular comorbidities (including diabetes, hypertension, hyperlipidemia, or ischemic heart disease) affecting 14.0%.[9]

A case-control study in California found that patients with MS were more likely to have been diagnosed with uveitis and inflammatory bowel disease before MS diagnosis.[25] Studies of comorbidity among prevalent MS cases are more common and recent systematic reviews of such studies have suggested that among individuals with prevalent MS, comorbid depression, anxiety, bipolar disorder, epilepsy, fibromyalgia, inflammatory bowel disease, ischemic heart disease, and chronic lung disease are more common than expected in MS.[26–30] Among other chronic inflammatory diseases, such as gout, the burden of comorbidities at diagnosis is also higher than expected.[31] Specifically, in rheumatoid arthritis, comorbid cardiovascular disease is more common at diagnosis than expected when compared to the general population.[32]

The observed sex differences in comorbidity status are of particular interest. Some were as expected, for example, depression, anxiety, and fibromyalgia were

Table 5 Crude prevalence of comorbidity in the MS population with an index year of 2000 or later compared to matched controls at diagnosis and 5 years before the diagnosis

	At diagnosis, n (%)			5 years before diagnosis, n (%)		
Comorbidity	MS (n = 14,503)	Matches (n = 72,199)	RR (95% CI)	MS (n = 14,503)	Matches (n = 72,199)	RR (95% CI)
Hypertension	2,467 (17.0)	10,337 (14.3)	1.19 (1.14–1.24)	1,544 (10.6)	6,061 (8.4)	1.27 (1.20–1.34)
Diabetes	940 (6.5)	3,961 (5.5)	1.18 (1.10–1.27)	540 (3.7)	2,305 (3.2)	1.17 (1.06–1.28)
Ischemic heart disease	985 (6.4)	3,809 (5.3)	1.29 (1.20–1.38)	577 (4.0)	2,361 (3.3)	1.22 (1.11–1.33)
Hyperlipidemia	1,160 (8.0)	5,583 (7.7)	1.03 (0.97–1.10)	691 (4.8)	3,079 (4.3)	1.12 (1.03–1.21)
Fibromyalgia	225 (1.5)	399 (0.55)	2.81 (2.39–3.30)	97 (0.67)	206 (0.29)	2.34 (1.84–2.98)
Inflammatory bowel disease	83 (0.57)	262 (0.36)	1.58 (1.23–2.02)	57 (0.39)	174 (0.24)	1.63 (1.21–2.20)
Chronic lung disease	2,067 (14.2)	7,543 (10.4)	1.36 (1.30–1.43)	1,456 (10.0)	6,607 (9.1)	1.10 (1.04–1.16)
Epilepsy	292 (2.0)	677 (0.94)	2.15 (1.87–2.46)	186 (1.3)	485 (0.67)	1.91 (1.61–2.26)
Depression	2,556 (17.6)	7,967 (11.0)	1.60 (1.53–1.66)	1,496 (10.3)	4,749 (6.6)	1.57 (1.48–1.66)
Anxiety	1,200 (8.3)	3,846 (5.3)	1.55 (1.46–1.65)	888 (6.1)	3,190 (4.4)	1.39 (1.29–1.49)
Bipolar	681 (4.7)	1,728 (2.4)	1.96 (1.36–1.61)	298 (2.0)	813 (1.1)	1.82 (1.60–2.08)
Schizophrenia	169 (1.2)	603 (0.84)	1.40 (1.18–1.65)	107 (0.74)	339 (0.47)	1.57 (1.27–1.95)

Abbreviations: CI = confidence interval; MS = multiple sclerosis; RR = rate ratio.

more common among women in both populations, and ischemic heart disease was more common in men. However, some of the associations between study population and comorbidity were modified by sex in ways that were not anticipated. In particular, women with MS had a disproportionately higher prevalence of chronic lung disease than did men with MS. In contrast, men with MS had a disproportionately higher prevalence of hypertension, diabetes, and epilepsy and of all of the psychiatric comorbidities studied (depression, anxiety, bipolar disorder, and schizophrenia) than did women with MS when compared to the matched population. The reasons for these findings are uncertain, but sex-based differences in the association between environmental factors and disease risk are recognized. For example, recent studies have suggested that female smokers are biologically more susceptible to chronic obstructive pulmonary disease than male smokers,[33] possibly due to hormonal effects. Further evaluation of the etiology of these sex-based differences is needed as these findings have implications for managing individuals with MS.

The burden of psychiatric comorbidity for both sexes even at MS diagnosis was striking. While depression and anxiety are recognized to be common in established MS, our findings and those of prior studies collectively indicate that these conditions are the most or nearly the most common preexisting comorbidities at diagnosis, particularly among those aged 20–44 years.[8,9] Depression and anxiety adversely affect health-related quality of life, adherence to therapy, and the risk of hospitalization.[34,35] Therefore, our findings suggest that these comorbidities deserve particular clinical attention from the time of diagnosis, and support the need for studies aimed at improved diagnosis and management of these conditions.

Our findings highlight that the burden of comorbidity even at diagnosis is important for clinicians to consider. Clinical trials often exclude individuals with (severe) comorbidities, such that we do not fully understand the efficacy, safety, or tolerability of disease-modifying therapies in these individuals. For example, it has been observed that individuals with migraine may have more difficulty tolerating one of the most commonly used disease-modifying treatments for MS (interferon-β) due to worsening headache profiles.[36] Some comorbidities are also known to increase the risk of serious adverse events. For example, diabetes increases the risk of macular edema associated with fingolimod, a recently licensed disease-modifying oral drug for MS.[7] Therefore, careful assessment of the presence of comorbid conditions is needed when considering such therapies even at the time of diagnosis. Future studies should consider formally evaluating whether treatment safety and effectiveness differs among individuals with the most common comorbidities to better inform clinical practice.

When compared to age-, sex-, and geographically matched controls, most of the comorbidities evaluated were more common in the MS population. The highest rate ratios were observed for fibromyalgia, inflammatory bowel disease, and epilepsy. The presence of one chronic condition may lead to improved ascertainment of comorbid conditions due to increased surveillance by clinicians or increased numbers of contacts with the health care system. Thus, having these conditions may increase the likelihood of getting a diagnosis of MS. Shared genetic or environmental factors may also account for some of the associations observed. For example, shared genetic factors[37] are associated with MS and inflammatory bowel disease. Vitamin D insufficiency is associated with an increased risk of MS and of ischemic heart disease and diabetes.[38] Future research should seek to explain the reasons for comorbidity in MS, recognizing they are likely to differ by comorbidity.

It was not feasible to perform this study in all Canadian provinces; however, the provinces studied spanned the country from west to east and included over 40% of the Canadian population. Since we included a matched control group in each province, we also accounted for the major confounders of age, sex, and region (including regional differences in health service delivery). Use of administrative data that are not collected for research purposes is another limitation but we used case definitions for MS and comorbidity that we had validated previously in 2 provinces.[15,20] We were unable to assess all relevant comorbidities, including conditions such as cancer, for which important gaps in the epidemiology persist,[39] including the prevalence at MS diagnosis. However, we assessed the prevalence of multiple comorbidities and focused on comorbidities that could be accurately assessed using administrative data, and that are frequent enough to be relevant at the population level. The mean age at MS diagnosis was 44 years, which appears slightly older than expected; however, we excluded individuals under age 20 years, which would have led to a higher mean age at diagnosis. We cannot exclude the possibility that some of the cases identified were prevalent not incident. Bias in the age at diagnosis is possible but previously we showed that age at the time of the incident MS-related claim is within 1 year of diagnosis date from medical charts in 67% of cases and within 3 years in 64% of cases.[14] Later age at diagnosis may produce higher prevalence estimates for comorbidity but do not affect rate ratios as we matched on age. Moreover, the age-specific estimates showed that comorbidity is common even among those aged 20–44 years at diagnosis. Symptom onset can occur

years before MS is diagnosed and diagnostic delays have changed over time. Therefore, unrecognized MS symptoms such as fatigue may lead to increased health care utilization before MS diagnosis,[23] and to increased or earlier diagnosis of comorbidities; however, our findings persisted even 5 years before MS diagnosis. Also, for several conditions, the mean time from diagnosis to the index date was shorter in the MS population. Data regarding the clinical characteristics of the MS participants were lacking such that we could not evaluate the associations of comorbidity with MS characteristics such as disability or disease course; this should be the subject of future research.

Comorbidity is more common than expected in MS, even around the time of diagnosis. The prevalence of psychiatric comorbidity is high, indicating the need for clinical attention to this issue. The observed sex-specific differences in the burden of comorbidity in MS, which differ from those in the matched population, warrant replication and investigation as to etiology.

AUTHOR CONTRIBUTIONS

Ruth Ann Marrie takes responsibility for the integrity of the data and the accuracy of the data analysis. The analysts and principal investigators at each site had full access to the data at each site (British Columbia: Helen Tremlett, Aruni Tennakoon, Stella Leung; Manitoba: Ruth Ann Marrie, Aruni Tennakoon; Quebec: Christina Wolfson, Bin Zhu; Nova Scotia: John Fisk, Yan Wang). Ruth Ann Marrie, John Fisk, Christina Wolfson, Helen Tremlett, and Sharon Warren designed the study and obtained funding. All authors contributed to the interpretation of the data. Ruth Ann Marrie drafted the manuscript. All authors revised the manuscript and approved of the final version to be published.

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