

High prevalence of comorbidities at diagnosis in immigrants with multiple sclerosis

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Abstract

Background: Multiple sclerosis (MS) has been associated with certain comorbidities in general population studies, but it is unknown how comorbidity may affect immigrants with MS.

Objective: To compare prevalence of comorbidities in immigrants and long-term residents at MS diagnosis, and in matched control populations without MS.

Methods: We identified incident MS cases using a validated definition applied to health administrative data in Ontario, Canada, from 1994 to 2017, and categorized them as immigrants or long-term residents. Immigrants and long-term residents without MS (controls) were matched to MS cases 3:1 on sex, age, and geography.

Results: There were 1534 immigrants and 23,731 long-term residents with MS matched with 4585 and 71,193 controls, respectively. Chronic obstructive pulmonary disease (COPD), diabetes, hypertension, ischemic heart disease, migraine, epilepsy, mood/anxiety disorders, schizophrenia, inflammatory bowel disease (IBD), and rheumatoid arthritis were significantly more prevalent among immigrants with MS compared to their controls. Prevalence of these conditions was generally similar comparing immigrants to long-term residents with MS, although COPD, epilepsy, IBD, and mood/anxiety disorders were less prevalent in immigrants.

Conclusion: Immigrants have a high prevalence of multiple comorbidities at MS diagnosis despite the “healthy immigrant effect.” Clinicians should pay close attention to identification and management of comorbidity in immigrants with MS.

Keywords: Multiple sclerosis, immigrants, comorbidity, prevalence

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Introduction

Comorbidity is common at multiple sclerosis (MS) diagnosis, as has been shown in studies in Canada,¹ the United Kingdom,² and the North American Research Committee on Multiple Sclerosis (NARCOMS) Registry in the United States.³ Particular conditions associated with MS include vascular diseases,^{4,5} mood and anxiety disorders,^{2,5} chronic lung disease,⁶ and epilepsy,² although there is some variability in associations between specific conditions and MS across regions.⁶ Comorbidity is associated with earlier disability progression in MS,^{7,8} and may contribute to worse prognosis in affected individuals.^{9,10} In previous studies, comorbidity at MS diagnosis was more prevalent in those with later disease onset,³ and the

comorbidity patterns differed in women versus men.¹ It is not well known whether comorbidities may differentially affect other special populations with MS, including immigrants. Previously, we showed that total comorbidity burden was associated with a higher risk of MS in immigrants to Ontario, Canada,¹¹ but did not characterize individual comorbidities.

Our objective was to identify specific comorbidities common in immigrants at MS diagnosis, and compare the prevalence of specific chronic conditions in immigrants with MS, immigrants without MS, and long-term residents with and without MS. We studied this question in Ontario, Canada, a region with universal health insurance and centralized collection of health

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administrative data, and a large, diverse population of immigrants.

Methods

Setting

Ontario is the most populous province in Canada, with a population of more than 13 million.¹² This was a retrospective matched cohort study using prospectively collected health administrative data. The data were collected through the universal Ontario Health Insurance Plan (OHIP) which is a publicly funded program that covers hospitalizations, outpatient physician visits without user fees, and outpatient prescription medications for persons aged 65+ years and those on social assistance. Most immigrants are eligible for OHIP coverage after a 3-month wait period; convention refugees are exempt from this wait period.

Data sources

Datasets were linked by unique encoded identifiers and analyzed at ICES as previously described.^{11,13} ICES (formerly known as the Institute for Clinical Evaluative Sciences) is an independent, non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze healthcare and demographic data, without consent, for health system evaluation and improvement. Data concerning immigrants arriving in Canada since 1985 are captured by the Immigration Refugees and Citizenship Canada's (IRCC) electronic Permanent Resident Database. Long-term residents were defined for this study as individuals born in Ontario or moved to Ontario prior to 1985. This approach has been used in several previous studies of immigrants in Ontario.^{14,15} Immigrant data from the IRCC have been linked to the Registered Persons Database in Ontario and provincial health administrative databases using probabilistic matching.¹⁴

MS cases

Cases were identified using a validated, previously published algorithm applied to health administrative billing data.¹⁶ Briefly, the algorithm required one hospitalization, or one emergency department visit, or at least five outpatient visits for MS (International Classification of Disease (ICD)-9/10-CA diagnosis codes 340/G35) over a 2-year period. Both primary and secondary discharge diagnoses of MS (340/G35) were included for hospitalizations. The index date was determined by the first in-patient or outpatient visit for a demyelinating condition as indicated by

ICD-9/10-CA diagnosis codes, including encephalomyelitis (323/G36 or G37), optic neuritis (377/H46), or MS (340/G35), in all those who later met the pre-defined algorithm.

Incident MS cases were identified between 1 April 1994 and 31 March 2018. OHIP eligibility of at least 3 years was required for cohort selection to ensure sufficient history to meet comorbidity algorithms and to ensure that prevalent MS cases were not mistaken as incident. Cases were required to be between 20 and 65 years inclusive. The lower limit on age was chosen because of the lack of validation of comorbidity definitions in children. The upper limit on age was applied because of the rarity of incident MS at age > 65 years and concerns regarding possible misdiagnosis in this age bracket.¹⁷ Individuals were excluded if Ontario residence could not be confirmed.

Incident MS cases were stratified into immigrant and long-term resident groups.

Controls

Two control groups were defined separately for the immigrant and long-term resident groups and matched to cases 3:1. Controls were randomly selected from immigrants and long-term residents, respectively, who had no code for a demyelinating condition before or on the index date, including any code for MS, optic neuritis, or encephalomyelitis. Controls were matched to cases at index date based on age \pm 2 years, sex, and place of residence (urban vs rural).

Comorbidities

Specific chronic conditions examined were selected from previous literature regarding comorbidities prevalent in individuals with MS.^{1,3,5,7} Comorbidities were defined based on previously validated algorithms applied to health administrative data over the 3 years prior to the MS index date (Table 1); this time window was utilized because of the limited OHIP history available in many of the immigrants. Thus, we were able to capture recent active comorbid conditions but not remote conditions where the algorithm would not have been met within the 3 years prior to MS index date. The selected conditions included: chronic obstructive pulmonary disease, diabetes mellitus, hyperlipidemia, hypertension, epilepsy, inflammatory bowel disease (IBD), ischemic heart disease (IHD), migraine, mood and anxiety disorders, rheumatoid arthritis (RA), and schizophrenia. Mood and anxiety disorders were grouped together because of overlapping codes for these disorders in Ontario.

Table 1. Individual comorbidity algorithms and data sources.

Comorbidity	Years required for case definition (e.g. 1, 2, or 3)	ICD-9/10-CA codes	OHIP diagnostic/fee codes	Case definition: number and type of claims (hospitalization (H) or physician (P))	Data sources	Comments
Chronic obstructive pulmonary disease (COPD) sensitive definition	1	491, 492, 496/J41–J44	491, 492, 496	≥ 1 H or ≥ 1 P	OHIP, DAD, SDS	Age of at least 35 years required
Diabetes mellitus (DM)	1	250/E10, E11, E13, E14	250/Q040, K030, K029, K045, K046	≥ 1 H or ≥ 2 P or ≥ 1 DM drug claim	OHIP, DAD, ODB	Gestational diabetes excluded
Epilepsy	2	345/G40	345	≥ 1 H or ≥ 3 P	OHIP, NACRS, DAD	If determined on an outpatient basis, claims must be separated by > 30 days
Hyperlipidemia	3	272/E780, E782, E784, E785	272	≥ 1 H or ≥ 2 P	OHIP, DAD	
Hypertension (HTN)	2	401–405/I10–I13, I15	401–405	≥ 1 H or ≥ 2 P	OHIP, DAD, SDS	Pregnancy-induced HTN excluded
Inflammatory bowel disease (IBD)	3	555, 556/K50, K51	555, 556	≥ 3 H or ≥ 3 P	OHIP, NACRS, DAD, SDS	
Ischemic heart disease (IHD)	1	410–414/I20–I25	410, 412, 413/R742, R743, Z434, G298	≥ 1 H or ≥ 2 P	OHIP, NACRS, DAD	If determined using OHIP claims, at least one must have been billed by a specialist or a family physician in a hospital or emergency room setting
Migraine	3	346/G43	346	≥ 1 H or ≥ 2 P	DAD, OHIP	
Mood/anxiety disorders	1	296, 300.0, 300.2, 300.3, 308.3, 309.0, 309.2, 309.3, 309.4, 309.8, 309.9, 311/F30–34, F38–43, F48.8, F48.9, F53.0, F93.1, F93.2	296, 300, 311	≥ 1 H or ≥ 2 P	OHIP, NACRS, DAD, OMHRS	
Rheumatoid arthritis (RA)	2	714/M05, M06	714	≥ 1 H or ≥ 3 P	OHIP, DAD	If determined on an outpatient basis, at least one claim by a musculoskeletal specialist
Schizophrenia (specific definition)	3	295/F20, F25	295	≥ 1 H or ≥ 3 P	OHIP, DAD, OMHRS	

ICD: International Classification of Disease; OHIP: Ontario Health Insurance Program; DAD: Discharge Abstract Database; SDS: same-day surgery; ODB: Ontario Drug Benefit Program; NACRS: National Ambulatory Care Reporting System; OMHRS: Ontario Mental Health Reporting System.

Malignancies were not included because the 3-year look-back period necessitated by the relatively brief medical history available in immigrants was thought to be insufficient for accurate ascertainment of malignancy history by virtue of the lower incidence and potential absence of any related healthcare claims for individuals in long-term remission.

Covariates

Total comorbidity burden was assessed in terms of Aggregated Diagnosis Group (ADG) number, which is a validated system for classifying comorbidity burden in the ambulatory setting.¹⁸ ADGs are based on the John Hopkins ACG system version 10 using hospitalization and physician visit information from 2 years prior to the index visit.

Other variables collected included age at index date, rural versus urban residence, and neighborhood income quintile. For immigrants, we also examined age at arrival in Canada, refugee status, duration of Canadian residence, and region of origin.

We determined potential confounders including age, sex, and socioeconomic status (SES), as measured by neighborhood income quintile, based on a review of the literature. Sex and age are known to independently affect both immigrant status and comorbidity.^{1,3,19} SES is known to affect comorbidity and may independently affect immigrant status due to preferential selection of skilled workers among immigrants to Canada.²⁰

Analysis

Baseline characteristics of immigrants with MS were summarized using descriptive statistics on the MS index date and compared to the control immigrant population. We also compared long-term residents on MS index date to controls without MS.

Prevalence ratios (PRs) were determined for each comorbidity in immigrants with versus without MS, and in long-term residents with versus without MS. A univariate generalized linear regression model with a Poisson distribution was used for calculation of PRs. Given the matched study design and equal duration of follow-up in all groups, these models effectively controlled for age, sex, and place of residence. We also created multivariable models to control for age, sex, place of residence, and SES. The models were run for three different PR comparisons: (1) immigrants with MS versus immigrant controls, (2) long-term residents with MS versus long-term resident controls, and

(3) immigrants with MS versus long-term residents with MS. Model underdispersion was accounted for by adjusting estimated errors using Pearson chi-square over degrees of freedom as the dispersion parameter. We also repeated the analysis stratified by sex given prior literature suggesting sex differences in comorbidities associated with MS.¹

Statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC).

This study was approved by the research ethics board at St. Michael's Hospital in Toronto, Ontario, Canada. Informed consent by participants was not required. ICES is a prescribed entity under section 45 of Ontario's Personal Health Information Protection Act. Section 45 authorizes ICES to collect personal health information without consent for the purpose of analysis or compiling statistical information with respect to the management of, evaluation, or monitoring of the allocation of resources to or planning for all or part of the health system. This project was conducted under section 45, and approved by the Privacy and Compliance Office of ICES.

Results

Study cohorts

We identified 25,269 incident MS cases including 1538 (6.1%) in immigrants and 23,731 (93.9%) in long-term residents (Figure 1). Immigrant ($n = 1534$) and long-term resident ($n = 23,731$) MS cases were successfully matched to 4585 and 71,193 controls, respectively; four cases of MS in immigrants went unmatched. As compared to immigrants without MS, immigrants with MS were more likely to live in high-income neighborhoods, have immigrated from Europe, or the Middle East and Africa, and had a higher mean overall comorbidity burden (Table 2). As compared to long-term residents with MS, immigrants with MS were slightly younger, less likely to dwell in rural areas, less likely to live in high-income neighborhoods, and had a higher mean comorbidity burden.

Comorbidities

The most common comorbidities in immigrants with MS were mood and anxiety disorders (27.4%), hypertension (9.1%), hyperlipidemia (4.7%), and migraine (4.7%; Table 3).

As compared to immigrants without MS, immigrants with MS had a significantly higher prevalence of COPD, diabetes, hypertension, IHD, epilepsy,

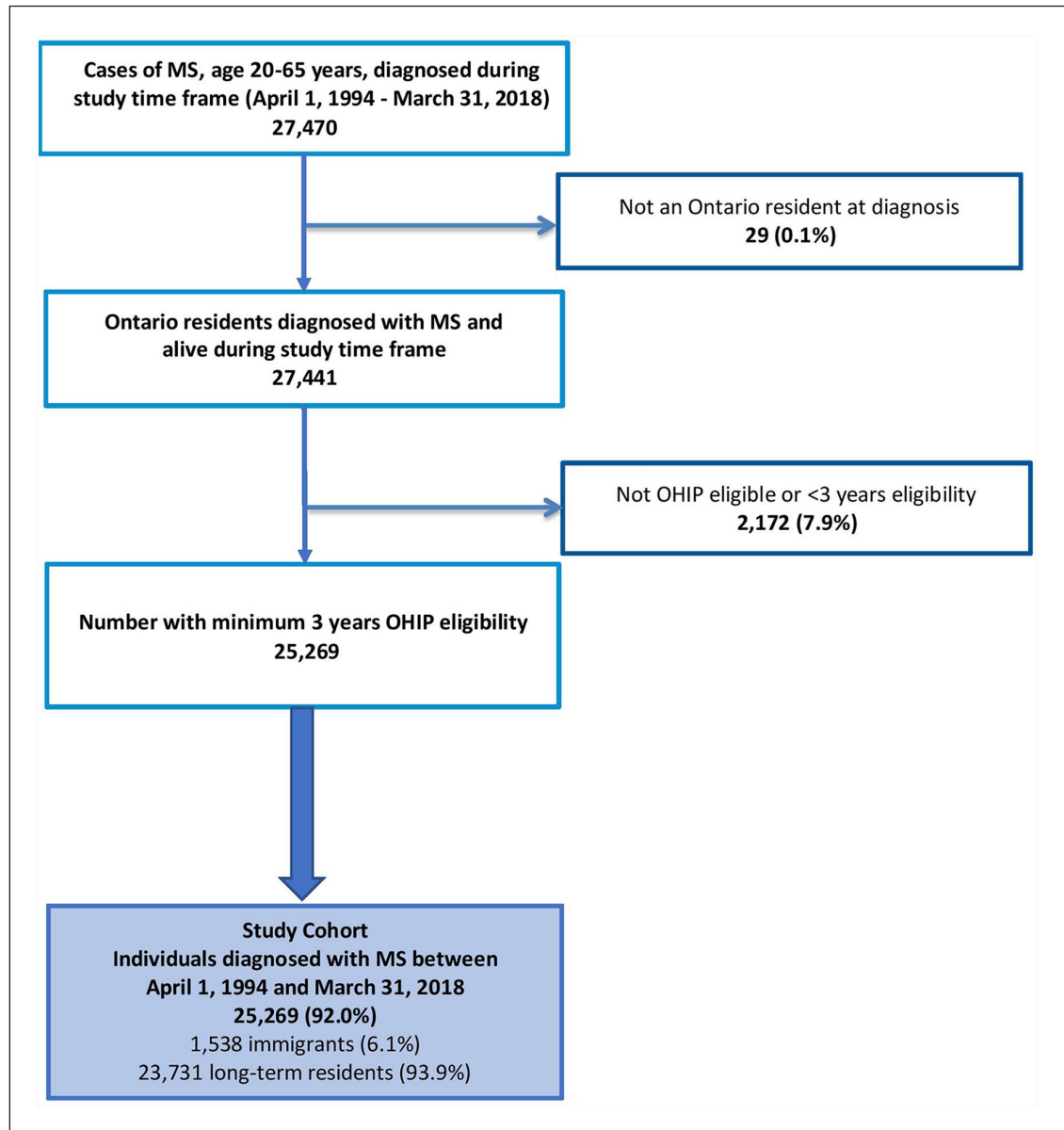


Figure 1. Cohort selection flowchart. The flowchart demonstrates how the study cohort was selected.

migraine, mood and anxiety disorders, schizophrenia, RA, and IBD (Table 3). Long-term residents with MS had a higher prevalence of these same conditions compared to those without MS. Relative to long-term residents with MS, immigrants with MS did not show any significant differences in the prevalence of diabetes, hypertension, IHD, migraine, or schizophrenia but exhibited a lower prevalence of COPD, epilepsy, IBD, and mood and anxiety disorders, and a higher prevalence of hyperlipidemia and RA. Comorbidity patterns were generally similar in immigrant women and men with MS (Figure 2).

Discussion

To our knowledge, this is the first population-based study to investigate comorbidity patterns in immigrants with MS. All the comorbidities studied (with the exception of hyperlipidemia) were more frequently observed in immigrants at MS diagnosis relative to their corresponding controls, including COPD, diabetes, hypertension, IHD, epilepsy, migraine, mood and anxiety disorders, schizophrenia, RA, and IBD. While similar to long-term residents with MS, the high prevalence of comorbidities in immigrants with MS is particularly striking given the

Table 2. Baseline characteristics of MS cases (immigrant vs long-term resident) and matched controls.

Variable	Value	Immigrant MS cases	Immigrant controls	LTR MS cases	LTR controls
		<i>N</i> = 1534	<i>N</i> = 4585	<i>N</i> = 23,731	<i>N</i> = 71,193
Female	Number (%)	1037 (67.6)	3101 (67.6)	16,539 (69.7)	49,617 (69.7)
Age (years) ^a	Mean ± SD	38.23 ± 10.34	38.19 ± 10.32	40.01 ± 11.04	40.01 ± 11.04
Age group (years)	20–35	653 (42.6)	1956 (42.7)	8944 (37.7)	26,832 (37.7)
	36–50	688 (44.9)	2056 (44.8)	10,194 (43.0)	30,582 (43.0)
	51–65	193 (12.6)	573 (12.5)	4593 (19.4)	13,779 (19.4)
Age on arrival in Canada	Mean ± SD	26.02 ± 11.37	26.50 ± 10.99	N/A	N/A
Rural residence	Number (%)	37 (2.4)	94 (2.1)	3150 (13.3)	9450 (13.3)
Neighborhood income quintile	1	407 (26.5)	1324 (28.9)	4301 (18.1)	12,290 (17.3)
	2	268 (17.5)	981 (21.4)	4599 (19.4)	13,730 (19.3)
	3	309 (20.1)	869 (19.0)	4801 (20.2)	14,400 (20.2)
	4	327 (21.3)	812 (17.7)	5022 (21.2)	15,088 (21.2)
	5	222 (14.5)	587 (12.8)	4909 (20.7)	15,440 (21.7)
Refugee status	Number (%)	280 (18.3)	819 (17.9)		
Region of origin	Africa & Middle East	356 (23.2)	628 (13.7)		
	Americas	220 (14.3)	722 (15.7)		
	Asia & Pacific	288 (18.8)	1884 (41.1)		
	Europe	560 (36.5)	1111 (24.2)		
	Stateless	50 (3.3)	150 (3.3)		
	United States of America	60 (3.9)	89 (1.9)		
Years of Ontario residence	<2	30 (2.0)	97 (2.1)		
	2–5	232 (15.1)	698 (15.2)		
	5–10	456 (29.7)	1392 (30.4)		
	10–15	338 (22.0)	1140 (24.9)		
	15+	473 (30.8)	1232 (26.9)		
Number of ADGs	Mean ± SD	8.05 ± 3.54	4.94 ± 3.35	7.49 ± 3.54	4.84 ± 3.34
	Median (IQR)	8 (6–10)	5 (2–7)	7 (5–10)	4 (2–7)
ADG, group	1–4 ADGs	236 (15.4)	1734 (37.8)	4525 (19.1)	29,587 (41.6)
	5–9 ADGs	774 (50.5)	1941 (42.3)	12,589 (53.0)	28,552 (40.1)
	10+ ADGs	511 (33.3)	449 (9.8)	6389 (26.9)	6695 (9.4)
	No ADGs	13 (0.8)	461 (10.1)	228 (1.0)	6359 (8.9)

MS: multiple sclerosis; LTR: long-term resident; SD: standard deviation; N/A: not available; IQR: interquartile range; ADG: Aggregated Diagnosis Group.

^aAge at index date, that is, first demyelinating event for MS cases.

low prevalence of medical conditions in immigrant controls and the “healthy immigrant effect”—reflecting the tendency of migrants to be healthier, wealthier, and better educated than the general population.²¹ Comorbidities are recognized to be common at diagnosis in the general MS population and are associated with delayed diagnosis,^{22,23} greater incidence of inflammatory disease activity,²⁴ decreased initiation of disease-modifying therapy (DMT),²⁵ and more rapid disability accrual.²⁶ Since immigrants may

already be at risk for delays in diagnosis and treatment due to language, cultural, and financial barriers^{27,28}, it is important that clinicians be aware of comorbidities associated with MS in immigrants and strive for early identification and management.

Mood and anxiety disorders were the most prevalent comorbidity observed in both immigrants and long-term residents with MS. Our findings echo a systematic review, which reported depression and anxiety

Table 3. Prevalence ratios of individual comorbidities comparing MS cases versus matched controls by immigrant status and immigrants with MS versus long-term residents with MS.

Condition	Immigrants		Long-term residents				Immigrants with MS vs LTR with MS	
	MS cases	Controls	Prevalence ratio (95% CI)	Adjusted prevalence ratio (95% CI)	MS cases	Controls	Prevalence ratio (95% CI)	Adjusted prevalence ratio (95% CI)
COPD	23 (1.5%)	32 (0.7%)	2.15 (1.84, 2.51) ^a	2.13 (1.84, 2.46) ^a	634 (2.7%)	1158 (1.6%)	1.64 (1.58, 1.71) ^a	1.62 (1.57, 1.68) ^a
Diabetes	28 (1.8%)	16 (0.4%)	5.23 (4.47, 6.13) ^a	5.31 (4.60, 6.12) ^a	433 (1.8%)	465 (0.7%)	2.79 (2.69, 2.90) ^a	2.75 (2.66, 2.86) ^a
Epilepsy	11 (0.7%)	9 (0.2%)	3.65 (3.09, 4.32) ^a	^b	257 (1.1%)	276 (0.4%)	2.79 (2.68, 2.91) ^a	2.77 (2.66, 2.89) ^a
Hypertension	139 (9.1%)	356 (7.8%)	1.17 (1.03, 1.32) ^c	1.17 (1.05, 1.31) ^d	2316 (9.8%)	5344 (7.5%)	1.30 (1.26, 1.34) ^a	1.30 (1.26, 1.33) ^a
IBD	6 (0.4%)	7 (0.2%)	2.56 (2.15, 3.05) ^a	^b	163 (0.7%)	381 (0.5%)	1.28 (1.23, 1.34) ^a	1.28 (1.23, 1.34) ^a
IHD	33 (2.2%)	61 (1.3%)	1.62 (1.39, 1.88) ^a	1.64 (1.43, 1.90) ^a	639 (2.7%)	916 (1.3%)	2.09 (2.02, 2.17) ^a	2.08 (2.01, 2.15) ^a
Hyperlipidemia	72 (4.7%)	237 (5.2%)	0.91 (0.79, 1.05)	0.91 (0.79, 1.04)	761 (3.2%)	2245 (3.2%)	1.02 (0.98, 1.06)	1.02 (0.98, 1.05)
Migraine	72 (4.7%)	67 (1.5%)	3.21 (2.81, 3.68) ^a	3.23 (2.83, 3.70) ^a	1246 (5.3%)	1545 (2.2%)	2.42 (2.34, 2.50) ^a	2.42 (2.34, 2.50) ^a
Mood/anxiety disorders	420 (27.4%)	565 (12.3%)	2.22 (2.02, 2.44) ^a	2.23 (2.03, 2.45) ^a	7400 (31.2%)	13292 (18.7%)	1.67 (1.63, 1.71) ^a	1.67 (1.63, 1.71) ^a
RA	8 (0.5%)	10 (0.2%)	2.39 (2.02, 2.84) ^a	2.30 (1.95, 2.71) ^a	107 (0.5%)	277 (0.4%)	1.16 (1.11, 1.21) ^a	1.16 (1.11, 1.21) ^a
Schizophrenia	13 (0.9%)	26 (0.6%)	1.49 (1.26, 1.77) ^a	^b	159 (0.7%)	309 (0.4%)	1.54 (1.48, 1.61) ^a	1.51 (1.45, 1.58) ^a

MS: multiple sclerosis; LTR: long-term resident; CI: confidence interval; COPD: chronic obstructive pulmonary disease; IBD: inflammatory bowel disease; IHD: ischemic heart disease; RA: rheumatoid arthritis.

^a*p* < 0.0001.

^bModels for these conditions did not converge, in part, due to small absolute case numbers and thus no adjusted estimate could be generated.

^c*p* < 0.05.

^d*p* < 0.01.

disorders in 23.7% and 21.9%, respectively, of persons with MS.⁵ Mood and anxiety disorders have been observed as part of what is known as the MS prodrome with higher rates of utilization of mental health services preceding MS diagnosis by up to 5 years.^{29,30} The high PR (adjusted PR: 2.23) of mood and anxiety disorders in immigrants with MS also reflects the low prevalence of these conditions in immigrant controls (12.3% vs 18.7% of long-term resident controls). This finding has three important implications. First, neurologic symptoms in an immigrant patient with a mental health condition should not be dismissed as secondary to the mental health issue. If the clinical context is appropriate, the possibility of demyelinating disease should be considered and investigated with a brain magnetic resonance imaging (MRI). Second, clinicians need to be aware

Figure 2. (Continued)

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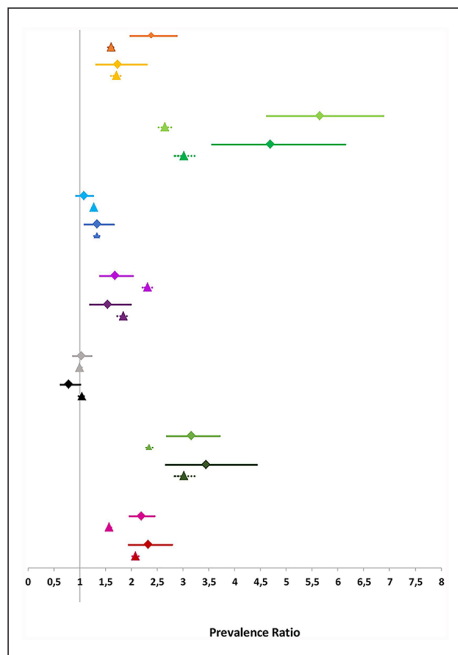
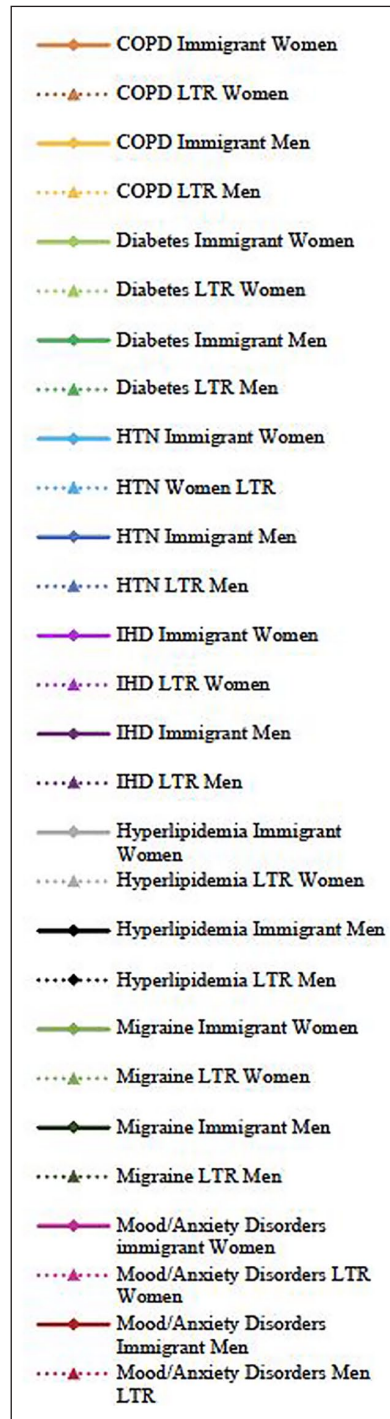


Figure 2. Prevalence ratios of individual comorbidities in MS cases versus matched controls by immigrant status and gender. This figure shows prevalence ratios for specific conditions in MS cases versus matched controls. For each condition, prevalence ratios are displayed for four different groups: immigrant women, long-term resident (LTR) women, immigrant men, and LTR men. For example, prevalence ratio for COPD immigrant women represents prevalence of COPD in immigrant women with MS divided by prevalence of COPD in immigrant women controls. Certain conditions (e.g. epilepsy, IBD, RA, schizophrenia) were omitted due to small absolute numbers of cases in the female and/or male immigrant cohorts and the resultant risk of loss of confidentiality. COPD: chronic obstructive pulmonary disease; HTN: hypertension; IHD: ischemic heart disease.

of the high prevalence of mood and anxiety disorders in both female and male immigrants newly diagnosed with MS and screen for these conditions. Immigrants may encounter unique barriers in accessing mental healthcare due to language difficulties, lack of health system literacy, and stigma toward mental health

problems in their communities^{27,28} Third, clinicians should follow these patients closely and consider early intervention as mental health conditions have been associated with greater long-term disability in MS, and immigrants and non-White persons may already be at risk for earlier disability accumulation.³¹⁻³³ In a large population-based cohort study of incident MS cases in Canada, psychiatric comorbidity was associated with subsequent greater accrual of neurologic disability as measured by the Expanded Disability Status Scale (EDSS).²⁶ Another large cohort study in Sweden found that persons having MS with depression had a higher risk of reaching major disability milestones, including EDSS scores of 3.0, 4.0, and 6.0.³⁴ Mood and anxiety disorders, as well as migraine, another prevalent comorbidity among our immigrant cohort, have been shown to be major causes of limited work activities in the Australian MS Longitudinal Study of 929 persons with MS.³⁵ Depression, along with physical comorbidity, was correlated with decreased health-related quality of life in a Canadian cross-sectional study of 949 persons with MS.³⁶

Overall, depression and anxiety are known to be underdiagnosed and undertreated in individuals with MS.^{37,38} Brief, self-reported psychometric scales can assist with screening for these conditions.³⁸ Pharmacotherapy, cognitive behavioral therapy, mindfulness-based therapy, and exercise programs may all offer therapeutic benefit although there is no gold standard approach to treatment.^{38,39}

Psychiatric, cerebrovascular, cardiovascular, lung, diabetes, cancer, and Parkinson's disease comorbidity, were found to predict earlier mortality in a large population-based Danish cohort study of nearly 9000 persons with MS.²³ In our cohort, immigrants who developed MS had a higher prevalence of COPD, diabetes, hypertension, and IHD compared to immigrant controls. These conditions may share common risk factors with MS such as smoking and obesity and may be provoked or exacerbated by adoption of Western lifestyle habits. In addition, multiple studies have demonstrated that cardiovascular disease may exacerbate MS disease course. In one retrospective study of 251 MS subjects, a one-point increase in baseline Framingham cardiovascular risk score was associated with a 31% higher risk of relapse, 19% higher risk of reaching an EDSS score of 6.0, and 62% higher risk of DMT escalation over 5 years.⁴⁰ A recent study using postmortem whole-body autopsy to assess vascular disease burden suggested an excessive burden of cerebral small vessel disease in persons with MS compared to controls who died at younger ages of ≤ 60

years.⁴¹ In a population-based study in the United Kingdom, persons with MS were found to have higher rates of macrovascular events and associated mortality than matched controls, which was irrespective of age and not fully accounted for by traditional vascular risk factors.⁴ However, since recognized vascular risk factors remain reversible targets with early intervention, clinicians should consider factors such as elevated blood pressure, obesity, and smoking soon after diagnosis in their MS patients, particularly in groups known to have increased susceptibility. High rates of cardiovascular disease have been observed in certain immigrant groups in Ontario, including those from South Asia and the Middle East.¹⁴

The question of whether comorbidities lead to delays in MS diagnosis in immigrants merits further study. Comorbidity has been associated with delayed diagnosis in the overall MS population for both physical^{22,23} and mental health conditions.²² Reasons for delayed diagnosis have not been completely elucidated but may be due to misattribution of MS symptoms to an established medical condition by either the patient or healthcare provider. The potential for misattribution could be compounded in immigrants due to under-recognition of MS in non-White individuals.

Strengths of our study include the large population-based sample, linkage of national immigrant data with health administrative data sources, use of validated comorbidity algorithms, and long interval for determination of incident MS cases. Our study has some important limitations. We cannot exclude the possibility that some individuals in the non-MS group were diagnosed with MS before 1994 or before moving to Ontario; however, the required 3-year period with no demyelinating disease claims prior to study entry makes this unlikely. Our estimates reflect recent active comorbid conditions as algorithms were only applied to health administrative data for the 3 years prior to MS index date. Lifetime prevalence of these conditions would be considerably higher, but the look-back period was dictated by our cohort of interest, the brief duration of Canadian residence for many immigrants, and the need to ensure a common period of ascertainment in both immigrant and long-term resident cohorts. SES was considered as a potential confounder in our adjusted analysis since educational status and associated occupational skills can facilitate immigration into Canada, although it is possible that it might be on the causal pathway between immigrant status and comorbidity, which could lead to overadjustment bias. However, we note that adjusted and unadjusted PRs were very similar. Some immigrants were

excluded because of fewer than the 3 years of health coverage required for determination of comorbidities (Figure 1). Incident cases of MS in immigrants who arrived prior to 1985 would have been classified as long-term resident cases due to the lack of immigration data from this era, but we expect the number to have been small given that the average age of MS onset is young adulthood. Moreover, there is evidence that the health characteristics of immigrants become more similar over time to those born in Canada.⁴² Finally, we were not able to examine certain comorbidities including cancer or health behaviors such as smoking due to limitations of our data sources.

In summary, we found that immigrants with MS had an increased prevalence of COPD, diabetes, hypertension, IHD, epilepsy, migraine, mood and anxiety disorders, schizophrenia, RA, and IBD relative to immigrant controls. The same conditions were more prevalent in long-term residents with MS compared to controls, and mirrored findings from previous studies of comorbidities in the general MS population. Prevalence of most conditions was similar or only slightly lower in immigrants compared to long-term residents with MS diagnosis, despite the “healthy immigrant effect” observed in unaffected immigrants. Therefore, the high prevalence of comorbidities in immigrants at MS diagnosis is particularly noteworthy. Since comorbidities are associated with worse long-term outcomes, clinicians should aim for early identification and management of comorbid conditions in immigrants with MS.

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Author Contributions

D.R. wrote the original grant proposal and drafted the manuscript. All authors had a role in study design, interpretation of the data, and manuscript review and approval. J.G. and P.P. performed the analyses.

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