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MS risk in immigrants in the McDonald era

A population-based study in Ontario, Canada

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Abstract

Objective

To determine risk factors for multiple sclerosis (MS) in immigrants and to compare MS risk in immigrants and long-term residents in Ontario, Canada.

Methods

We applied a validated algorithm to linked, population-based immigration and health claims data to identify incident cases of MS in immigrants and long-term residents between 1994 and 2016. We conducted 2 multivariable Cox proportional hazards regression analyses: 1 analysis limited to the immigrant cohort assessing potential risk factors for developing MS, and 1 analysis comparing MS risk between immigrants and matched long-term residents (1:3 match).

Results

We identified 2,304,302 immigrants for the immigrant-only analysis, of whom 1,526 (0.066%) developed MS. Risk was greatest in those <15 years old at landing (referent <15 years; 16–30 years: hazard ratio [HR] 0.73, 95% confidence interval [CI] 0.63–0.85; 31–45 years: HR 0.55, 95% CI 0.47–0.64). Immigrants from the Middle East (HR 1.22, 95% CI 1.06–1.40) were at greater MS risk than immigrants from Western nations; all other regions had lower risk (p < 0.0001). The matched analysis included 2,207,751 immigrants and 6,362,169 long-term residents. Immigrants were less likely to develop MS than long-term residents (p < 0.0001), although this lower risk was attenuated with longer residence in Canada.

Conclusions

MS incidence in immigrants to Ontario, Canada, varied widely by region of origin, with greatest risk seen in those from the Middle East. Longer residence in Canada was associated with increased risk, even with migration in adulthood, suggesting that environmental exposures into adulthood contribute to MS risk.

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Glossary

ADG = Aggregated Diagnosis Groups; **ICD-9** = *International Classification of Disease, 9th revision*; **ICD-10-CA** = *International Classification of Disease, 10th revision, Canada*; **ICES** = Institute for Clinical Evaluative Sciences; **IRCC** = Permanent Resident Database of Immigration, Refugees and Citizenship Canada; **MS** = multiple sclerosis; **OHIP** = Ontario Health Insurance Plan; **RPDB** = Registered Persons Database; **SES** = socioeconomic status.

Global estimates have shown an increase in the prevalence of multiple sclerosis (MS) in recent years, due in part to improved survival, wider dissemination of MRI technology, and revised diagnostic criteria.[1] However, prevalence is still reported to vary substantially by region, with a higher prevalence in northern Europe and North America.[1–4] Investigators in the 1960s conducted migration studies to investigate the observed range in MS prevalence.[5–7] Early work reported that individuals born in northern Europe who migrated to South Africa or Israel in early life demonstrated a markedly lower risk of developing MS than those in their native countries.[5,6] Conversely, migration from low- to high-risk countries in childhood was associated with an increase in the risk of developing MS.[8] However, if migrants moved after 15 years of age, they maintained the MS risk of their native country, implying a critical window in early life for environmental influences on MS risk.[5] A more recent study of immigrants from the United Kingdom and Ireland to Australia found that MS risk declined regardless of age at migration (<15 vs >15 years).[9] Thus, it is uncertain whether there is a critical window for environmental exposures leading to MS or whether changes in environment may continue to influence MS risk into adulthood. This has important potential implications for disease prevention and for the health of immigrants moving into high-risk regions.

We conducted a retrospective, population-based study examining incident cases of MS over the last 2 decades (1994–2016) in Ontario, Canada, a region with an MS prevalence among the highest in the world.[10] Our aims were to evaluate risk factors for developing MS in immigrants and to compare the risk of MS in immigrants vs long-term residents. Ontario's large, ethnically diverse population and universal health insurance system provided a unique setting to address limitations of past migration studies, including small cohort sizes, lack of population-based data, and single migrant groups with limited differentiation between immigrants by country or region of origin.

Methods

Setting

This was a retrospective cohort study using linked administrative data in Ontario, Canada, from January 1, 1994, through December 31, 2016. Ontario's population includes >3 million immigrants, one of the largest immigrant populations in the world. Ontario's residents are covered by a universal provincial health insurance program known as the Ontario Health Insurance Plan (OHIP), which captures all physician billings for inpatient and outpatient services. OHIP is 100% covered by the government of Ontario, and all immigrants to Ontario are eligible for OHIP after residence of at least 153 days.

The study included 2 components: an analysis of MS risk factors in immigrants to Ontario and a matched cohort analysis evaluating MS risk in immigrants matched to long-term Ontario residents.

Immigrants

Immigrants to Ontario were identified through the electronic Permanent Resident Database of Immigration, Refugees and Citizenship Canada (IRCC), which contains data on immigrants arriving in Canada from 1985 on. Data from the IRCC have previously been linked to the Registered Persons Database (RPDB) in Ontario and with OHIP data using probabilistic matching.[11] The IRCC database records age at landing, sex, country of origin, immigrant category (e.g., refugee), Canadian language ability (English, French, neither), and highest educational attainment at the time of landing. Although we lacked data on immigrants before 1985, given the study duration of >20 years and mean age at MS onset, most of the cases of MS among immigrants from 1994 to 2016 should have been captured. Similar approaches have been taken in other migration studies.[11,12]

Immigrants were eligible for inclusion if they were alive and ≥20 years of age as of December 31, 2014, and <66 years as of January 1, 1994 (figure 1). We considered individuals only ≥20 years of age because MS is rare in the pediatric population and at the time of this study the MS case algorithm had not been validated in children.[13] We chose not to consider individuals >65 years of age because of small numbers and concerns about possible misdiagnosis of incident MS cases at the upper limits of age, given the rarity with which this occurs.[14] An OHIP eligibility requirement of ≥2 years was imposed to ensure that prevalent MS cases were not misclassified as incident. Immigrants were required to have ≥2 years of follow-up to allow for meeting the MS algorithm. Because OHIP data were available only up to the end of 2016, immigrants had to have arrived in Canada by December 31, 2012.

Immigrants were excluded if they had an MS diagnosis (see below) before January 1, 1994, before 20 years of age, or before study eligibility. Furthermore, they were excluded if they were not an Ontario resident as determined by data

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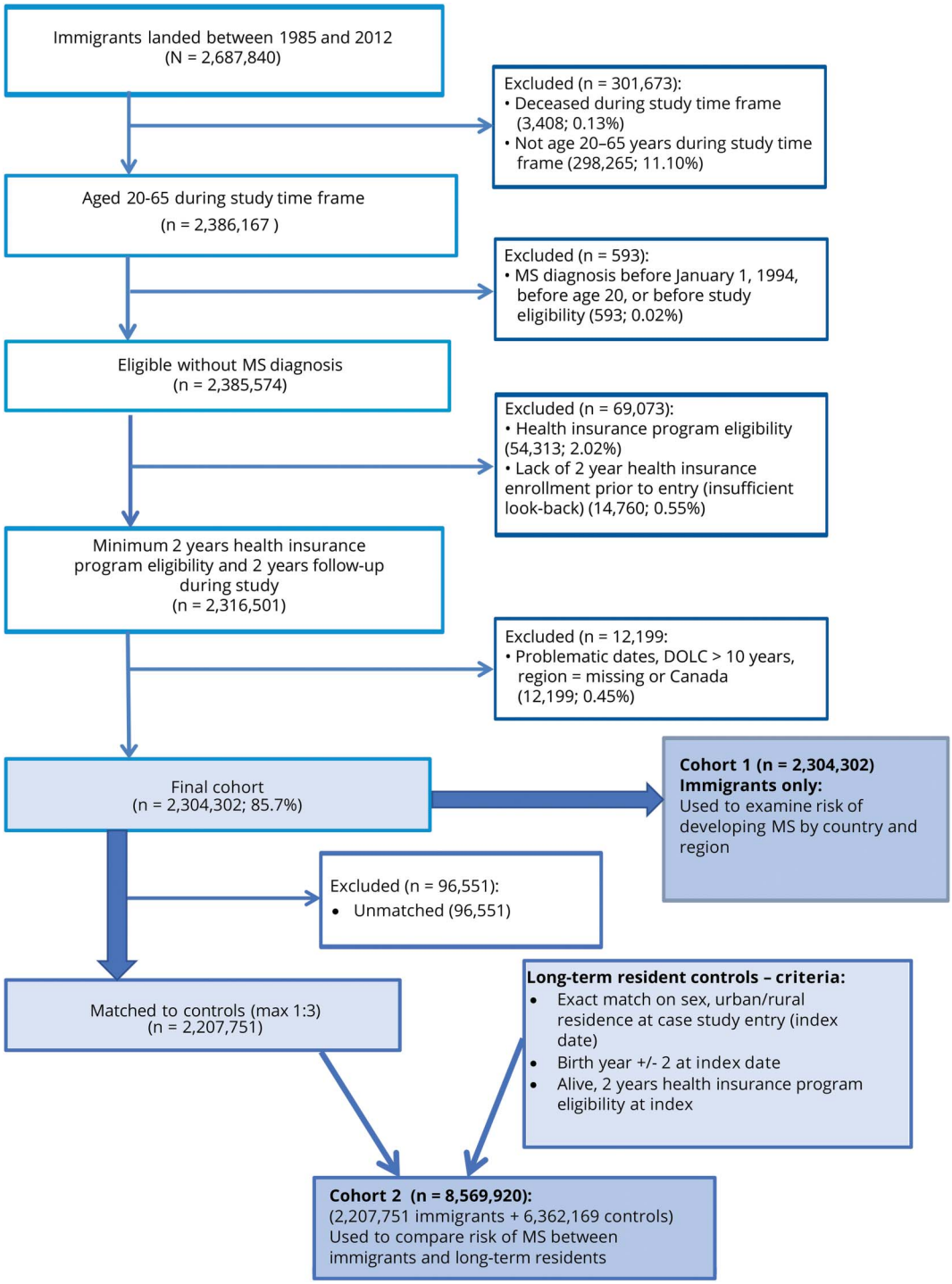
Figure 1 Selection of the overall immigrant and matched immigrant cohorts



We selected immigrants arriving from 1985 on who had at least 2 years of Ontario Health Insurance Plan eligibility and 2 years of follow-up during the study. All eligible immigrants made up the first cohort. The second cohort comprised all immigrants who could be matched against long-term Ontario residents by age, sex, and urban residence. DOLC = date of last contact; MS = multiple sclerosis.

linkage with the RPDB or if the last date of OHIP contact was >10 years before cohort entry date to account for individuals who had likely left the country. Finally, immigrants were excluded if their recorded date of birth was after their landing date. Immigrants entered the cohort on the first date when they met all criteria.

Long-term residents

Long-term residents of Ontario were defined as those who were resident in the province; <65 years of age on January 1, 1994, and ≥20 years of age on December 31, 2016; and OHIP eligible and who had not immigrated after 1984. Individuals were excluded if they were no longer resident in

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Ontario or had a last date of OHIP contact of >10 years earlier.

MS cases

MS cases were identified with health claims data.[13,15] Physician claims include the date of service and are classified by main diagnostic purpose of the visit with ICD-9 codes. The National Ambulatory Care Reporting System captures emergency room visits, including visit date and the reason for visit recorded with ICD 10-CA codes. The Discharge Abstract Database captures hospitalizations, including dates of admission and discharge and diagnoses, which are recorded with ICD-9 codes before 2002 and ICD-10-CA codes from 2003 on. Demographic information was obtained from the RPDB of Ontario, which contains demographic data such as age, sex, health insurance eligibility, postal code of residence, and death information.

These datasets were linked by unique encoded identifiers and analyzed at the Institute for Clinical Evaluative Sciences (ICES). The full OHIP database is made available in unedited form to researchers at ICES through an agreement with the Ontario Ministry of Health and Long Term Care.

The primary outcome was a diagnosis of MS. As previously described, incident MS cases were identified with a validated algorithm[15] that required 1 hospital admission for MS or 5 physician billings over 2 years with the ICD-9/10-CA codes 340/G35. Primary and secondary hospital discharge diagnoses of MS were included. This algorithm has a sensitivity of ≈85% and specificity approaching 100%. After MS cases were identified, their index date was defined as the first inpatient or outpatient contact for a demyelinating condition as identified by ICD-9/10-CA codes, including encephalomyelitis (323/G36 or G37), optic neuritis (377/H46), or MS (340/G35).

Standard protocol approvals, registration, and patient consents

This study was approved by the research ethics boards 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, 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 ICES Privacy and Compliance Office.

Analysis

We conducted 2 analyses: an analysis of risk factors for developing MS in the immigrant-only cohort, which included all immigrants to Ontario who met study inclusion criteria, and a matched analysis comparing the risk of MS in immigrants to the risk in long-term residents.

Immigrant-only analysis

We used a Cox proportional hazards model to examine risk factors for developing MS among all immigrants who met the inclusion criteria. Person-time was calculated from the study entry date. Participants were censored with the event of interest (MS onset), death, age of 66 years, or loss of OHIP eligibility.

Covariates

Covariates included sex, age at landing (categorized as ≤15, 16–30, 31–45, and 46–65 years), immigrant refugee status (refugee vs nonrefugee), region of origin, urban vs rural residence, neighborhood income, comorbidity burden (weighted Aggregated Diagnosis Groups [ADG] score), and immigrant status/time elapsed in Canada. Due to violation of the proportional hazards assumption, immigrant status was included as a covariate and categorized by duration of residence in Canada: 2 to 5, 5 to 10, 10 to 15, and ≥15 years. Urban residence, neighborhood income, comorbidity burden, and time elapsed in Canada were calculated as time-varying covariates, updated annually. Region of origin was categorized as Africa, the Caribbean, East Asia (Cambodia, China, Hong Kong, Indonesia, Japan, Korea, Malaysia, Myanmar, Pacific Islands, Philippines, Singapore, Taiwan, Thailand, Vietnam), Hispanic America (Mexico, Central America, South America), the Middle East (Northern Africa, the Gulf States, Iran, and Iraq), South Asia (Afghanistan, Bangladesh, India, Pakistan, Sri Lanka), Western countries (Europe, Russia, Australia, New Zealand, and the United States), and other (any other countries). We measured socioeconomic status (SES) by linking postal code of residence to census data to determine neighborhood income quintile; the lowest 2 quintiles were collapsed to represent low income, and the remaining quintiles represent high income. Comorbidity burden was measured with the ADG Mortality Risk Score, a weighted score incorporating ADGs that predicts 1-year mortality.[16] ADGs are based on the Johns Hopkins ACG System version 10 and measured using hospitalization and physician visit information from 2 years before index.

We repeated the analysis using the same covariates, substituting country for region of origin, for all countries with ≥20 MS cases by December 31, 2016; the United Kingdom was used as the reference group.

Matched analysis

Immigrants were matched to long-term residents in a 1:3 ratio by age (±2 years), sex, and place of residence (urban vs rural). We compared the baseline characteristics of the full immigrant cohort, immigrants with ≥1 matches, and matched long-term residents. At the end of the study, demographic characteristics of MS cases in matched immigrants vs nonimmigrants were compared by use of *t* tests for continuous variables and χ^2 tests for categorical variables. We used a Cox proportional hazards model to compare the risk of MS between immigrants and nonimmigrants, controlling for age at study entry, sex, urban vs rural residence, SES, comorbidity

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Table 1 Baseline characteristics of the matched immigrant and long-term resident populations

Variable	Value	All immigrants (matched and unmatched) (n = 2,304,302)	Immigrants with at least 1 match (n = 2,207,751)	Matched general population (n = 6,362,169)
Age at study entry, y	Mean ± SD	33.56 ± 11.46	33.99 ± 11.43	34.01 ± 11.46
	Median (IQR)	32 (24–40)	33 (25–41)	32 (25–41)
Age at landing, y	Mean ± SD,	29.57 ± 13.36	30.08 ± 13.27	
	Median (IQR)	29 (21–38)	30 (22–38)	
Sex, n (%)	F	1,174,251 (50.96)	1,115,284 (50.52)	3,181,820 (50.01)
Neighborhood income quintile, n (%)	1 (lowest)	814,506 (35.35)	790,805 (35.82)	1,173,172 (18.44)
	2	519,634 (22.55)	504,510 (22.85)	1,251,633 (19.67)
	3	388,658 (16.87)	377,931 (17.12)	1,283,750 (20.18)
	4	305,850 (13.27)	297,637 (13.48)	1,317,174 (20.70)
	5 (Highest)	222,561 (9.66)	216,172 (9.79)	1,314,196 (20.66)
Educational qualification, n (%)	1. Secondary or less	1,214,660 (52.71)	1,137,073 (51.50)	
	2. Trade, diploma, some university	417,716 (18.13)	410,849 (18.61)	
	3. Bachelor's degree	495,949 (21.52)	487,314 (22.07)	
	4. Postgraduate	175,889 (7.63)	172,434 (7.81)	
	5. Unknown	88 (0.00)	81 (0.00)	
Urban residence at study entry, n (%)		2,238,815 (97.16)	2,174,644 (98.50)	6,274,133 (98.62)
Reason for study entry, n (%)	Study start date	333,873 (14.49)	323,651 (14.66)	
	20th birthdate	417,470 (18.12)	360,044 (16.31)	
	At least 2 years of y eligibility	1,077,781 (46.77)	1,056,121 (47.84)	
	At least 2 y after landing date	475,178 (20.62)	467,935 (21.20)	
Reason for exiting study, n (%)	Study end date	1,881,801 (81.66)	1,800,444 (81.55)	5,096,817 (80.11)
	66th birthdate	214,746 (9.32)	214,353 (9.71)	640,979 (10.07)
	Date of OHIP ineligibility	180,965 (7.85)	166,777 (7.55)	446,919 (7.02)
	MS diagnosis	1,526 (0.07)	1,420 (0.06)	15,093 (0.24)
	Date of death	25,264 (1.10)	24,757 (1.12)	162,361 (2.55)
No. of years in study	Mean ± SD	12.23 ± 6.57	12.08 ± 6.56	11.84 ± 6.74
	Median (IQR)	12 (7–18)	12 (7–17)	11 (6–17)
MS diagnosis at the end of study, n (%)		1,526 (0.07)	1,420 (0.06)	15,093 (0.24)
Weighted ADG score	Mean ± SD	0.91 ± 7.82	0.95 ± 7.87	1.74 ± 8.49
	Median (IQR)	0 (−1 to 4)	0 (−1 to 4)	0 (−2 to 4)
Landed as refugee, n (%)	Yes	357,871 (15.53)	341,336 (15.46)	

Continued

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Table 1 Baseline characteristics of the matched immigrant and long-term resident populations *(continued)*

Variable	Value	All immigrants (matched and unmatched) (n = 2,304,302)	Immigrants with at least 1 match (n = 2,207,751)	Matched general population (n = 6,362,169)
Region based on country of origin, n (%)	Africa	133,948 (5.81)	127,017 (5.75)	
	Caribbean	127,968 (5.55)	119,975 (5.43)	
	East Asia	609,081 (26.43)	586,006 (26.54)	
	Hispanic America	178,850 (7.76)	169,545 (7.68)	
	Middle East	253,251 (10.99)	242,941 (11.00)	—
	Other	521 (0.02)	494 (0.02)	
	South Asia	542,317 (23.53)	525,699 (23.81)	
	Western	458,366 (19.89)	436,074 (19.75)	
Time elapsed since landing at study entry, n (%)	2–5 y	1,811,683 (78.62)	1,760,318 (79.73)	
	5–10 y	313,616 (13.61)	282,471 (12.79)	
	10–15 y	128,868 (5.38)	112,035 (5.07)	
	≥15 y	55,135 (2.39)	52,927 (2.40)	

Abbreviations: ADG = Aggregated Diagnosis Groups; IQR = interquartile range; MS = multiple sclerosis; OHIP = Ontario Health Insurance Plan.

burden (weighted ADG), calendar year of cohort entry, and time elapsed in Canada. As in the first analysis, place of residence, SES, comorbidity burden, and duration of residence in Canada were included as time-varying covariates, updated annually. Person-time was calculated from the study entry date, and participants were censored with the event of interest (MS onset), death, age of 66 years, or loss of OHIP eligibility.

Complementary analyses

We checked for effect modification of the association between immigrant status and MS risk by age group and sex in the immigrant cohort using a combination of models with interaction terms (immigrant status × age group) and stratified models.

Model assumptions were tested with standard methods.[17] Statistical analyses were conducted with SAS version 9.4 (SAS Institute, Inc, Cary, NC).

Data availability

The individual-level data underlying this study are based on records generated from the administration of Ontario's publicly funded health system. The ICES has a special designation under Ontario's Personal Health Information Protection Act to use this data in studies that evaluate health care delivery and outcomes. This designation is granted by the Information and Privacy Commissioner of Ontario and is contingent on a triennial review and ongoing oversight of the privacy practices at ICES. A variety of measures are deployed to protect the personal health information entrusted to ICES, and under the Personal Health Information Protection Act (Ontario Regulation 329/04), the underlying data are legally not allowed for public repository.

While data-sharing agreements prohibit ICES from making the dataset publicly available, access may be granted to those who meet prespecified criteria for confidential access, available at ices.on.ca/DAS. The full dataset creation plan and underlying analytic code are available from the authors on request, with the understanding that the programs may rely on coding templates or macros that are unique to ICES.

Results

Risk factors for MS in the immigrant cohort

Out of 3,080,227 immigrants, 2,304,302 (74.8%) were eligible for inclusion (figure 1 and table 1). Of these, there were 1,526 incident MS cases from 1994 to 2016. At baseline, immigrants who developed MS were more likely to be female, more likely to have arrived from Western countries or the Middle East, more likely to have been in Canada for at least 5 years, and of younger age at landing in Canada.

In the Cox model, risk of MS was associated with age at landing, sex, region of origin, SES, comorbidity burden, and time elapsed since landing (table 2). Compared to those ≤15 years of age at landing, those who were older had a reduced risk, which became progressively less as age at landing increased. Compared to immigrants from Western countries, risk was greater in those from the Middle East, whereas other regions of origin were associated with

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Table 2 Cox proportional hazards model investigating risk of incident MS among immigrants to Ontario, Canada, 1994 to 2016

Parameter	HR	95% CI	*p* Value
Age at landing (reference = ≤15), y			
16–30	0.73	0.63–0.85	<0.0001
31–45	0.55	0.47–0.64	<0.0001
46–65	0.31	0.24–0.41	<0.0001
Female	2.23	2.00–2.49	<0.0001
Low neighborhood income quintile[a]	0.84	0.76–0.94	0.0014
Urban[a]	1.20	0.86–1.68	0.2943
Landed as refugee	0.89	0.77–1.02	0.0963
Region of origin (reference = Western countries[b]**)**			
Africa	0.45	0.35–0.57	<0.0001
Caribbean	0.58	0.47–0.71	<0.0001
East Asia	0.15	0.12–0.18	<0.0001
Hispanic America	0.42	0.34–0.52	<0.0001
Middle East	1.22	1.06–1.40	0.0042
Other	1.36	0.19–9.69	0.7560
South Asia	0.33	0.28–0.39	<0.0001
Weighted ADG scores[a]	1.05	1.04–1.06	<0.0001
Immigrant status (reference = time elapsed since landing 2–5 y)[a]			
Time elapsed since landing: 5–10 y	1.57	1.32–1.87	<0.0001
Time elapsed since landing: 10–15 y	1.25	1.08–1.45	0.0033
Time elapsed since landing: ≥15 y	1.04	0.90–1.21	0.5888

Abbreviations: ADG = Aggregated Diagnosis Groups; CI = confidence interval; HR = hazard ratio; MS = multiple sclerosis.
[a] Time-varying covariate, updated annually.
[b] Europe, Russia, Australia, and the United States.

a lower risk of MS; the lowest risk was in those from East Asia.

In the model substituting country for region of origin, we found higher risks of MS in immigrants from Iran, Lebanon, the former Yugoslavia, and the United States compared to the United Kingdom (figure 2). The risk in immigrants from Iran was >3-fold that of UK immigrants, whereas lower risks of MS were observed in immigrants from China, the Philippines, Sri Lanka, India, Guyana, and Pakistan.

Risk of developing MS in matched immigrants vs long-term residents

Of the 2,304,302 immigrants in the first analysis, 2,207,751 immigrants (95.8%) were matched to long-term residents (figure 1). The matched immigrant cohort was similar to the overall immigrant cohort, although slight differences were observed. Unmatched immigrants were younger, were more likely to be female and to dwell in urban centers, and had a lower comorbidity burden than the remainder of the immigrant cohort (table 1). After matching, there were 1,420 MS cases among immigrants and 15,093 MS cases among matched long-term residents. Compared to matched long-term residents with MS, immigrants with MS had an older mean age at MS onset, were more likely to enter the study and to be diagnosed with MS at a later calendar year, had a lower SES, and were more likely to live in urban settings (table 3). Sex ratio and comorbidity burden were similar in immigrants and long-term residents with MS.

The risk of developing MS was lower in immigrants compared to long-term residents at all time points (tables 4 and 5). The reduction in risk was greatest within 2 to 5 years of landing, with MS risk increasing with duration of time in Canada. Risk of MS decreased with older age at study entry and was lower in men. Greater comorbidity burden was associated with increased MS risk, but no association was observed with urban residence or SES. Compared to participants who entered the cohort in 1994, those who entered in 1996 to 2014 had an increased risk of MS. We did not observe any effect modification of the relationship between immigrant status and MS risk by sex. For age group at cohort entry, there was statistical evidence of effect modification, but the magnitude of the effect size was small and not thought to be clinically meaningful.

Discussion

In this large population-based retrospective cohort study, we studied a diverse multinational population of >2.3 million immigrants, including >1,500 incident cases of MS after arrival in Canada. It is one of the few migration studies performed in the McDonald era with widespread use of MRI to facilitate MS diagnosis. We observed a markedly lower risk of MS in immigrants compared to long-term residents in Ontario, Canada, a region with one of the highest MS prevalence and incidence rates in the world.[10] MS risk varied widely by region and country of origin despite access to the same publicly funded health care system. Immigrants from the Middle East had the highest risk of developing MS, followed by immigrants from Western nations; immigrants from East Asia had the lowest risk. MS risk was also associated with female sex and greater comorbidity burden. MS risk declined gradually with age at migration, but considerable risk of developing MS persisted even with migration after 15 years of age, in contrast to past studies. SES was not consistently associated with MS risk in this study, but we cannot exclude an effect of SES in early life due to lack of data on previous SES of immigrants.

Our findings illustrate the contribution of age at and duration of environmental exposures to MS risk. The high MS

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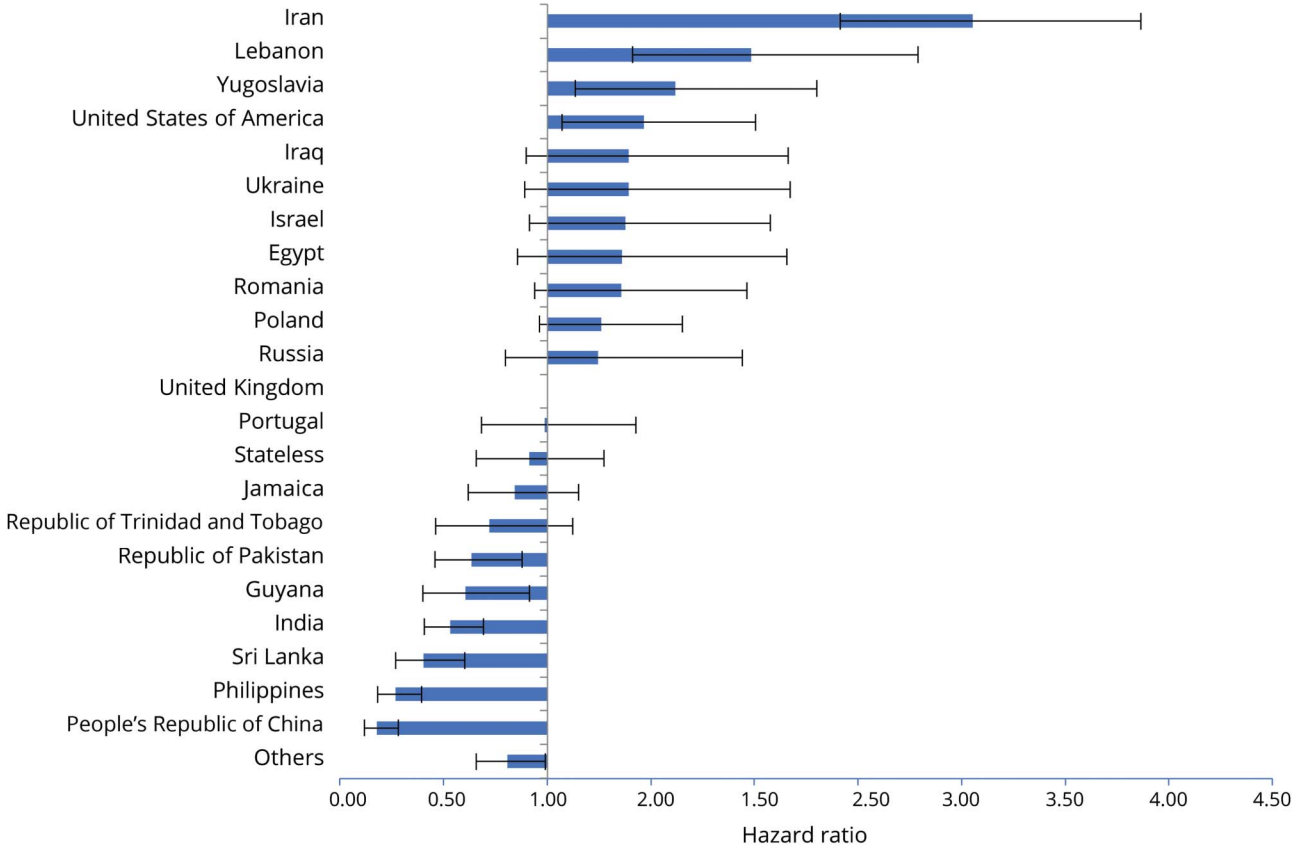
Figure 2 Risk of MS in immigrants to Ontario by country of origin



Risk was estimated with a Cox proportional hazards model adjusted for age, sex, neighborhood income quintile (low vs high), weighted Aggregated Diagnosis Groups score, refugee status, urban residence, and time elapsed since landing. Error bars depict 95% confidence intervals. Countries listed individually had at least 20 multiple sclerosis (MS) cases by December 21, 2014. The United Kingdom was used as the reference group.

prevalence in Ontario may be related to its latitude, where there is reduced sunlight exposure and vitamin D deficiency is common.[10] Other potential contributing factors may include obesity and the North American diet, which is lower in fish intake and relatively high in saturated fats.[18,19] A genetic founder effect is unlikely in Ontario given the diverse national and ethnic origins of its population. The increase in MS incidence with duration of residence in Canada suggests possible dose-response effects of high-risk MS environments. This relationship was not uncovered by past migration studies, most likely because of a lack of longitudinal data, although second-generation immigrants in Western countries reportedly have a higher risk of MS than their parents.[20,21]

Younger age at time of landing in Canada was associated with a higher risk of developing MS, but MS risk declined by only ≈20% to 25% for each 15-year increase in age at landing. In contrast, past migration studies suggested that there was a cutoff age for environmental effect on MS risk at 15 years.[5,6] A more recent, larger study of immigrants from the United Kingdom to Australia did not find a difference in MS risk in those who migrated before and after 15 years of age.[9] There could be several explanations for these conflicting findings. Many of the earlier studies focused on migration from high- to low-risk countries,[5,6] and it is possible that a critical age window may depend on the direction of migration. Past studies may have created an artificial threshold around 15 years of age because age at migration was analyzed as a dichotomous variable due to small numbers. Previous studies did not control for potential confounders of MS risk. There may have been an element of ascertainment bias due to the lack of recognition of MS in nonwhites, particularly before the widespread use of MRI to assist MS diagnosis.

Although studies of geographic variation in MS risk have often focused on latitude, many of the high-risk regions of origin we observed such as the Middle East cannot be explained on this basis. As early as the 1970s, a high MS risk was noted in immigrants from Middle Eastern countries to London, England, although numbers were small.[22] More recently, a high prevalence of MS was noted among Iranian immigrants in Sweden and Norway.[20,23] The reason for the higher risk in Middle Eastern migrants is unknown, but genetic factors likely contribute. Genetic constitution of the Lebanese population overlapped significantly with European cohorts in a genome-wide study, and this also may apply to other Middle

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Table 3 Demographic characteristics of matched immigrants and long-term residents who developed MS by the end of the study

Variable	Value	MS at the end of study			
		Long-term resident, (n = 15,093), n (%)	Immigrant (n = 1,420), n (%)	Total (n = 16,513), n (%)	*p* Value
Year at study entry	1994–1999	8,435 (55.89)	703 (49.51)	9,138 (55.34)	<0.001
	2000–2004	3,317 (21.98)	328 (23.10)	3,645 (22.07)	
	2005–2009	2,571 (17.03)	261 (18.38)	2,832 (17.15)	
	2010–2014	770 (5.10)	128 (9.01)	898 (5.44)	
Year of MS diagnosis	1994–1999	3,009 (19.94)	186 (13.10)	3,195 (19.35)	<0.001
	2000–2004	3,311 (21.94)	235 (16.55)	3,546 (21.47)	
	2005–2009	4,058 (26.89)	390 (27.46)	4,448 (26.94)	
	2010–2014	3,730 (24.71)	460 (32.39)	4,190 (25.37)	
	2015–2016	985 (6.53)	149 (10.49)	1,134 (6.87)	
Age at MS diagnosis, y	Mean ± SD	36.99 ± 9.93	38.65 ± 10.37	37.13 ± 9.98	<0.001
	Median (IQR)	36 (29–44)	38 (30–46)	36 (29–44)	<0.001
Sex	F	10,434 (69.13)	960 (67.61)	11,394 (69.00)	0.235
Neighborhood income quintile at year of MS diagnosis	1 (Lowest)	2,703 (17.91)	396 (27.89)	3,099 (18.77)	<0.001
	2	2,925 (19.38)	246 (17.32)	3,171 (19.20)	
	3	3,075 (20.37)	272 (19.15)	3,347 (20.27)	
	4	3,266 (21.64)	306 (21.55)	3,572 (21.63)	
	5 (Highest)	3,048 (20.19)	196 (13.80)	3,244 (19.65)	
Urban (vs rural) residence at year of MS diagnosis	Urban	14,160 (93.82)	1,385 (97.54)	15,545 (94.14)	<0.001
Weighted ADG score at year of MS diagnosis	Mean ± SD	4.57 ± 10.94	4.47 ± 11.01	4.56 ± 10.95	0.746
	Median (IQR)	3 (−1 to 10)	3 (−1 to 9)	3 (−1 to 10)	0.980
Length of follow-up from study entry to MS diagnosis, y	Mean ± SD	6.21 ± 5.03	7.10 ± 5.33	6.29 ± 5.06	<0.001
	Median (IQR)	5 (2–9)	6 (3–11)	5 (2–9)	<0.001

Abbreviations: IQR = interquartile range; MS = multiple sclerosis.

Eastern populations.[24] Gene-environment interactions may become more relevant when the environment changes substantially with migration. Vitamin D receptor polymorphisms, increased vitamin D receptor expression, and HLA DRB1*01 have been associated with MS risk in Iranian and Lebanese populations.[25,26] The effects of vitamin D dysregulation may be exacerbated by a lower sunlight environment such as Canada.

A potential effect of environmental factors such as toxic exposures, physical trauma, and psychological stress should be considered given the high hazard ratios observed in immigrants from Iran, Lebanon, and the former Yugoslavia, all countries with a history of conflict and chemical exposures within the last decades. Although a study of US army veterans did not find any increase in MS risk with deployment to the Persian Gulf War,[27] several studies have observed an association between organic solvents and the development of MS.[28,29] Stress may activate proinflammatory pathways; another large population-based cohort study found an increased risk of MS in parents who had lost a child.[30]

We observed a much lower risk of MS in East Asian immigrants to Canada. This finding is consistent with previous epidemiologic studies reporting a lower prevalence of MS in East Asian countries compared to other regions.[31] The reason for this is unknown, but it may be due to lesser genetic susceptibility or differences in environmental exposures. In

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Table 4 Cox proportional hazards analysis investigating risk of MS in immigrants vs long-term Ontario residents in the matched cohort, 1994 to 2016

Parameter	HR	95% CI	*p* Value
Age at study entry (reference = 20–35 y), y[a]			
36–50	0.60	0.58–0.61	<0.0001
51–65	0.30	0.29–0.31	<0.0001
Female[a]	2.40	2.34–2.46	<0.0001
Urban[b]	0.91	0.79–1.04	0.1762
Weighted ADG scores[b]	1.13	1.11–1.15	<0.0001
Low neighborhood income quintile[b]	1.01	0.98–1.04	0.6378
Immigrant status (reference = long-term residents)[b]			
Time elapsed since landing: 2–5 y	0.25	0.24–0.27	<0.0001
Time elapsed since landing: 5–10 y	0.29	0.25–0.33	<0.0001
Time elapsed since landing: 10–15 y	0.34	0.27–0.43	<0.0001
Time elapsed since landing: ≥15 y	0.47	0.34–0.65	<0.0001
Year of entry (reference = 1994)			
1995	1.01	0.96–1.07	0.6508
1996	1.14	1.08–1.21	<0.0001
1997	1.30	1.22–1.39	<0.0001
1998	1.28	1.20–1.36	<0.0001
1999	1.34	1.25–1.44	<0.0001
2000	1.44	1.34–1.55	<0.0001
2001	1.58	1.47–1.71	<0.0001
2002	1.52	1.41–1.65	<0.0001
2003	1.44	1.33–1.56	<0.0001
2004	1.58	1.46–1.72	<0.0001
2005	1.60	1.47–1.74	<0.0001
2006	1.72	1.57–1.88	<0.0001
2007	1.60	1.46–1.75	<0.0001
2008	1.50	1.37–1.65	<0.0001
2009	1.62	1.47–1.78	<0.0001
2010	1.57	1.43–1.73	<0.0001
2011	1.65	1.50–1.83	<0.0001
2012	1.57	1.42–1.74	<0.0001
2013	1.33	1.20–1.48	<0.0001
2014	1.18	1.06–1.31	0.0034

Abbreviations: ADG = Aggregated Diagnosis Groups; CI = confidence interval; HR = hazard ratio; MS = multiple sclerosis.
Immigrants and long-term residents were matched on age, sex, and geographic residence before analysis of MS cases.
[a] See table 5.
[b] Time-varying covariate, updated annually.

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Table 5 Analysis for effect modification by sex and age group at study entry

	HR (95% CI)	
	Women	Men
Immigrant vs long-term resident at age at entry group 20–35 y	0.24 (0.22–0.26)	0.26 (0.22–0.30)
Immigrant vs long-term resident at age at entry group 36–50 y	0.33 (0.32–0.33)	0.34 (0.34–0.35)
Immigrant vs long-term resident at age at entry group 51–65 y	0.28 (0.28–0.29)	0.26 (0.26–0.26)

Abbreviations: CI = confidence interval; MS = multiple sclerosis.

support of lower genetic susceptibility, a previous study found that there was a lower share of familial MS cases in Asian individuals compared to whites.[32]

It is important to note that comparisons of MS risk in immigrants to the risk of all individuals from the same region are confounded because migrant populations are on average healthier, younger, better educated, and of higher SES than the general population in their native countries.[33] Perhaps the most important implications of this study relate to public health and medical education. The belief that MS risk is minimal among immigrants to North America can lead to underrecognition and treatment of this disease in the already vulnerable immigrant population. Non-Western immigrants have been reported to have increased MS-related disability than others with the disease, which may be partially due to delayed recognition.[34] Identification of groups of immigrants at higher risk of MS could support targeted education interventions, clinical triaging strategies, and further research into new candidate risk factors for developing MS.

Strengths of this study included the availability of linked immigrant and health administrative data in a large population-based cohort and the use of incident rather than prevalent MS cases. We adjusted for several known confounders of MS risk, which had not been possible in past migration studies. Limitations include omission of some potential contributors to MS risk from the multivariable models, including health behaviors such as smoking, sun exposure, and physical activity. In the matched analysis, ≈5% of immigrants went unmatched, and these were more likely to be younger individuals, women, and rural dwellers and to have fewer comorbid conditions. Nonetheless, the number of unmatched participants was small, and findings were similar in the overall immigrant cohort and in the matched analysis. We cannot exclude the possibility that differences in incidence reflect differences in health care use by immigrants or failure of health care providers to recognize possible symptoms of MS in ethnic groups in whom MS occurs less often; however, prior studies in Ontario suggest that general use of health care services is similar among immigrants and nonimmigrants in Ontario.[35,36] Moreover, a study of inflammatory bowel disease, another complex immune-mediated disease, in immigrants to Ontario found no delay in time to diagnosis.[35] Some prevalent cases could have been misclassified as incident, but the exclusion criterion of 2 years of OHIP eligibility should have minimized these cases. However, this requirement meant that the most recent immigrants were excluded. It is difficult to isolate true incident cases in newly arrived immigrants, but we can extrapolate from the association observed between MS risk and duration of time in Canada that MS incidence in this group would have been lower than in the overall immigrant cohort. Some MS cases may have been missed because we used a stringent algorithm with high specificity.[37]

We found a lower risk of MS in immigrants to Ontario, Canada, compared to long-term residents. Risk of MS in immigrants was strongly associated with region of origin, with wide variation across regions. Our findings underscore the importance of both genetic susceptibility and environmental factors in the development of MS. MS risk increased with duration of exposure to the Canadian environment and decreased with age at arrival, although we did not see a steep decline in risk with migration after age of 15 years. These results suggest that environmental exposures may influence MS risk well beyond childhood and adolescence.

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