

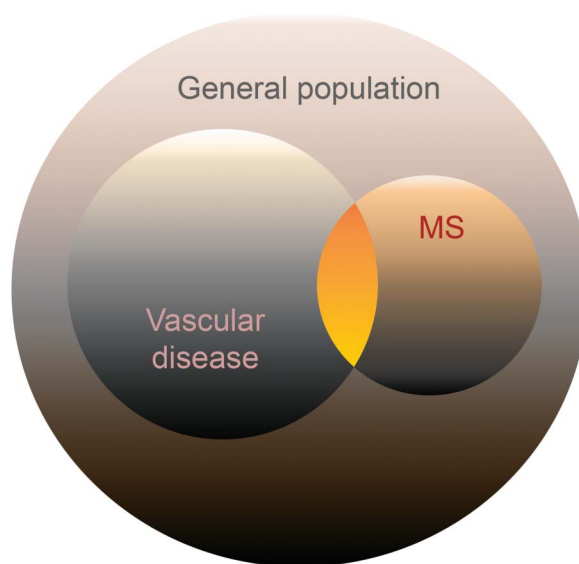
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Differing trends in the incidence of vascular comorbidity in MS and the general population

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Abstract

Background: Although the adverse effects of vascular comorbidities are increasingly recognized in multiple sclerosis (MS), the epidemiology of these conditions remains poorly understood. **Methods:** Using population-based administrative data, we identified 44,452 Canadians with MS and 220,849 age-, sex- and geographically matched controls. We applied validated definitions to estimate the incidence of diabetes, hypertension, hyperlipidemia, and ischemic heart disease (IHD) from 1995 to 2005. **Results:** Of the MS cases, 31,757 (71.4%) were in female participants, with a mean (SD) age at the index date of 43.8 (13.7) years. Over time, the age-standardized incidence of diabetes rose more in the MS population (incidence rate ratio [IRR] per year 1.06; 95% confidence interval [CI] 1.03–1.08) than in the matched population (IRR per year 1.02; 95% CI 1.01–1.03). Temporal trends in the age-standardized incidence of hyperlipidemia, hypertension, and IHD were similar in both populations. Among those aged 20–44 years, the incidence of IHD was higher in the MS population (IRR 1.59; 95% CI 1.19–2.11). The increased incidence of IHD in the MS population was attenuated among those aged 60 years and older (IRR 1.01; 95% CI 0.97–1.06). **Conclusions:** The incidence rates of diabetes, hypertension, and hyperlipidemia are rising within the MS population. Programs to systematically prevent and treat these conditions are needed. *Neurol Clin Pract* 2016;6:120–128



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While prevalence is more readily measured, incidence estimates are critical for determining disease risk. These estimates are particularly useful for etiologic studies, and are also relevant for pharmacovigilance and population disease surveillance. Although several studies have reported the prevalence of medical comorbidities within the multiple sclerosis (MS) population, few have reported the incidence of medical comorbidities in this population.¹

Few population-based studies of incident comorbidities in MS have focused on common conditions such as hypertension,¹ and none has reported age-specific incidence estimates, even though the burden of comorbidity increases with age.² Given the recognized adverse effects of vascular comorbidities (diabetes, hypertension, hyperlipidemia, ischemic heart disease [IHD]) on outcomes in MS such as disability progression,³ their epidemiology requires attention as a better understanding of the associations between comorbidity and MS is necessary to support studies to evaluate the pathophysiology of these associations.

We aimed to assess the age-specific incidence of vascular comorbidity in MS, temporal trends in the incidence of vascular comorbidity, and differences in the incidence of comorbidity according to sex because of the strong female predominance in MS. We compared these findings in the MS population to those in matched controls.

METHODS

Administrative data

We conducted this cohort study in 4 Canadian provinces—British Columbia, Manitoba, Quebec, and Nova Scotia—over the years 1995–2005. These provinces capture nearly 43% of the Canadian population,⁴ and each has procedures for accessing their anonymized, administrative (health) data, which capture nearly all residents in their jurisdictions. The data accessed included population registries, and hospital and physician claims for the years 1990–2010, except in British Columbia, where data extended to 2008.^{5–7} These datasets can be linked within provinces using a unique identification number. The population registries capture sex, region of residence (postal code), and dates of birth and death. Dates of health care coverage are recorded, including when an individual migrates in or out of the province. Hospital claims include dates of admission and discharge, and diagnosis codes classified using the International Classification of Disease (ICD)–9 or ICD-10 system, depending on the year. Physician claims include service date and diagnosis. Due to provincial privacy regulations, which prevent line-level data from leaving the province of origin, we performed analyses in parallel at each site, adopting the approach of the Canadian Network for Observational Drug Effect Studies.⁸

Standard protocol approvals, registrations, and patient consents

The Research Ethics Boards at each participating site approved the study. The relevant body within each province (British Columbia Ministry of Health, Manitoba Health Information Privacy Committee, Commission d'Accès à l'Information du Québec, Health Data Nova Scotia) approved administrative data access.

Study populations

Using a validated case definition,⁹ we identified all persons with MS in each province as those with ≥ 3 hospital or physician claims for MS (ICD-9/10 = 340/G35). We selected a matched cohort from the general population, excluding individuals with any diagnostic codes (ICD-9/10) for demyelinating disease (see appendix e-1 at Neurology.org/cp). Statistical efficiency is optimized at 4 to 6 matches, therefore we identified up to 5 matches for each case, matched on sex, year of birth, and region of residence (postal [mailing] code or first 3 digits of the postal code if unable to match on the full postal code). For each person with MS, we assigned the date of the first health claim for demyelinating disease as the date of diagnosis. The same date (index date) was assigned to their matched controls.

Supplemental Data

Neurology.org/cp

Table Data sources, number of cases and controls, age, and sex

Characteristics	British Columbia	Manitoba	Quebec	Nova Scotia
Provincial population in 2001 ^a	3,868,875	1,103,700	5,939,715	897,570
Multiple sclerosis cases	14,049	5,797	21,368	4,124
Female	10,072 (71.7)	4,140 (71.4)	15,069 (70.5)	3,060 (74.2)
Age at index date, y	44.4 (13.0)	41.8 (13.5)	43.7 (14.4)	42.5 (12.5)
Matched controls	70,217	28,807	106,832	20,526
Female	50,344 (71.7)	20,566 (71.4)	75,338 (70.5)	15,219 (74.1)
Age at index date, y	44.4 (13.0)	41.8 (13.5)	43.7 (14.4)	42.5 (12.5)

^aStudy midpoint.

Comorbidities

In each province, we applied case definitions for diabetes, hypertension, hyperlipidemia, and IHD that were validated in Manitoba and Nova Scotia (appendix e-1).¹⁰ To estimate incidence, we required a 5-year run-in period preceding the first comorbidity claim to ensure that comorbidity cases were truly incident. In the MS cohort, a comorbidity case was considered incident if the first comorbidity claim occurred after the date of MS diagnosis. For the matched cohort, a comorbidity case was considered incident if the first comorbidity claim occurred after the index date assigned to their matched case. Artifactual drops in incidence can occur at the end of the study period because new cases lack sufficient follow-up time to meet the case definition. Therefore we report incidence for 1995–2005. Due to small cell sizes in some provinces, age was categorized as 20–44, 45–59, and ≥ 60 years and we examined age effects using average annual age-specific incidence over the study period. We age-standardized findings to the 2001 Canadian population (census year closest to study midpoint) using the direct method, and calculated 95% confidence intervals (CI) assuming a Poisson distribution. Cell sizes < 5 were suppressed to comply with privacy requirements, limiting the ability to model crude rates. Therefore we modeled age-standardized incidence using Poisson regression, adjusting for year and sex.¹¹ This approach controls for age effects without introducing age in the model as a covariate.¹¹ We pooled province-specific estimates using random-effects meta-analysis. We report I^2 (measure of heterogeneity) and τ^2 (measure of between study variance) with forest plots to illustrate variation in estimates across provinces (see appendix e-1).

Analyses were performed using SAS V9.3 (SAS Institute Inc., Cary, NC) and an Excel spreadsheet for meta-analyses.¹²

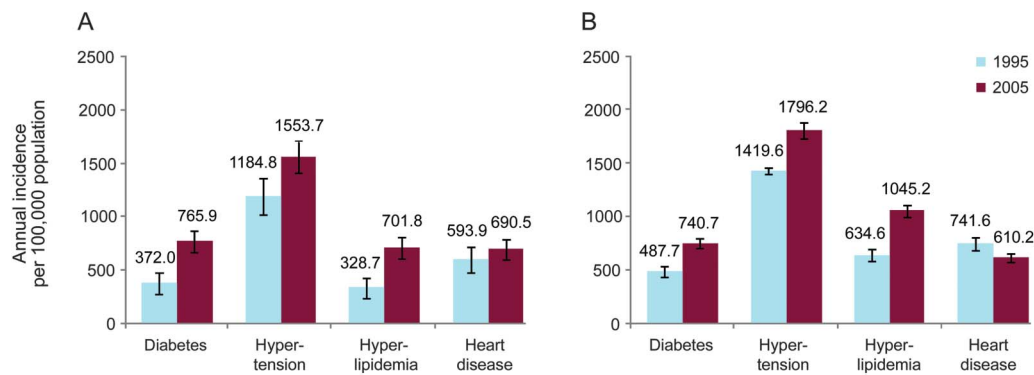
RESULTS

We identified 44,452 MS cases, 31,757 (71.4%) of whom were female, and 220,849 matched controls (table). All incidence rates are pooled estimates from random effects meta-analysis, reported per 100,000 persons per year (95% CI). In 1995 and 2005, the highest crude incidence rates in both populations were for hypertension (figure 1, A and B). The incidence of all comorbidities increased with age in the MS (figures e-1A–e-4A) and matched (figures e-1B–e-4B) populations.

Diabetes

In 2005, the crude incidence of diabetes in the MS population was 765.9, while it was 740.7 in the matched population (figure 1, A and B). Adjusting for year and sex, the age-standardized incidence of diabetes did not differ between populations over the study period (incidence rate ratio [IRR] 0.90; 0.79–1.02, figure 2). The age-standardized incidence of diabetes was 25%

Figure 1 Annual incidence of comorbidity per 100,000 persons with multiple sclerosis (A) and in 100,000 persons in the matched population (B) in 1995 and 2005



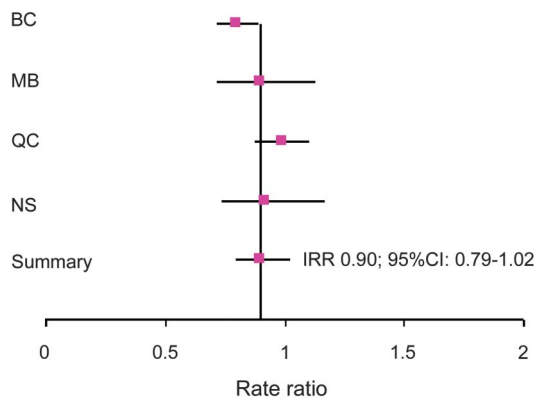
lower in women than men (IRR 0.75; 0.72–0.78, figure e-5). Average annual age-specific incidence rates also did not differ between the MS and matched populations (data not shown). There was an interaction between population and year ($p = 0.04$); the age-standardized incidence of diabetes increased more (IRR 1.06; 1.03–1.08, figure e-6) in the MS population than in the matched population (IRR 1.02; 1.01–1.03, figure e-7).

Hypertension

In 2005, the crude incidence of hypertension in the MS population was 1,553.7, while it was 1,796.2 in the matched population (figure 1, A and B). Adjusting for year and sex, the age-standardized incidence of hypertension was lower in the MS population than in the matched population over the study period (IRR 0.87; 0.75–0.99, figure 3). The age-standardized incidence of hypertension did not differ between women and men (IRR 0.98; 0.84–1.15, figure e-8), and was stable over time (IRR per year 1.02; 0.99–1.05, figure e-9).

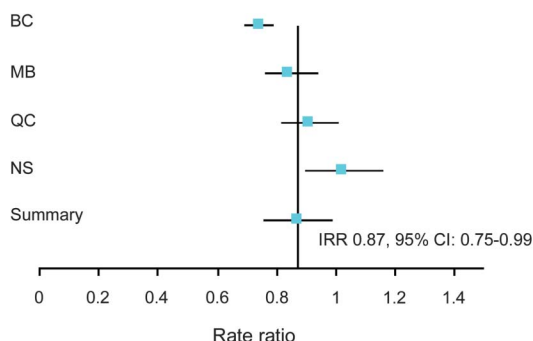
The lower overall incidence of hypertension in the MS population appeared to reflect differences in the incidence rates between the 2 populations for persons aged ≥ 60 years (p for interaction = 0.021). The incidence of hypertension did not differ between the populations for those aged 20–44 years (IRR 0.98; 0.90–1.08), or those aged 45–59 years (IRR 0.94; 0.85–1.04). However, among those aged ≥ 60 years, the incidence of hypertension was lower in the MS population (IRR 0.75; 0.60–0.95, figure e-10).

Figure 2 Forest plot of the adjusted association of diabetes incidence and population, 1995-2005



$\tau^2 = 0.16$, $I^2 = 68.7$ ($p = 0.0224$). BC = British Columbia; CI = confidence interval; IRR = incidence rate ratio; MB = Manitoba; NS = Nova Scotia; QC = Quebec.

Figure 3 Forest plot of the adjusted association of hypertension incidence and population, 1995-2005



$\tau^2 = 0.060$, $I^2 = 86.9$ ($p < 0.0001$). BC = British Columbia; CI = confidence interval; IRR = incidence rate ratio; MB = Manitoba; NS = Nova Scotia; QC = Quebec.

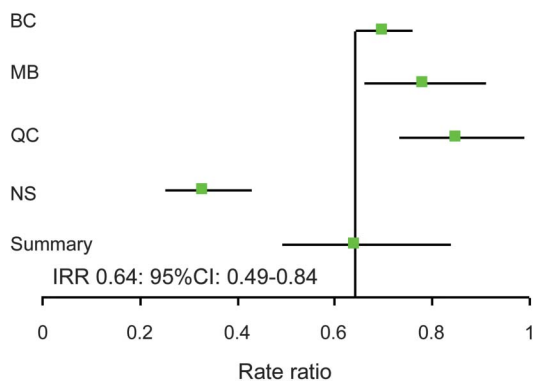
Hyperlipidemia

In 2005, the crude incidence of hyperlipidemia in the MS population was 701.8, while it was 1,045.2 in the matched population (figure 1, A and B). Adjusting for year and sex, the age-standardized incidence rate of hyperlipidemia was 36% lower in the MS population than in the matched population over the period 1995–2005 (IRR 0.64; 0.49–0.84, figure 4). This finding was consistent across age groups (data not shown). The age-standardized incidence of hyperlipidemia was 43% lower in women than men (IRR 0.66; 0.57–0.77, figure e-11). The age-standardized incidence of hyperlipidemia increased over time in both populations (IRR per year 1.04; 1.01–1.08, figure e-12).

Ischemic heart disease

In 2005, the crude incidence of IHD in the MS population was 690.5, while it was 610.2 in the matched population (figure 1, A and B). Adjusting for year and sex, the age-standardized incidence of heart disease did not differ between the populations (IRR 1.00; 0.94–1.06, figure e-13), but was 56% lower in women than men (IRR 0.54; 0.50–0.60, figure e-14). The age-standardized incidence of IHD was stable or declined very slightly over time (IRR 0.99; 0.98–1.00, figure e-15).

Figure 4 Forest plot of the adjusted association of hyperlipidemia incidence and population, 1995-2005



$\tau^2 = 0.070$, $I^2 = 91.9$ ($p < 0.0001$). BC = British Columbia; CI = confidence interval; IRR = incidence rate ratio; MB = Manitoba; NS = Nova Scotia; QC = Quebec.

Persons with MS in the lowest age group had a substantially increased risk of IHD that was attenuated at older ages.

Age-specific incidence rates differed between the populations. Among those aged 20–44 years, the incidence of IHD was 59% higher in the MS population (IRR 1.59; 1.19–2.11, figure e-16), but did not differ among those aged ≥ 60 years (IRR 1.01; 0.97–1.06).

DISCUSSION

In this population-based study, we estimated the incidence of 4 major conditions—diabetes, hypertension, hyperlipidemia, and IHD—in MS and reference cohorts. Consistent with expectations for the Canadian population,² the crude incidence rates of all comorbidities increased with age in the matched populations, and were higher in men than women. Findings were similar in the MS population. The incidence of vascular comorbidity varied across provinces, as previously observed in the Canadian population,¹³ likely reflecting differences in health behaviors and social factors. The incidence of diabetes and hyperlipidemia rose in the MS and matched populations over the 10-year study period. Although the rising rates of diabetes in the matched populations were consistent with those of the Canadian population,¹⁴ the incidence rates of diabetes and hyperlipidemia rose faster in the MS population.

In 2005, the crude incidence of diabetes in the MS population was 765.9 per 100,000 persons, slightly exceeding that of the matched population that year (740.7/100,000). Our estimate falls within the bounds of 2 prior studies, although their estimates of the incidence of diabetes in persons with MS varied between 1 and 1,010 per 10,000 persons.¹ One Danish study reported the incidence of hypertension to be 373 per 100,000 population in an incident MS cohort,¹⁵ an estimate substantially lower than we observed. However, the Danish study used data from hospitalizations rather than outpatient care for much of the study period, potentially underestimating the incidence of hypertension. In 2005, we found that the crude incidence of IHD in the MS population was 690.5 per 100,000 persons, consistent with our prior report in Manitoba for an incident, rather than prevalent, MS cohort.¹⁶ Two Nordic studies reported the incidence of myocardial infarction in incident MS cohorts to range from 236 to 275 per 100,000 population (reviewed in reference 1). These lower estimates reflect the restriction of cases to myocardial infarction, and may also reflect worldwide variation in the burden of IHD.¹⁷

Over the 10-year study period, the incidence of diabetes did not differ between the MS and matched populations, while the incidence rates of hypertension and of hyperlipidemia were lower in the MS population, but these associations changed over time. The incidence of diabetes rose 3 times faster in the MS than in the matched population over time, such that by 2005 the incidence of diabetes was higher in the MS population. This rising incidence might reflect improved ascertainment in the MS population over time as compared to the general population. However, this should have also been expected for the other comorbidities studied, and yet the findings clearly differed among them. Consistent with the aforementioned Danish study,¹⁵ we found that the incidence rate of hypertension remained lower in the MS population than the matched population throughout the study period. However, this difference was primarily due to a lower incidence of hypertension for persons with MS aged ≥ 60 years.

Over the 10-year study period, the incidence of IHD did not differ between populations, but age-specific differences existed. Persons with MS in the lowest age group had a substantially increased risk of IHD that was attenuated at older ages. One possible explanation may be more frequent health care contacts for those with MS leading to earlier or more frequent diagnosis of IHD. However, physician visits have declined faster in the MS population over time than in the

Growing evidence suggests that vascular comorbidities are associated with more rapid disability progression in patients with MS.

general population,¹⁸ and most of the Canadian general population has regular contact with the health system. Further, this was only observed for IHD in younger persons with MS. True differences in risk may also exist. Such was suggested by previous findings that the risk of myocardial infarction was increased during the first year after MS diagnosis (IRR = 1.84; 95% CI 1.28–2.65) in an incident cohort.¹⁵ The associations between MS and IHD may reflect shared environmental and genetic factors, or be secondary to MS. Smoking and obesity are risk factors for MS³ and IHD,¹⁹ and physical inactivity after MS onset may also increase the risk of IHD. Persons with MS are more likely to smoke, be overweight or obese, and be less physically active than the general population.³ Other immune-mediated diseases such as rheumatoid arthritis increase the risk of IHD independent of vascular risk factors including diabetes, hypertension, hyperlipidemia, and smoking, presumably due to inflammation.²⁰ HLA alleles are associated with the risk of MS and are also implicated in the increased risk of IHD in rheumatoid arthritis²¹; such associations should be evaluated in MS.

The rising incidence of comorbidity with age and over time is highly relevant to clinical care in MS. Growing evidence suggests that vascular comorbidities are associated with more rapid disability progression in patients with MS.³ Risks of adverse effects for some therapies are also increased in the presence of comorbidities such as cardiac disease or diabetes; thus the risks of therapies may change as individuals develop new comorbidities. As some disease-modifying therapies also increase the risk of comorbidities such as hypertension, it is important to determine the incidence of vascular comorbidities before these therapies are widely used, so as to better identify their effects in real-world safety and effectiveness studies, beyond clinical trials.

Limitations of this study should be considered. It was not feasible to include all Canadian provinces; however, we captured 43% of the Canadian population. Administrative data are not collected for research purposes, but we have previously validated our case definitions for the comorbidities studied.¹⁰ The need to suppress small cell sizes for privacy requirements and the naturally lower incidences in younger individuals meant our age groups were broad. Nonetheless, our study provides the age-specific incidence estimates lacking in the literature. We did not evaluate the reasons for the observed differences between populations, or the potentially complex relationships between these comorbidities and health behaviors. Finally, we lacked information regarding clinical characteristics of the MS population such as subtype and disease duration and could not evaluate associations between clinical characteristics and the incidence of vascular comorbidities.

Within the MS population, as in the general population, men and those at older ages are at increased risk of developing vascular comorbidities. This will become increasingly important as the peak prevalence of MS shifts to older ages.⁹ The rising incidence rates of diabetes and hyperlipidemia are concerning given their potential adverse effects on outcomes.³ Programs to systematically prevent and treat these conditions in the MS population are needed and will require specific attention to health behaviors, using collaborative models of care.

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AUTHOR CONTRIBUTIONS

The corresponding author (RAM) 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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