ORIGINAL ARTICLE

Prevalence of Multiple Sclerosis in Canada: A Systematic Review

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ABSTRACT: ***Background:*** Studies of the prevalence of multiple sclerosis (MS) in Canada have generally been isolated to specific regions. Given the importance of multiple sclerosis as a cause of disability in adults, a comprehensive review of Canadian MS prevalence examining current data, interregional variation, deficiencies in knowledge and frontiers for research is timely. ***Methods:*** A systematic review of all studies addressing the prevalence of MS in Canada or regions within Canada, published in English or French since 1985, was conducted. Studies were identified using MEDLINE, EMBASE and bibliographic review. Ten studies were evaluated for methodological rigour and a test of heterogeneity across studies was performed and a measure of consistency (I^2) estimated. ***Results:*** Studies were generally of high quality. Nine were restricted to regions within Canada and one provided an estimated national prevalence based on self-reported cases. All reported a high prevalence (>50 per 100 000). Latitude and longitude gradients were not striking while assessment of heterogeneity confirmed that regional differences were unlikely to be the result of sampling variability. ***Conclusions:*** This review confirms Canada as a country of very high MS prevalence and it is the first study to demonstrate that variation in regional estimates represents true differences in prevalence within Canada. Avenues for future MS prevalence research, including adoption of a national MS registry, are proposed.

RÉSUMÉ: Revue systématique de la prévalence de la sclérose en plaques au Canada. ***Contexte :*** Les études de prévalence de la sclérose en plaques (SEP) au Canada ont généralement porté sur des régions spécifiques du pays. Étant donné l'importance de la SEP comme cause d'invalidité chez les adultes, il est opportun de réviser la prévalence de la SEP au Canada en examinant les données actuelles, la variation interrégionale, les lacunes et les avenues de recherche. ***Méthodes :*** Nous avons révisé systématiquement toutes les études portant sur la prévalence globale ou régionale de la SEP au Canada, publiées en anglais ou en français depuis 1985. Nous avons utilisé MEDLINE, EMBASE et une revue bibliographique pour identifier les études. Nous avons évalué la rigueur méthodologique de dix études, ainsi que l'hétérogénéité entre les études et estimé la consistance interne des études. ***Résultats :*** Les études étaient généralement de bonne qualité. Neuf des études étaient des études régionales et une estimait la prévalence nationale à partir de cas autorapportés. Toutes ces études rapportaient une prévalence élevée (> 50 par 100 000). Un gradient de latitude ou de longitude n'était pas évident et l'évaluation de l'hétérogénéité a confirmé que des différences régionales n'étaient vraisemblablement pas le résultat de la variabilité de l'échantillonnage. ***Conclusions :*** Cette étude confirme que la prévalence de la SEP est très élevée au Canada. C'est la première étude à démontrer que la variation entre les estimations régionales représente des différences réelles dans la prévalence entre différentes régions du Canada. Nous proposons des avenues de recherche pour les études futures sur la prévalence de la SEP, dont la constitution d'un registre national de la SEP.

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Multiple sclerosis (MS) is a chronic illness affecting the central nervous system.[1] Through an inflammatory autoimmune process, there is injury to both myelin and axons resulting in myriad clinical features, including motor weakness, sensory disturbances, visual loss, gait ataxia, sphincter dysfunction and cognitive changes.[1] While the etiology of multiple sclerosis remains unknown, current evidence suggests an interplay between environmental and genetic factors.[1,2] Epidemiological studies of MS have demonstrated geographic and demographic variability in both prevalence and incidence.[1] These results have in turn contributed to hypothesis generation with regard to MS etiology.

The existing literature suggests that Canada is an area of high MS prevalence[3-15] Canada is a vast nation comprised of ten provinces and three territories and lies at latitude 60N and longitude 95W. It has a population of 32,805,041, of which 70% is between 15 and 64 years of age.[16] Two-thirds of the population is concentrated in urban centres and, while ethnically diverse in

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many of these centres, most inhabitants are primarily of Caucasian European ancestry (over 60% French or British descent).[16] An important aboriginal population also resides in Canada although few studies have addressed MS prevalence in this population group.[17-20] Access to healthcare is universal and renders relatively uniform the opportunity for diagnosis and treatment of diseases across the country.

Having accurate figures for MS prevalence in Canada is important in ascertaining the true burden of disease in the country. This in turn can help guide the allocation of research efforts and allow for more precise estimates of the economic weight the disease carries. In addition, knowledge of the current prevalence of MS in Canada would allow for an evaluation of temporal trends in prevalence as well as an estimation of the impact of any future interventions or events that may affect the prevalence or, indeed, the incidence of MS. There are challenges in comparing and combining results from existing studies due to differences in case ascertainment, age distribution, ethnic diversity and possible changes in prevalence over time. Nevertheless, the potential utility of systematically reviewing the existing prevalence data and determining whether a synthesis of these data is possible, justifies the exercise.

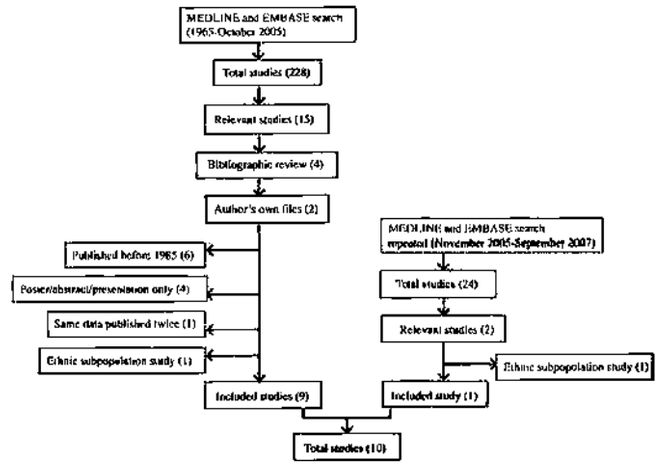

Figure 1: Flow diagram of study selection.

Methods

Identification of Studies

This systematic review was designed in accordance with the guidelines outlined by the Meta-Analysis of Observational Studies in Epidemiology recommendations.[21] Searches of the medical literature (1965-October 2005) were conducted using MEDLINE with the broad subject headings "multiple sclerosis" and "Canada", the latter as an exploded term. The search was conducted for articles written in French or English. A total of 228 references were found. Because single-database searching may have limited yield, the same search was conducted using EMBASE, but this provided no additional references.[22] Titles were reviewed, potentially relevant articles were retained and full text obtained. The bibliographies of these articles were then hand searched for additional references. A total of 21 studies were found, four through bibliographic review and two through one author's own files (CW). Six studies were published before 1985 and excluded.[23-28] Of the remaining 15 studies, one was available only as an abstract, two as posters and one as a presentation; these were not included in the formal review.[4,7,11,19] In one case, data were published twice, once as a poster and once as a paper and only the paper was included.[11] Finally, one targeted an ethnic subpopulation and was excluded.[18] This process yielded nine papers for inclusion in our systematic review (Figure 1).

The same search strategy was repeated using MEDLINE for the period from November 2005 to September 2007 to identify any additional relevant studies published during that period. This search yielded 24 results. A review of titles and abstracts confirmed two potentially relevant papers.[15,20] One included data from a study available only as a presentation prior to November 2005.[19,20] As it was devoted to a special subpopulation, this study was not included. The second study[15] was included, bringing the total number of studies to ten (Table 1).

Table 1: Studies included in systematic review

Reference No.	Reference
10	Sweeney VP et al. Prevalence of multiple sclerosis in British Columbia. *Can J Neurol Sci* 1986; 13: 47-51.
6	Pryse-Phillips WEM et al. The incidence and prevalence of multiple sclerosis in Newfoundland and Labrador, 1960-1984. *Ann Neurol* 1986; 20:323-328.
4	Hader WJ et al. Epidemiology of multiple sclerosis in London and Middlesex County, Ontario, Canada. *Neurology* 1988; 38:617-621.
9	Warren S and Warren KG. Prevalence of multiple sclerosis in Barrhead County, Alberta, Canada. *Can J Neurol Sci* 1992; 19:72-75.
12	Warren S and Warren KG. Prevalence, incidence, and characteristics of multiple sclerosis in Westlock County, Alberta, Canada. *Neurology* 1993; 42:1760-1763.
11	Klein GM et al. A prevalence study of multiple sclerosis in the Crowsnest Pass region of southern Alberta. *Can J Neurol Sci* 1994; 21:262-265.
14	Svenson LW et al. Regional variations in the prevalence rates of multiple sclerosis in the province of Alberta, Canada. *Neuroepidemiology* 1994; 13:8-13.
5	Sloka JS et al. Incidence and prevalence of multiple sclerosis in Newfoundland and Labrador. *Can J Neurol Sci* 2005; 32:37-42.
13	Beck CA et al. Regional variation of multiple sclerosis prevalence in Canada. *Multiple Sclerosis* 2005; 11:516-519.
15	Hader WJ et al. Incidence and prevalence of multiple sclerosis in Saskatoon, Saskatchewan. *Neurology* 2007; 69 :1224-1229.

Inclusion Criteria

Inclusion criteria were broad and encompassed any study that reported primary data on MS prevalence in Canada, or regions therein, published in French or English between January 1985 and September 2007. All studies meeting inclusion criteria were published in English. We found two studies from the same group examining MS prevalence in the same territory (Newfoundland and Labrador) at different time points.[5,6] Both studies were included for analysis.

Exclusion Criteria

We excluded genetic epidemiological studies looking at prevalence of MS in family members of affected probands.[29,30] Studies devoted to special subpopulations (such as First Nations or the Hutterites) were excluded.[18-20] Economic burden and mortality studies were also excluded as were data presented only in posters, abstracts, letters or presentations.

Data Extraction

Once accepted for inclusion, studies were assessed using a quality assessment tool designed for studies of prevalence and relevant information was extracted using a data abstraction grid. Quality assessment parameters included proper definition of study population characteristics, method of case ascertainment (i.e. chart review, patient examination), reproducibility of case definition, clear statement of prevalence dates and description of statistical analyses used to derive prevalence figures. Check boxes permitted differentiation between "Very Good", "Good" and "Poor" for each quality assessment parameter. "Very Good" was used when the parameter was addressed completely, "Good" when it was addressed but incompletely, and "Poor" when it was not addressed at all. Whichever descriptor was applied most often to a particular study determined the overall quality rating for that study. Two authors (AYP, CW) reviewed the studies independently and when necessary, disagreements were resolved by consensus.

Data abstraction included information about the study (authors, year of publication, region studied), information about study methods (study population, case definition, case ascertainment) and study results (crude prevalence rates, age- and sex-specific prevalence and other relevant results).

Data Analyses

Extracted data concerning study methodology and results were tabulated (Table 2). Several studies examined both prevalence and incidence of MS but given the aim of this review, only prevalence values were extracted. All studies provided prevalence as number of cases per 100 000 population and all but two provided confidence intervals. Age- and sex-standardization were not reported in all studies.

A test for heterogeneity across studies was conducted to test the null hypothesis that all studies are estimating the same parameter.[31] Rejecting this null hypothesis would support the notion that there is in fact true variation in MS prevalence between the study populations not due to sampling error. Higgins et al provide a measure of consistency across studies that is derived from the Q statistic and is not dependent on the number of studies included for comparison.[31] This measure, I^2 is calculated as $I^2 = 100\% (Q - df)/Q$, where df = degrees of freedom = number of studies -1. The value is expressed as a value between 0 and 100%, where 0 indicates no heterogeneity and increasingly larger values suggest increasing heterogeneity. Generally, an I^2 of less than 25% indicates low heterogeneity, 25% to 50%, moderate heterogeneity and over 50%, high heterogeneity.[31,32]

Given that the data are derived from different populations at different time points, pooling of these data may mask regional and temporal differences. A high degree of inconsistency across studies further argues against statistical pooling of results.[31,32]

Results

Study characteristics

Ten studies met inclusion criteria (Table 1). Publication dates ranged from 1986 to 2007 and all studies were considered of "Good" or "Very Good" quality. Four studies examined provincial MS prevalence, five examined prevalence within smaller geopolitical regions (cities or counties) and one examined national prevalence and prevalence within larger subdivisions of Canada. Of the provincial and regional studies, four were from Alberta, two from Newfoundland and Labrador, one from Saskatchewan, one from Ontario and one from British Columbia (Figure 2). The number of identified cases ranged from 7 to 5548 (median = 274.5) and population denominators ranged from 6 912 to 2 791 398 (median = 742 592). It is likely that the same cases may have been "double counted" in separate studies of the same region. All studies estimated point-prevalence although two did not provide an exact prevalence date.[13,14]

Cases were ascertained in a similar manner in all but two studies, that is, through MS registries, MS clinic charts, neurologists' files, hospital admissions, MS society documents, mailing lists and other physicians. Patients were examined by a neurologist-investigator in only three of the ten studies.[4,9,12] These methods are generally supported by a recent study on the thoroughness of MS case ascertainment in small communities.[33] Interrater reliability for the diagnosis of MS was not reported, but agreement on such a diagnosis among neurologists is presumably high given defined diagnostic criteria. Comparisons of Poser and 2001 MacDonald criteria have suggested similar rates of MS diagnosis.[33,34] One of the studies used billing data from the Alberta Health Care Insurance Plan (AHCIP) (ICD-9 code 340).[14] The national study was based on self-report of an MS diagnosis among respondents to the Canadian Community Health Survey (CCHS).[13]

The studies in this review span 20 years and earlier studies predate the routine inclusion of MRI criteria in the diagnosis of MS. Of those eight studies not relying on billing data or self-report, the two oldest studies utilized Schumacher criteria (1965),[6,10] two used modified Schumacher criteria (no age criterion),[4,11] three used Poser criteria (1983)[5,9,12] and one[15] used a combination of these, including the more recent MRI-based McDonald criteria.[35,36]

Table 2: Prevalence of MS from studies included in systematic review

				Self-referrals (MS group members, ads)					
Pryse-Phillips (6)	1986	Mar 31, 1985	Newfoundland & Labrador	Inpatient records from 3 General Hospitals Letters to neurologist, internists, Ophthalmologists & GPs Neurologist files, MS society, Physician claims	Schumacher	320	567 879	N/A	55.2 (No CI provided)
Hader* (4)	1988	Jan 1, 1984	London	London MS clinic, Admission records Neurologist files, Community clinic, nursing homes, home care, MS society Patients examined	Modified Schumacher	229	260 050	2.5:1	88 (77-100)
Hader* (4)	1988	Jan 1, 1984	Middlesex County			54	63 895	2.2:1	85 (64-111)
Warren (9)	1992	Jan 1, 1990	Barrhead County, Alberta	MS clinic records, Region GPs General Hospital, nursing home, public clinic, MS society, Patients examined	Poser	19	9 720	1:1	196 (118-305)
Warren (12)	1993	Jan 1, 1991	Westlock County, Alberta	MS clinic, County medical society members Gen Hosp, LTC, clinic, MS society Patients examined by same neurologist	Poser	23	11 510	1.4:1	200 (127-300)
Klein§ (11)	1994	June 21, 1989	Crowsnest, Alberta	MS clinic files Area GPs	Modified Schumacher	15	6 912	2:1	217 (121.5-358)
Klein§ (11)	1994	June 21, 1989	Cardston, Alberta			7	7 916	N/A	88 (36-182)
Svenson (14)	1994	Period b/w Apr 1, 1984 and Mar 31, 1989	Alberta	AHCIP records ICD-9 code 340	N/A	5548	2 560 000¶	2.03:1	216.7 (No CI provided)
Sloka (5)	2005	Dec 31, 2001	Newfoundland & Labrador	8/9 neurologist files, MS clinic Billing data (April 1/96-March 31/03) 3 databases	Poser	493	521 986	2.69:1	94.4 (90.2-98.7)
Beck£ (13)	2005	Sep 2000-Oct 2001	Canada (10 provinces) Territories excluded due to low numbers of MS cases	Canadian Community Health Survey (CCHS) Telephone survey - self-report of MS	N/A	332 No regional Numerators given	116 109 Regional (%): BC:16 487 (14.2) Prairies:27 634 (23.8) Ontario:35 529 (30.6) Quebec:20 551 (17.7) Atlantic:16 023 (13.8)	N/A	240 (210-280) Regional: BC: 240 (160-320) Prairies: 340 (240-340) Ontario: 230 (150-300) Quebec: 180 (90-260) Atlantic: 350 (230-470)
Hader (15)	2007	**Jan 1, 2005**	Saskatoon, Saskatchewan	MS registry established in 1969 from Nursing homes, Home Care Program, MS Society Saskatoon, MS Rehab Clinic, family physicians, neurologists and provincial records. Surveys repeated in 1986, 1996 and 2003. *Admission and emergency records from 2001 to* 2005 from 3 local hospitals.	Allison and Millar Schumacher Poser McDonald	587	196 815	2.4:1	298.3 (274.7-323.6)

* and § signify studies in which data for distinct regions were included in the same publication; ¥ Figure not given in original paper (derived from Klein et al. 1994); ¶ Figure not provided in original paper (derived from 1986 Alberta Census); £ Prevalence figures from this study are not crude prevalence estimates; MD=doctor of medicine; GP=general practitioner; LTC=long-term care; AHCIP= Alberta Health Care Insurance Plan; ICD=International Classification of Diseases

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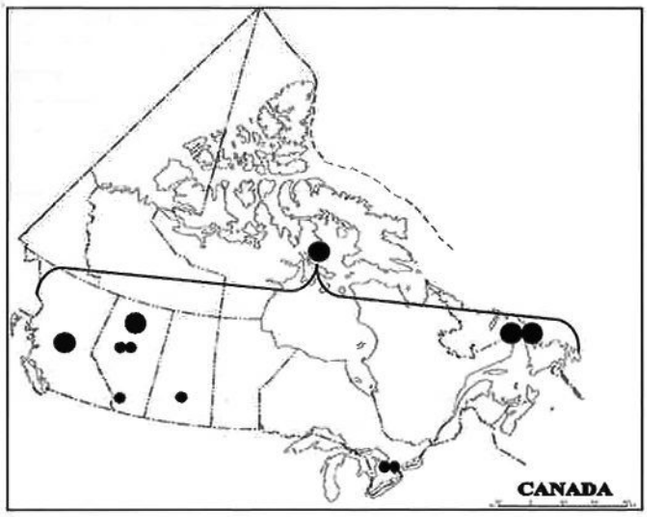

Figure 2: Geographic distribution of MS prevalence studies in Canada (larger circles: national or provincial studies, smaller circles: city or county studies).

Results by region

British Columbia

British Columbia (BC) is Canada's westernmost and third most populated province. Central latitude and longitude are 55N, 125W and the population is primarily concentrated in Vancouver and its surrounding areas. One study found a crude prevalence of MS in BC of 93.3 per 100 000 on prevalence day July 1, 1982.[10] When adjusted to the Canadian population, the prevalence was 91 per 100 000. A total of 2596 cases were found but no denominator (i.e. population of BC) or confidence interval was provided in the original paper. However, in a subsequent study, Klein et al. calculated the confidence interval to be 89.42 to 96.58 per 100 000 assuming a population of 2 791 398.[11] Female prevalence was higher at 126.4 per 100 000 compared to 59.8 per 100 000 for males. This study used Schumacher criteria to classify cases as definite/probable MS and relied on neurologist chart reviews, communication with other physicians, long-term care facilities and self-referrals to identify cases.

The study by Beck et al also provides estimates for BC, suggesting a much higher prevalence of 240 per 100 000 (95% CI 160 – 320). This study used data from a national population health survey (CCHS) conducted by telephone. Identification of cases was based on self-report in answer to the question "We are interested in long-term conditions that have…been diagnosed by a health professional. Do you have multiple sclerosis?"[13] Diagnoses were not confirmed through chart review, physician contact or patient encounter. Because of small samples in the territories, only respondents living in one of the ten provinces were included in the analysis. A total of 116 109 respondents out of 131 535 were over 17 years-old and responded to the survey question pertaining to MS, making them eligible for analysis of MS prevalence.

Prairie provinces

Alberta, Saskatchewan and Manitoba comprise Canada's "Prairie provinces". Alberta and Saskatchewan are discussed below but we found no published data exclusive to Manitoba meeting our inclusion criteria. Two studies of MS prevalence in Winnipeg, Manitoba's capital, were published prior to 1985, one in 1953 and the second in 1964.[23,26]

The Prairie provinces were considered as a single territory in the Beck et al study and a prevalence of 340 per 100 000 (95% CI: 240-340) was estimated.[13]

Alberta

Alberta is the province for which there exist the most data regarding MS prevalence. In fact, four of the ten studies reviewed pertain to this westernmost Prairie province whose central geographical coordinates are 55N, 115W. The population is clustered primarily in two urban centres, Calgary and Edmonton, although there is also significant rural and aboriginal representation.

A study in Barrhead County, a rural area northwest of Edmonton, found a prevalence of 196 per 100 000 (95% CI: 118-305) in 1990.[9] The authors of this study also examined MS prevalence in 1991 in a neighbouring region, Westlock County.[12] The results were standardized to the population of Alberta from the 1986 census yielding a figure of 200 per 100 000 (95% CI: 127-300).

The Crowsnest Pass region and Cardston and southern Alberta were studied in 1989 using MS society lists and patient files from general practitioners for case ascertainment.[11] Modified Schumacher criteria were used and a prevalence of 217 per 100 000 (95% CI: 121.5-358) was found for Crowsnest and 88 per 100 000 (95% CI: 36-182) was found for Cardston.

Avoiding the statistical limitations of small population studies, Svenson et al. used data from the Alberta Health Care Insurance Plan collected between April 1st, 1984 and March 31st, 1989 to estimate MS prevalence for the province of Alberta.[14] The AHCIP contains records of all registered residents, although the use of this database for determining MS prevalence has not been fully validated. The MS cases were identified using the diagnostic code ICD-9 No. 340. In total, 5 548 cases were identified, yielding a mean crude prevalence of 216.7 per 100 000 with a female to male ratio of 2.03:1. The use of claims administrative data may underestimate true MS prevalence given the absence of early, undiagnosed cases and patients unseen by a physician within the studied five-year period, both of which likely exceed the number of misdiagnosed cases.

The Beck et al study further examined MS prevalence in Alberta and used AHCIP data to confirm the validity of the CCHS results.[13] Within the AHCIP, cases were identified if patients had been assigned a diagnostic code for MS twice between 1991 and 2001. Using this method and a total population of 2.97 million, a prevalence of 386 per 100 000 (95% CI: 377-394) was found.

Saskatchewan

Three MS prevalence studies in Saskatoon (52° 10' N, 106W), this province's largest city, have been published. The

first in 1982, and not formally included in our review, reported a period prevalence of 135 per 100 000 between 1970 and 1979.[28] This value was upwardly revised in 1999 using MS clinic registry data as well as medical records and provincial resources.[7] The most recent study estimated MS prevalence on January 1st, 2005.[15] The authors ascertained cases using an MS registry started in 1969 as well as information from nursing homes, home care programs, the MS Society of Saskatoon, family physicians, neurologists and provincial records. Medical records for admissions and emergency department visits between 2001 and 2005 were also screened. Uniform diagnostic criteria were not applied to all patients since different criteria have been used over time to admit patients to the MS registry. On prevalence day, 587 living cases were identified. With a city population of 196 815, a crude prevalence figure of 298.3 per 100 000 (95% CI 274.7 to 323.6) was calculated. A female to male ratio of 2.4:1 was found and when age- and sex-adjusted to the Canadian 2001 population, the prevalence was 329 per 100 000. The authors similarly standardized their results to the world 2000 population (240.4 per 100 000), as has been suggested by others.[37] Such standardized figures allow for more meaningful comparisons between regional prevalence studies than do crude prevalence values.

Claims of a cluster-focus of MS in the hamlet of Henribourg, Saskatchewan due to a postulated common environmental exposure have also been extensively studied.[38] The existence of genuine MS clusters or epidemics has been questioned and the contribution of such studies to estimates of "background" MS prevalence in the population is likely limited.[1]

Ontario

Ontario is Canada's most populated province with central coordinates 50N and 86W. The population is primarily urban and concentrated in a corridor extending from Windsor to Kingston. Two studies published prior to 1985 were not included in our review: a survey of MS patients in Kingston in 1959 and in Ottawa in 1977.[24,27] Only one study has been published since 1985 examining MS prevalence in Ontario alone.[4] This study examined both prevalence and incidence of MS in London and nearby rural Middlesex County, both in southwestern Ontario. Case identification included using MS clinic records as well as review of local hospital admissions, long-term care facilities, home care programs and MS Society membership lists. Identified patients were examined by the authors. Crude prevalence for definite MS was 88 per 100 000 (95% CI: 77-100) for London and 85 per 100 000 (95% CI: 64-111) for Middlesex County. When adjusted to the 1981 Canadian population, a prevalence of 90 per 100 000 was found for clinically definite cases in London. Higher prevalence was noted among women, particularly those in the 35-44 age group.

The more recent CCHS study found a prevalence of 230 per 100 000 (95% CI: 150-300) for Ontario as a whole.

Quebec

Quebec has central coordinates 52N and 72W, and despite being Canada's second-most populous province, there is surprisingly little data regarding the prevalence of MS in this region. In fact, no prevalence studies isolated to Quebec as a whole or Quebec communities were identified in our literature search. Quebec's population resides primarily in the south-western region between Montreal and Quebec City and is also ethnically different in that the large majority of its inhabitants are of French ancestry. The only provincial prevalence information available comes from the CCHS study in which a prevalence of 180 per 100 000 (95% CI: 90-260) was found, making it the region with the lowest MS prevalence in Canada using that methodology.

Atlantic Provinces

The Atlantic provinces on Canada's eastern coast include Newfoundland and Labrador, as well as New Brunswick, Nova Scotia and Prince Edward Island. Overall, these provinces are less populated than central and western Canada and are composed primarily of people of British, Irish and Scottish ancestry with both a rural and urban distribution. Other ethnic groups, including Acadians and Natives also contribute to the local demography.

The Atlantic provinces were examined as a group in the Beck et al study, in which a prevalence of 350 per 100 000 (95% CI: 230-470) was found.[13] This was the highest regional prevalence identified in the CCHS, however this figure is much higher than that found in those studies specifically examining Nova Scotia and Newfoundland and Labrador.

Newfoundland and Labrador

The island of Newfoundland lies between latitudes 46 and 52N and longitudes 52 and 59W and Labrador is situated between 52 and 61N and 56 and 67W. On the island of Newfoundland the population is primarily clustered near St. John's and in large part, inhabitants are of southern English and Irish descent.

Two studies conducted by the same group examined MS prevalence in this territory at two different time points, 1985 and 2001.[5,6] The authors propose that the more recent study is more likely to accurately reflect true prevalence because of better case ascertainment and more uniform diagnostic capabilities throughout the province.[5] The earlier study identified cases using *in- and outpatient medical records as well as MS society* membership lists and physician claims data available from 1983 onwards. Prevalence day was March 31st, 1985 and 32 cases with definite or probable MS by Schumacher criteria were identified, yielding a crude prevalence of 55.2 per 100 000.

The 2001 study sought to update the previous data and took advantage of billing data using diagnostic codes, files from the only MS clinic in the province and three previously compiled databases to achieve more thorough case ascertainment.[5] A total of 493 cases were found on prevalence day (December 31st, 2001) using Poser criteria, giving a crude prevalence of 94.4 (95% CI: 90.2-98.7).

Other Atlantic Provinces

Other than Newfoundland and Labrador only Nova Scotia has been studied with regards to MS prevalence. One study focusing on Nova Scotia's capital, Halifax, was published in 1960 and excluded from this review.[25] A more recent study was also excluded because data were published only as a poster.[8] In this study, provincial prevalence in 2001 was ascertained using records from the only MS clinic in the province in conjunction

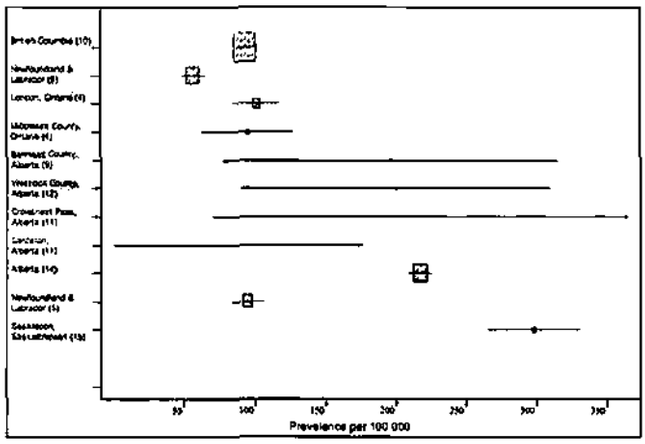

Figure 3: *Plot of crude MS prevalence for regions from included studies.*

Table 3: Canadian regional MS prevalence estimates from included studies, by latitude and longitude

Location	Latitude (degrees)	Longitude (degrees)	Prevalence per 100 000 (95% CI)
London, Ontario	43N	81W	88 (77-100)
Middlesex County, Ontario	43N	81W	85 (64-111)
Crowsnest Pass, Alberta	49N*	113W*	217 (121.4-358)
Cardston, Alberta	49N*	113W*	88 (36-182)
Province of Ontario	50N§	86W§	230 (150-300)
Newfoundland	46-52N	52-59W	55.2
Labrador	52-61N	56-67W	94.4 (90.2-98.7)
Saskatoon, Saskatchewan	52° 10' N	106W	298.3 (274.7-323.6)
Province of Quebec	54N§	72W§	180 (90-260)
Barrhead County, Alberta	54N	114W	196 (118-305)
Westlock, Alberta	54N	114W	200 (127-300)
Province of Alberta	55N*	115W*	216.7
Province of British Columbia	55N	125W	93.3 (89.42-96.58) 240 (160-320)

§estimated geographical centre of territory; *geographical coordinates not provided in paper

with government administrative databases.[8] The authors suggest that the best estimate is likely in the range of 200 to 218 per 100 000.

Canada

No single study examined national MS prevalence before the Beck et al study. In this study, 332 respondents reported a diagnosis of MS among the 116 109 eligible to participate. This produced a national prevalence of 240 per 100 000 (95% CI: 210-280) and this has engendered an upward revision of traditional national MS prevalence figures forwarded in years past.

Prevalence studies have often been compromised by small sample sizes and therefore large, overlapping confidence intervals that raise the possibility of there being no true regional differences within the country (Figure 3). Determining whether finding a single national prevalence for MS is meaningful rests in large part on whether interregional differences are real. If so, then a single national prevalence estimate may in fact underestimate the burden of disease in some Canadian territories, while overestimating it in others.

In addition, although a latitude gradient of MS prevalence has been found in other parts of the world, including the USA, Australia and Italy, none could be demonstrated within Canada (Table 3).[3] Presumably, this is because the large majority of the Canadian population lives within a relatively narrow latitude corridor in the southern part of the country.

Heterogeneity among studies

For the computation of I^2 to examine variability, two studies were excluded due to major differences in methodology.[13,14] Also, the earlier Newfoundland and Labrador study[6] was excluded from the analysis given that more recent data for that province likely better reflect true MS prevalence. In two other studies, separate data were provided for neighbouring regions and these were considered as distinct data sets in our analysis.[4,11] Therefore, nine sets of data were included in the analysis and a high degree of heterogeneity (I^2 =98.86) was found with a very large Q statistic: Q=703.30, df=8, p<0.0001. Studies published more recently generally yielded higher prevalence estimates.

Discussion

Several regional studies of MS prevalence have been conducted and suggest wide variation within the country. Our review suggests a range from a low of 55.2 per 100 000 in Newfoundland and Labrador to a high of 350 per 100 000 (95% CI: 230-470) in the Atlantic provinces.[6,13] Of course, the Newfoundland study has since been repeated and yielded a higher prevalence while the methodology of the CCHS study which has suggested by far the highest prevalence figures to date, differs immensely from the other publications included for review. The I^2 value obtained confirms that the different prevalence estimates in the studies likely constitute true differences. This lends strong credence to the assertion that arriving at a single point estimate of national prevalence is a difficult and possibly misleading enterprise.

It is clear that more recent studies are producing higher prevalence figures than older ones. One might speculate that this reflects an increased incidence of disease, although other explanations are also plausible. In particular, improved case ascertainment via better access to neurologists and diagnostic tests likely explains the increased prevalence found in more recent studies as it did in the later Newfoundland study. Improved medical care leading to longer life spans among MS patients may also account for this apparent increase in prevalence. Analysis of sex ratios of MS by year of birth in a longitudinal population based dataset of over 29 000 Canadian MS patients (Canadian Collaborative Project on Genetic Susceptibility to Multiple Sclerosis) suggests an increasing ratio of female to male cases.[39,40] This might imply an increasing disease incidence over the last 50 years, particularly in women, the cause of which may be environmental.

Most prevalence studies reviewed here reported a female to male ratio of approximately 2:1, from a low of 1:1 in Barrhead County, Alberta to a high of 2.69:1 in Newfoundland and

Labrador.[5,9] It should be noted, that unlike incidence, prevalence does not necessarily reflect a true geographic "risk" of developing MS since prevalent cases might tend to migrate to larger centres seeking tertiary medical care. This may falsely increase prevalence figures in metropolitan areas, as suggested by some,[15] but discounted by others.[6]

However, the regional variation in prevalence remains largely unexplained and raises questions regarding environmental and genetic influences. Given universal, publicly funded healthcare, differential access to diagnosis and treatment should ideally not result in regional ascertainment bias. A trend towards higher prevalence in the west as opposed to central Canada is suggested.[13,14] Ethnic and migrational differences in persons of European ancestry have been promulgated as possible explanations for the north-south gradient in MS prevalence suggested in American studies.[3] No such ethnic differences readily explain the regional variation seen in Canada given that the populations of all Canadian provinces are comprised primarily of Caucasians of European ancestry. However, in an Albertan study of parental ancestry of MS patients, non-specific European ancestry was positively correlated with MS, while British ancestry was associated with a reduced risk.[41] Ethnically distinct groups in Canada have not been widely studied, including First Nation Canadians. However, existing studies of First Nations do suggest a lower prevalence of MS than their Caucasian neighbours with whom they presumably share similar environmental exposures.[17-20,41] Studies of Germanic Hutterite communities with lower MS prevalence than non-Hutterite Canadians[42] also support the influence of genetic differences in determining MS prevalence. Multiple sclerosis prevalence in French Canadians, as a genetically and geographically isolated population, has not been studied in any detail.

Genetic susceptibility is well described[43] and further supported by four prevalence studies which cite a family history of MS in up to 40% of prevalent cases.[4,9,12,15] Variation of MS prevalence within countries has been well described in France, Italy and the UK.[44,45] In these instances, a satisfactory explanation is also still lacking. No robust data yet support environmental toxins, infections or other non-genetic risk factors as a sufficient or necessary cause.[46] Furthermore, genetic differences are also unlikely to be the sole explanation.

As with all systematic reviews, the current study is susceptible to certain limitations. First, such a review can only be as good as those studies included for analysis. Although search parameters were broad, some relevant studies may have been missed or the results of included studies misinterpreted. It is also evident that some regions in Canada are very well studied (i.e. Alberta) while others having greater demographic weight have barely been studied at all (i.e. Quebec). The differences in study methodologies, case definition, population sizes and demographics and the dates the studies were performed all render meaningful comparisons and pooling of data difficult and approximate. The general non-reporting of sex- and age-standardized prevalence figures only further adds to the difficulty in comparing studies. Our analyses of heterogeneity and calculation of confidence intervals relied on the completeness of data published in the original studies.

Despite these limitations, the current review helps consolidate current knowledge of MS prevalence in Canada and confirms that this country has a national prevalence among the highest in the world of at least 100 per 100 000, and likely much higher. It also confirms that the regional variation in prevalence suggested in previous studies is genuine. Perhaps most importantly, it makes evident the gaps in knowledge that still exist concerning Canadian MS epidemiology. Future studies of MS prevalence should use more uniform case definition and ascertainment methods and provide prevalence values standardized to the Canadian population (by age and sex) to facilitate comparisons between regional studies. In addition, values standardized to the world population would help with comparisons between national studies, as has been advocated by others.[37,44] Canada serves as an ideal territory for the study of MS epidemiology given the high prevalence of disease, regional variation, the presence of a well-established community of MS researchers and publicly-funded, universally accessible healthcare. Establishment of a national MS registry, as has been done in Norway, would further strengthen such research efforts.[47]

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