

# Incidence of Multiple Sclerosis among First Nations People in Alberta, Canada

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## Key Words

Multiple sclerosis incidence · Incidence, multiple sclerosis · Aborigines, multiple sclerosis incidence

## Abstract

Multiple sclerosis (MS) is thought to be rare among North American aboriginals, although few population-based frequency studies have been conducted. Data from government health databases were used to describe the incidence of MS among First Nations aboriginal people in the province of Alberta compared to the general population from 1994 to 2002. The general population rates were consistently higher than First Nations rates, but were essentially stable across this time span for both groups. For First Nations the MS incidence was 7.6 per 100,000 and 20.6 per 100,000 for the general population in 2002. During 2000–2002 for First Nations the incidence was 12.7 for females and 7.6 for males, with a female-to-male ratio of 1.7:1. During the same period the general population incidence was 32.2 for females and 12.7 for males, with a female-to-male ratio of 2.5:1. The peak incidence for both First Nations and the general population of Alberta was in the age group 30–39 years in 2002. The high incidence rates are consistent with high prevalence rates reported for both groups in 2002: 99.9 per 100,000 for First Nations and 335.0 per 100,000 for the general population. While

the MS incidence in First Nations people is lower than in the general population of Alberta, it is not rare by worldwide standards.

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## Introduction

It has been suggested that multiple sclerosis (MS) is rare among North American aboriginals [1–3], despite frequent intermarriage with people of European ancestry, among whom the rate of MS is often high. However, until the work by Mirsattari et al. [4], no population-based studies on either incidence or prevalence of MS among North American aboriginals had been conducted. Mirsattari et al. [4] identified seven aboriginal Canadians with MS in Manitoba, one of the Canadian Prairie Provinces, for a period prevalence of 40.0 per 100,000 population from 1970 through 1996. This prevalence rate is not low by worldwide standards. Traditionally countries or racial groups have been classified as low risk for MS, if their prevalence is less than 4 per 100,000 population, as medium risk, if the prevalence ranges from 4 to 29 per 100,000 population, and as high risk, if their prevalence is 30 per 100,000 population or greater [5]. Incidence rates generally parallel prevalence rates by country or ra-

cial group [6]. Consequently, it might be reasonable to infer from the work by Mirsattari et al. [4] that the incidence of MS among aboriginals in Manitoba, like the prevalence, would not be low by worldwide standards. However, these researchers did not assess the incidence of MS among Manitoban aboriginals.

Prevalence rates are useful for establishing the burden of disease and the need for health services. Incidence rates are more relevant for exploring disease etiology, because they represent new cases occurring within a given area during some period of time and are more likely to be correlated with the occurrence of an environmental cause, especially one which may have a long latency period [7]. At least one environmental cause of MS is thought to occur before age 15 years, although the peak age of disease onset is about 30 years [8].

The purpose of this study was to determine the incidence rate of MS among aboriginals in Alberta, another Canadian Prairie Province, compared to the general population. Under the *Constitution Act* of Canada, 1982, section 35, the term aboriginal refers to indigenous populations that occupied the country before European colonization (Indian/First Nations and Inuit) and also includes Métis (typically Indian/First Nations and French ancestry). The MS incidence rates described in this paper cover the years from 1994 to 2002 and specifically focus on First Nations aboriginals.

Alberta is one of the three Canadian Prairie Provinces which also include Manitoba and Saskatchewan. The Prairie Provinces are in the middle of Canada between Ontario and British Columbia. Alberta is situated between 49° south and 60° north latitude and between 110° east and 120° west longitude. It has an area of 661,185 square kilometers. Land accounts for 97% of the province. The general topographical areas are prairies, parkland (mixed forests and plains), forests, and the Rocky Mountain region in the western part of the province. The climate is sunny and dry, with average temperatures ranging from 15 to 23°C in July and from -8 to -23°C in January. Occupational activities include farming, ranching, and various industries, particularly related to the production of oil, natural gas, and coal. Over the past decade, the economy has experienced rapid growth in the petrochemical and forest product industries, among others, resulting in considerable in-migration of people from other parts of the country. The majority of the population resides in the two metropolitan areas of Edmonton and Calgary. The First Nations people of Alberta are predominantly grouped into Algonkian (Blackfoot, Blood, Peigan, Gros Ventre, and Cree) and Athapaskan (Beaver,

Sarsi, and Chipewyan) cultural and linguistic groups, whose lands are spread throughout the province.

## Methods

### *Sources of Data*

The data needed to calculate MS incidence rates were extracted from the Alberta Central Stakeholder Registry (CSR), the Alberta Health Care Insurance Plan (AHCIP) database, and hospital in-patient and physician fee-for-service databases maintained by the province of Alberta's Ministry of Health and Wellness, as part of a larger study on both incidence and prevalence.

The CSR includes all residents of Alberta eligible for coverage with the AHCIP. All provincial residents must register with AHCIP. First Nations people who hold treaty registration status under the Indian Act of Canada can be identified in the CSR, because the federal government (Health Canada) pays their health care insurance premiums. A treaty registration status First Nations person is one who is listed in the Indian Register, an official record maintained by the federal government. Eligibility criteria are complex and change periodically, but, in brief, they encompass persons who are members of a band, or direct descendants of a band member, who use or are entitled to use a reserve which has been set aside by treaty with various British and Canadian governments in the history of the country. The CSR also includes non-treaty registration status First Nations, Inuit, and Métis, although there is no way to separate out their data. The CSR excludes members of the military, Royal Canadian Mounted Police, and federal prison inmates.

Each person in the CSR is assigned a unique lifetime personal identifier (personal health number) which makes it possible to merge individuals' information across databases. Individuals who have not paid their health insurance premiums can still access services, so non-payment of premiums is believed to have minimal impact on a person's ability to receive care (i.e., it is unlikely that health status information on these people would be excluded from the databases). Comparisons between the CSR and Alberta Census data confirm that the AHCIP databases include approximately 99% of the province's population.

The hospital in-patient database contains a record of hospitalizations, approximately 380,000 per year. As many as 16 diagnostic codes can be recorded per hospitalization in the database. This database uses the International Classification of Diseases (ICD-9-CM) coding at the four-digit level. The physician fee-for-service database records all physician visits and can include up to three diagnostic codes per claim, also using the ICD-9-CM coding scheme at the four-digit level. The diagnostic code does not impact the amount of physician payment which is based on the procedure codes.

### *Data Extraction Procedures*

For this study, all hospital in-patient and physician fee-for-service records from 1983 through 2002, where a diagnosis of MS (according to the ICD-9-CM, 340 for MS) was mentioned, were extracted. Individuals were defined as cases, if they had one or more hospitalizations for MS or two or more physician visits, although in fact many cases exceeded the minimum criteria. These particular criteria were chosen to give good specificity at the ex-

**Table 1.** MS incidence per 100,000 population and 95% CIs for First Nations people (FN) and the general population (GP) of Alberta, 1994–2002 (age standardized to the 1996 Canadian population)

Year	Cases		Population		Incidence rates (95% CIs)	
	FN	GP	FN	GP	FN	GP
1994	7	599	86,442	2,688,321	12.4 (2.1, 22.6)	22.9 (21.1, 24.8)
1995	5	598	87,410	2,706,927	7.8 (0.6, 15.0)	22.7 (20.9, 24.5)
1996	6	586	91,095	2,734,303	7.5 (1.2, 13.7)	21.8 (20.0, 23.6)
1997	4	617	95,060	2,784,042	4.7 (–0.3, 9.7)	22.5 (20.7, 24.3)
1998	6	637	99,044	2,845,167	6.6 (1.2, 11.9)	22.7 (20.9, 24.4)
1999	9	680	103,464	2,915,381	8.2 (2.7, 13.7)	23.6 (21.8, 25.3)
2000	10	725	107,541	2,959,798	11.9 (4.3, 19.7)	24.6 (22.8, 26.4)
2001	7	667	111,170	3,013,585	8.4 (1.9, 14.9)	22.4 (20.7, 24.1)
2002	9	626	114,337	3,076,860	7.6 (2.6, 12.7)	20.6 (18.9, 22.2)

pense of sensitivity, therefore, erring on the side of increased false negatives in favor of few false positives.

A case was designated as incident rather than prevalent, if the person first appeared in the database with a diagnosis of MS from 1994 onward, but had no record of services for MS in the previous 10 years. The 10-year run-in period for incidence was considered sufficient, because the average annual relapse rate indicates that a person would have at least one relapse within a 5-year period given that the relapse rate is generally thought to be about one in each 2 years [9]. In other words, considering the probability of surviving 2 years without a relapse is 50%, then 97% of the subjects would be expected to have at least one relapse within 10 years. A cumulative incidence of 50% at 2 years indicates an annual relapse rate of 0.346 per year, and this rate projects to a cumulative incidence at 10 years of  $1 - \exp(-r \cdot 10) = 0.968$ .

The year 1994 was selected as a starting point for presentation of incidence estimates in this paper, because in 1994 a new coding system was introduced which made it possible to more accurately identify treaty registration status First Nations people in the database than before. This was also around the time of the last major change in eligibility criteria which allowed women who had lost their treaty registration status through marriage to reclaim it, so that any influx of this group or their offspring should not have influenced the pattern of incidence rates.

Demographic information for identified cases was derived from the CRS, specifically gender, age, and treaty registration status. Treaty registration status First Nations cases, the same aboriginal group assessed in the study done by Mirsattari et al. [4], were separated out from the general population of Alberta by the referred-to code which indicates that Health Canada pays health care insurance premiums on their behalf. General population cases included all people in the CSR with MS. The denominators used to calculate incidence rates were all treaty registration status First Nations people and all members of the general population of Alberta, respectively, without MS.

Names of persons with MS were not tracked by Alberta Health personnel who derived and aggregated the data nor released to any other researchers involved in the study, to comply with ethical guidelines operating within the province. None of the data used in the study allowed identification of specific individuals.

#### Data Analysis

MS incidence rates per 100,000 population and 95% confidence intervals (CIs) were calculated for the total registered status First Nations population and the general population of Alberta for each year from 1994 through 2002. The direct method (i.e., weighting a set of observed category-specific rates according to a standard distribution) was used to standardize rates to the 1996 Canadian population. The 1996 Canadian population figures were the most recent ones available at the time.

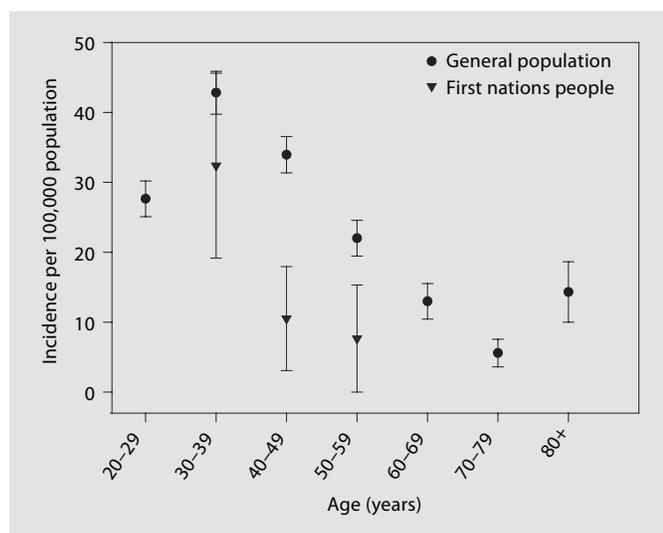
In addition to age-standardized rates, gender- and age-specific rates were also calculated. There were too few cases among First Nations to derive incidence rates by gender for each year from 1994 through 2002, so that cases were averaged over 2000–2002 for gender-specific rates among both First Nations and the general population. For the same reason, age-specific rates were calculated for both groups as a whole, not by gender, and for 2002 only. Age-specific rates were also restricted to cases from age 20 years onward, since few cases were reported prior to that age among the general population and none among First Nations people.

#### Results

Table 1 shows the age-standardized MS incidence rates per 100,000 population and 95% CIs for registered First Nations people and the general population of Alberta, for each year from 1994 through 2002. The rates for First Nations were considerably lower than for the general population for each year during this time period. Differences were unlikely to occur by chance, as judged by non-overlapping CIs. The CIs for First Nations were much wider than for the Alberta population due to the small number of cases, and the rates would thus also be more susceptible to misclassification of any cases due to methods of defining them. The First Nations rates seem

**Table 2.** Female and male MS incidence rates per 100,000 population and 95% CIs for First Nations people and the general population of Alberta, 2000–2002 (age standardized to the 1996 Canadian population)

	Incidence rate (95% CIs)		Female:male ratio
	female	male	
First Nations people	12.7 (4.9, 20.4)	7.6 (1.2, 14.0)	1.7:1
General population	32.2 (29.2, 35.0)	12.7 (10.9, 14.6)	2.5:1



**Fig. 1.** Age-specific MS incidence rates per 100,000 population and 95% CIs for First Nations people and the general population of Alberta, 2002. Of the two upper CIs shown in the 30- to 39-year age category, the lower one applies to First Nations people.

to fluctuate more than those of the general population, but neither group appears to have experienced an increase in incidence for the time period 1994–2002. Age standardization influenced First Nations rates more, because the age structure of the Alberta population approximates the Canadian population age structure, while the First Nations have an age structure which includes more people in the younger age categories.

Table 2 shows the female and male incidence rates for First Nations people and the general population of Alberta averaged over 2000–2002. The rate for females was higher than for males among both First Nations people and the general population during this time period. Again the CIs for First Nations were much wider than for the general population due to the small number of cases.

Figure 1 shows the age-specific incidence rates per 100,000 population for First Nations people and for the general population of Alberta for 2002. There were no

cases of MS in First Nations in the 20- to 29-year age category. The peak incidence for both First Nations people and the general population of Alberta was in the 30- to 39-year age category. There were no MS cases in First Nations beyond the 50- to 59-year age category, while there were MS cases in the general population up to the age of 80 plus.

## Discussion

The incidence rates reported in this study were calculated using information recorded in provincial health databases. The validity of diagnoses such as MS included in government databases has been questioned. In particular, concerns have been raised that possible as well as probable/definite cases are included which could inflate the resultant MS rates. However, the incidence rates for the general population derived from Alberta Ministry of Health and Wellness data are similar to those reported by provincial studies, in which the diagnosis was verified by examination [10, 11], supporting the accuracy of database information.

In a study touching on the validity of using health databases for frequency studies, Bhan et al. [12] picked two physician visits (similar to this study) which apparently agreed well with the diagnosis by a neurologist at the Dalhousie Multiple Sclerosis Research Unit in Halifax (Nova Scotia, Canada). The increased use of magnetic resonance imaging (MRI) in Alberta has also likely reduced the number of false-positive differential diagnoses since the 1990s. Since MS has been considered rare among aboriginals, any recorded case of MS in the provincial databases is likely to have been most thoroughly investigated for confirmation.

The First Nations rates in this study do not necessarily apply to people with no European ancestry, since ancestry data were not available for First Nations people included in Alberta government health databases. Only 1 of the 7 First Nations people with MS identified in the study performed by Mirsattari et al. [4] did not report any

European ancestry; however, it was generally rare and distant: 1 person reported a parent, and 5 reported one great grandparent each. First Nations people with MS in Alberta might have a similar rate and degree of European ancestry, since, like the group studied by Mirsattari et al. [4], they included only treaty registration status aboriginals, but this is impossible to tell from the data available. Data on band membership were not available for this study, because it might increase the possibility of identifying specific individuals, in opposition to privacy considerations. Since it is known that the First Nations people of Alberta are generally members of the Athapaskan and Algonkian linguistic and cultural groups [13], the incidence rates reported in this study may apply to members of these groups. However, there is no way to know whether rates differ by group. In the study performed by Mirsattari et al. [4], all of the 7 identified aboriginals were Algonkian (6 Cree and 1 Ojibway).

#### *Magnitude of First Nations People Incidence Rates*

The results of this study indicate that neither First Nations people nor the general population MS incidence rates in Alberta are low by worldwide standards. An average of recently reported MS incidence rates worldwide would approximate 3.7 per 100,000 population [6], with a reported low of 1.7 in Reggio Emilia and Modena, Italy [14], and a high of 8.7 in Uusimaa, Finland [15]. In fact, compared to this range, the First Nations rate in Alberta at 7.6 per 100,000 population in 2002 would place it among the world's highest rates. The general population rate for Alberta, at 20.6 per 100,000 population in 2002, is more than double the next highest rate worldwide. In comparing incidence rates worldwide, however, it is important to note that the rates refer to different time periods and have been collected using a variety of diagnostic criteria and case ascertainment methods which complicates any conclusion about their relative magnitude. In particular, access to MRI in Alberta might increase its incidence rates relative to some other countries.

#### *Temporal Trends in Incidence Rates*

The high incidence rate observed in both First Nations people and the general population of Alberta is consistent with the high prevalence rates observed for both groups and for aboriginals in the study of Mirsattari et al. [4]. Table 3 shows MS annualized period prevalence rates per 100,000 population for First Nations people and the general population of Alberta, 1994–2002, standardized to the 1996 Canadian population using the direct method [L.W. Svenson, Alberta Ministry of Health and Wellness,

**Table 3.** MS prevalence rates per 100,000 population for First Nations people and the general population of Alberta, 1994–2002 (age standardized to the 1996 Canadian population)

Year	First Nations prevalence rate	General population prevalence rate
1994	56.3	262.6
1995	61.0	274.4
1996	68.4	285.3
1997	72.0	293.7
1998	81.1	302.9
1999	88.2	312.0
2000	97.6	322.0
2001	103.1	330.3
2002	99.9	335.0

personal commun., 2005]. Unlike incidence rates, however, prevalence rates have essentially shown a steady increase over this time period: for First Nations people a 43.6% increase from 1994 to 2002 and for the general population a 21.6% increase from 1994 to 2002. These increases in prevalence do not appear to be due to increases in incidence from 1994 onward based on data reported in this paper. A considerable jump in MS incidence seems to have occurred in the general population of Alberta, however, from approximately 5.2 per 100,000 population in 1985–1989 [16] to the 1990s. It is unclear whether the First Nations MS incidence was lower in the past, since no comparable figures are currently available for prior years, although the prevalence rates would indicate that incident cases did occur. If the MS incidence were higher than before in both groups, it would remain unclear whether this is a real increase or due to other factors, including the availability of new diagnostic technologies such as MRI. MRI not only allows the diagnosis of milder MS/relapsing-remitting MS cases, but also confirmation of the diagnosis in groups earlier considered unlikely candidates for the disease, such as First Nations people.

#### *Gender-Specific Incidence Rates*

In most geographic locations, the female MS incidence rates are higher than male incidence rates [6], as they are in both First Nations people and in the general population of Alberta. The female-to-male incidence ratios among both First Nations people and the general population of Alberta are within the range of the female-to-male incidence ratios reported worldwide [6]. The highest recently reported ratio is for Perth, Australia, at 2.8 [17] and

the lowest at 1.1 in Iceland [18]. Despite overlapping CIs among First Nations people, it seems likely that the incidence among females is actually higher, since First Nations prevalence rates were significantly higher among females at 158.1 than males at 38.0, for a female-to-male ratio of 4.2:1, in 2002 [L.W. Svenson, Alberta Ministry of Health and Wellness, personal commun., 2005]. The CIs for these prevalence rates do not overlap, likely due to the larger number of cases involved.

#### *Age-Specific Incidence Rates*

A peak onset age of about 30 years is quite typical worldwide [6]. The fact that no First Nations people appeared in age-specific incidence rates until category 30–39 years in 2002 may indicate a later diagnosis because of a previous lack of awareness among physicians that MS could occur in this group. Alternatively, it might indicate that this group tends to have a later onset which has been associated with a more aggressive disease course [6, 19]. Mirsattari et al. [4] reported that Manitoban First Nations people were at a greater risk of an aggressive type of MS (resembling neuromyelitis optica) than non-aboriginal MS controls based on a comparison of Expanded Disability Status Scale scores, although it should be noted that the aboriginal/non-aboriginal groups did not differ in average onset age. A generally shorter life expectancy might account for the absence of First Nations cases beyond the 50- to 59-year age category in comparison with the general population.

#### *Implications for Etiology*

Incidence studies are useful for a variety of reasons, including that they provide clues to the etiology of diseases like MS. The incidence rates reported in this study are essentially based on the date of diagnosis (i.e., first billing for symptoms of MS); therefore, it is possible that both new First Nations and general population cases in this study acquired the disease outside of Alberta but only manifested symptoms once they had arrived in the province. While this study does not have information on date of onset, speculation about the implications of incidence for etiology should keep this in mind.

The high MS incidence rate among Albertan First Nations people compared to worldwide figures may suggest that, like the general population of Alberta, they are more frequently exposed to some environmental risk factor for MS. Since the incidence rates appear to have remained stable during the time period studied, this may mean that exposure to any such environmental risk factor has also remained stable during 1994–2002. However, evidence of

a considerable jump in incidence among the general population from the late 1980s may suggest that this factor experienced an increase and then leveling off. Similar jumps elsewhere, such as in Sardinia [20], have been attributed to increasing industrialization (as has occurred in Alberta in the past decade) and consequent increases in potentially negative influences like air pollution. However, many countries worldwide with lower MS incidence rates are highly industrialized, and have been for years.

It is not clear whether the stability in Alberta incidence rates among both First Nations people and the general population from 1994 onward will continue or whether it will be followed by an increase or even a decline. Studies of incidence rates over time worldwide have produced notably conflicting patterns, including stability, general tendencies to increase or decline, or even patterns of substantial peaks and troughs [6]. Regardless of overall trends, many geographical areas exhibit slight cyclic fluctuations within these patterns [6], just as the incidence rates from 1994 through 2002 among both First Nations people and the general population of Alberta appear to have fluctuated within a generally stable pattern. Fluctuating patterns are often cited as evidence for an infectious environmental cause, because such agents fluctuate, while factors like diet, housing, and sanitation tend to improve, and factors like climate tend to remain stable. It is possible that both First Nations people and the general population of Alberta are more frequently exposed to a fluctuating infection which causes MS, but alternatively it may be that the province's citizens are more susceptible to such an agent due to a relatively hygienic environment in Alberta as compared with other locations both within and beyond Canada. The hygiene hypothesis states that the absence of chronic infections in an environment is a risk factor for MS, because people in hygienic environments do not develop adequate capacity to regulate autoimmune reactions if exposed to a causal agent [21]. Data from Alberta have shown a negative correlation between the incidence of MS and the incidence of most communicable respiratory disorders throughout the province's health regions [22], which would tend to support the credibility of this hypothesis.

The fact that First Nations people have a lower rate of MS than the general population of Alberta may simply suggest that they have a lower genetic predisposition to the disease, consistent with lower rates observed in other non-Caucasian groups. Low incidence rates are typically found in countries which are predominantly non-Caucasian, and in countries with a mix of Caucasian and non-Caucasian racial groups, the MS incidence rates are con-

sistently lower among non-Caucasians [6]. Mirsattari et al. [4] examined class II HLA alleles in the Manitoban aboriginals with MS to determine whether they had HLA types that might increase their susceptibility to development of the disease. The patients had a variety of HLA DRB1 and DQB1 types previously reported to be common in aboriginals in Manitoba: 1 patient had HLA DRB1\*15, but none had the HLA DQB1\*0602 type previously reported to be frequent among MS patients.

An additional explanation for the lower MS incidence rate in First Nations people than in the general population of Alberta may be that they experience a causal environmental factor in some different way. For example, it has been hypothesized that, if an infection is involved in the cause of MS, that infection is more likely to result in the disease if acquired at a later age [23]. This hypothesis is consistent with the suggestion that MS is less common in tropical than temperate climates, because people in tropical climates are exposed to more infections at a younger age, due to factors like high housing density and

poor sanitation, when an MS causal factor has less impact [24]. First Nations people in Alberta have been documented as experiencing a range of infectious diseases at a younger age than the general population [L.W. Svenson, Ministry of Alberta Health and Wellness, personal commun., 2005]. The lower MS incidence rates among First Nations people than among the general population of Alberta might result from some combination of a younger age of exposure to a causal infection due to differing socio-economic conditions and a lesser genetic predisposition to the disease.

Etiologic studies comparing groups with divergent incidence rates living in the same geographic region, such as First Nations people and the general population of Alberta, might provide further clues to environmental risk factors. With the high incidence now observed among First Nations people in two Canadian provinces, more systematic studies of the occurrence of MS in various aboriginal groups might confirm high rates elsewhere worldwide.

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