Temporal changes in age at onset of multiple sclerosis: Importance of controlling for equal observation time

Mihaela Pirvoaica[1]; Elaine Kingwell, PhD[2]; Afsaneh Shirani, MD[3]; Feng Zhu, MSc[2]; Yinshan Zhao, PhD[2]; John D. Fisk, PhD[4]; Virender Bhan, MBBS, FRCPC[5]; Robert Carruthers, MD[6]; Ruth Ann Marrie, MD, PhD, FRCPC[7]; Helen Tremlett, PhD[8]
Citation: UBCMJ. 2016: 8.1 (23-26)

Abstract

Background Previous studies examining whether changes in the age of multiple sclerosis (MS) onset have occurred over time have yielded inconsistent findings.

Objectives We investigated temporal trends in MS age at onset in three Canadian provinces and assessed the effect of controlling for equal observation time between birth year groups.

Methods We included 9459 MS patients from MS clinic databases in British Columbia (BC, n=5423), Manitoba (MB, n=1419), and Nova Scotia (NS, n=2617). Birth years were grouped into five–year blocks and analysed via ANOVA and linear regression to assess temporal trends in age at onset. The complete cohort included all MS patients. The restricted cohort allowed comparable observation times for each birth year group and included patients who had reached age 40 and had MS onset at age 40 or younger.

Results The complete cohort showed a steep decline in age at onset (averaging 2.0 years between birth year groups), from 37.0±10.8 years (1941-1945 births) to 28.0±6.4 years (1966-1970 births), $p<0.001$. In the restricted cohort (n=6003), only BC patients showed a significant decrease in the mean age at onset (averaging 0.3 years between birth year groups): 29.6±6.5 years (1941-1945 births) and 27.4±5.8 years (1966-1970 births), $p<0.001$. No significant decrease in age at onset was evident in the NS or MB restricted cohorts.

Conclusions If the age at MS symptom onset has changed in the last four decades, shifts have been small. Temporal changes in age at MS onset between birth cohorts can be inflated without due consideration to comparable observation time.

Introduction

Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system that affects over 2.5 million people worldwide. The underlying etiology is not well understood, although it is likely a combination of environmental and genetic factors.[1-4] It can be speculated that if any of the environmental factors were to change, an impact on the age at onset (i.e. age at first symptoms) might be seen. Several studies have reported temporal changes in the demographic characteristics of MS, including a decreasing average age at onset.[5,6] This has prompted investigations into the observed changes in MS age of onset, the timescale of which might suggest a shift in etiologically relevant environmental factors.[7,8] The age at which MS symptoms first begin ranges from early childhood to late adulthood. However, the average age at MS onset is widely quoted as being around 30 years of age, with most presenting with MS between the ages of 20-40 years.[9-11]

Previous studies that have investigated differences in the age at MS disease symptom onset between different birth year groups have reported that the average age at onset decreased over time.[5,6] However, a follow–up study by one of these groups demonstrated that analyses without equal observation time could lead to spurious findings suggesting changes over time, or differences between generations in age at disease onset;[12] these differences disappeared once the adjustment for equal observation time was applied.[12] Without adjustment for unequal follow–up time, younger (more recent) birth cohorts would appear to have a younger average age at onset because they had not had the opportunity to reach an older age by the end of follow–up. We aimed to assess the potential effects of restricting the cohort with equal observation times and to determine whether changes in age at onset were evident between birth cohorts.

Materials and methods

Data Sources

This study utilised data collected from three cohorts of MS patients from three different provinces in Canada: British Columba (BC), Manitoba (MB), and Nova Scotia (NS). Data were collected prospectively in BC and NS, while in MB, data were collected through a combination of chart reviews and prospective data collection. Each database contained information on all MS patients attending the MS clinics within the respective province. These databases have been used extensively for research purposes to address questions on MS.[11,13-17] Briefly, the British Columbia Multiple Sclerosis (BCMS) database contains details on patients visiting one of four MS clinics in BC since the opening of the first clinic in 1980. These four clinics are based in Vancouver, Victoria, Kelowna, and Prince George, and were the only MS specialty clinics in the province until the end of 2004. A fifth clinic, which opened in 2005, is not linked to the BCMS database. The MB MS database has collected information on patients attending the University of Manitoba's MS clinic (the only MS clinic in the province) since 1998. The Dalhousie MS Research Unit (DMSRU) database in NS collates information on individuals attending the sole outpatient clinic in NS that specializes in MS care since 1980. For the purposes of this study, each site provided demographic and clinical data (year of birth, age at MS onset, and sex) to the end of 2008 (the predetermined study endpoint).

Selection of study cohorts

All patients with a diagnosis of definite MS by Poser or McDonald criteria,[20,21] a recorded MS symptom onset date, and year of birth between 1941 and 1980 were selected from each province's database.

[1]MD Student, Faculty of Medicine, University of British Columbia, Vancouver, BC
[2]Division of Neurology, Department of Medicine, University of British Columbia, Vancouver, BC
[3]University of Texas Southwestern Medical Center, Dallas, TX
[4]Department of Psychology, Dalhousie University, Halifax, NS
[5]Department of Neurology, Dalhousie University, Halifax, NS
[6]Division of Neurology, Department of Medicine, University of British Columbia, Vancouver, BC
[7]Department of Internal Medicine and Community Health Sciences, University of Manitoba, Winnipeg, MB
[8]Division of Neurology, Department of Medicine, University of British Columbia, Vancouver, BC

Correspondence to
Mihaela Pirvoaica (m1pirvoaica@gmail.com)

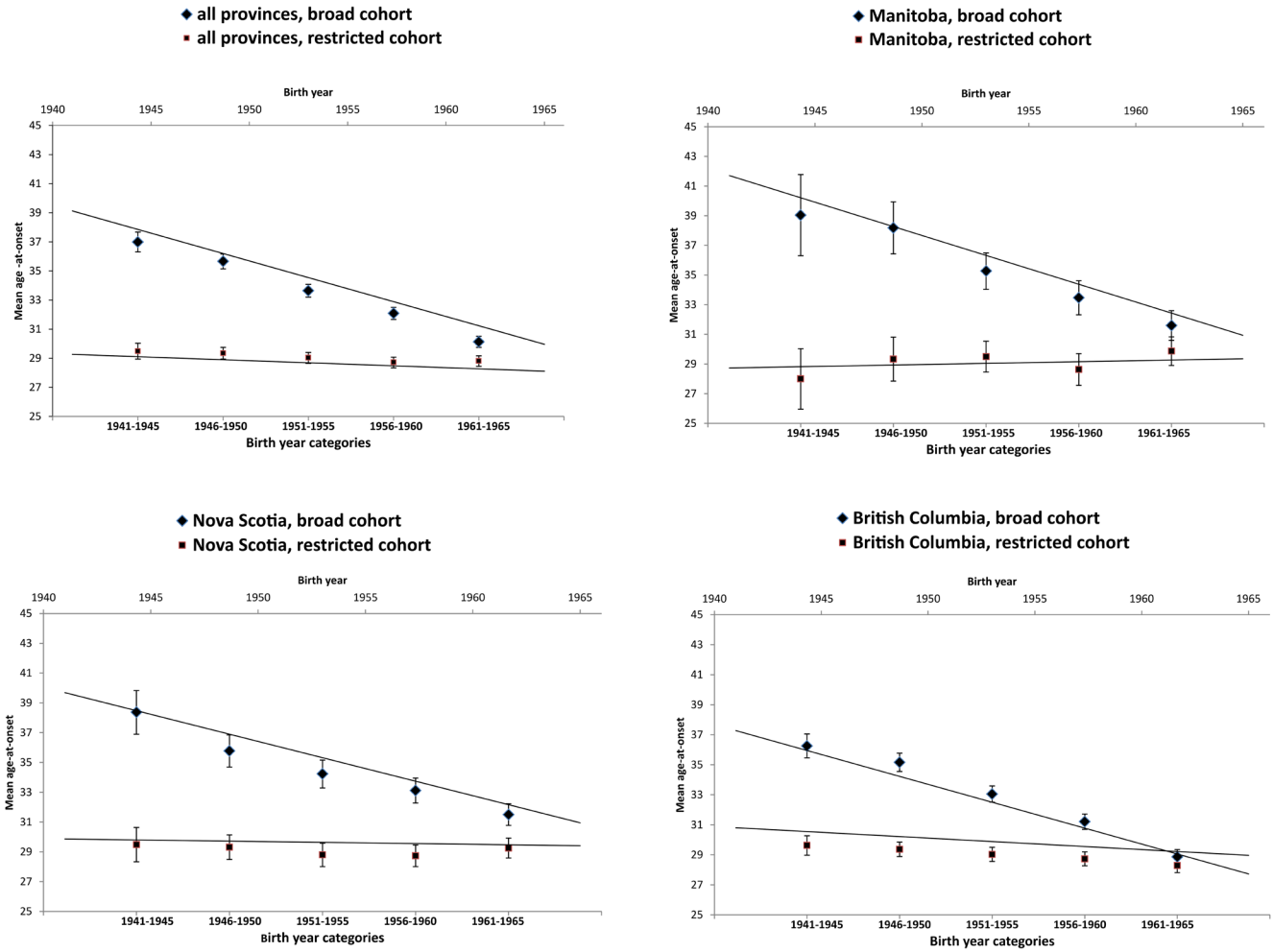

Figure 1 | Graphs of the combined data and each of the three provinces separately showing the mean age at onset (with 95% confidence intervals) by birth year group for the broad cohort and for the restricted cohort. The lines represent the results of regression of age at onset on birth year (as a continuous variable).

All individuals fulfilling these criteria were included in the 'complete cohort'; patients were excluded if they were born before 1941 or after 1980, and if they were missing the MS symptom date of onset. From this complete cohort, a restricted cohort was selected to ensure equal observation time; cases were restricted to those with a birth year between 1941 and 1967 (i.e. those who were at least 40 years old by the study end) with an MS age at onset <40 years. Birth years were categorized into 5–year intervals where possible, from 1941-1945 to 1976-1980 for the complete cohort, and from 1941-1945 to 1966-1967 for the restricted cohort. The last category for the restricted cohort included only those born in 1966 and 1967 as per the time restriction.

This study was approved by the University of British Columbia's Clinical Research Ethics Board (approval # H11-00386).

Statistical analyses

Analyses were performed on the complete and restricted cohorts in the combined dataset and stratified by individual province. The demographics (sex and birth year) and clinical characteristics (age at symptom onset) of all patients from each of the provinces were reported descriptively.

To explore whether there were observable trends in MS age at onset over time, the mean age at onset was compared between the birth year groups using Analysis of Variance (ANOVA). The association between birth year and the age at MS onset was also examined by linear regression analysis with birth year treated as a continuous variable. Alpha (α) was set at 0.05. All analyses were performed using ®IBM SPSS Statistics 22 (IBM Corporation 1994, 2015).

Results

In total, 9459 individuals met the inclusion criteria; 5423 from BC, 1419 from MB, and 2617 from NS. The demographic and clinical characteristics of participants are shown in Table 1. The proportion of women was comparable between the sites and between the complete (74.3% female) and restricted (74.7% female) cohorts. The mean age at onset was also similar across provinces; the average MS age at onset was 31.8 years in the combined complete cohort and 28.9 years in the restricted cohort (Table 1).

The ANOVA results from the combined complete cohort suggest that the mean age at onset decreased significantly over time, from 36.9±10.8 years in the 1941-1945 birth year group to 28.0±6.4 years in the 1966-1970 birth year group. Similarly, significant decreases in age at onset were evident for each of the provinces individually with reductions of approximately 9-10 years in age at onset between the earliest and most recent birth cohorts (see Table 2 and Figure 1). However, in the combined restricted cohort, the difference between age at onset in the earlier and later birth cohorts, although evident, was much smaller. The 1941-1945 birth year group had a mean age at onset of 29.5±6.5 years while the 1966-1970 birth year group had a mean

Table 1 | Characteristics of the MS cohort from British Columbia, Manitoba and Nova Scotia

	British Columbia		Manitoba		Nova Scotia		All Provinces	
	Complete cohort, n=5423	Restricted cohort, n=3545	Complete cohort, n=1419	Restricted cohort, n=728	Complete cohort, n=2617	Restricted cohort, n=1476	Complete cohort, n=9459	Restricted cohort, n=5749
Sex: female, n (%)	3995 (73.7)	2616 (73.8)	1055 (74.4)	558 (76.6)	1973 (75.4)	1123 (76.1)	7023 (74.3)	4297 (74.7)
Birth year:								
1941-1945	651	400	78	37	230	120	959	557
1946-1950	933	557	168	91	365	232	1466	925
1951-1955	1056	773	232	148	434	293	1722	1214
1956-1960	969	794	258	176	472	340	1699	1310
1961-1965	759	726	237	204	450	374	1446	1304
1966-1970*	547	250	193	72	319	117	1059	439
1971-1975	343	N/A	140	N/A	185	N/A	668	N/A
1976-1980	165	N/A	113	N/A	162	N/A	440	N/A
Age at onset: Mean (SD)	31.4 (8.98)	28.8 (6.46)	32.2 (9.72)	29.3 (6.76)	32.4 (9.51)	29.0 (6.59)	31.8 (9.25)	28.9 (6.53)

*data only available between 1966-67 for the restricted cohort

Key: broad cohort = all definite MS patients in the three databases

restricted cohort = all definite MS patients that had reached their 40th birthday by study end and had MS onset by age 40

age at onset of 28.1±6.0 years; this was a mean difference of 1.4 years (Table 2 and Figure 1).

The results from the linear regression analyses of the complete cohorts indicated that the mean age at onset decreased as the birth year increased. This was consistent for the combined cohort and each of the individual provincial cohorts. However, when the analyses were repeated with the restricted cohorts, the difference in age at onset decreased considerably for both the combined cohort (1.4–year age difference between the earliest and latest birth year groups) and BC cohort (2.2–year age difference between the earliest and latest birth year groups) (see Table 2 and Table 3). There was no statistically significant association between birth year and age at onset for the NS or MB restricted cohorts (Table 3).

Discussion

Using equal observation times, we found no evidence of a change in the MS age at onset over a 27–year period (birth cohort) in two Canadian provinces (Manitoba and Nova Scotia). While the MS age at onset might have decreased somewhat with time in BC, this decrease was not comparable to the magnitude of change in age at onset reported by others.[5,6] An overall small decrease was seen in the combined cohort, which is presumed to be driven by the larger BC cohort. These findings are in contrast to other studies that have not allowed for equal observation time, including a Sardinian cohort study that reported large differences between the mean age at MS onset (41 years in the most remote decade of birth and 22 years in the most recent decade of birth),[6] and a Spanish cohort study that found a median MS age at onset of 30 years in the most remote birth decade and 22 years in the most recent birth decade.[5]

Reasons for the small decrease in MS age at onset observed in BC are unknown. However, possible reasons might include the changing ethnicity of the BC population over recent years and the greater ethnic diversity of BC compared to MB and NS, as well as an increased awareness of MS symptoms.[20,21] Although the underlying etiology of MS is not well understood, it is believed to involve a complex interaction of genetic and environmental factors. The environmental factors that have been implicated include sunlight exposure, Vitamin D, timing of infection with Epstein Barr Virus, and smoking;[1-2] exposure to any or all of these factors is likely to have changed over recent decades, but the role that such changes play in shortening the time between birth and onset of MS would be speculative.

It is important to assess changes in age at onset appropriately because a trend toward decreasing age at onset would point to potential changes in environmental factors that influence the onset of MS clinical symptoms. A true reduction in the age at onset would also affect estimates of incidence and prevalence and changes in these measures over time. Furthermore, study findings that suggest that an increasing ratio of remitting-relapsing MS (RRMS) to primary progressive MS (PPMS) over time[22] might be based on spurious results if insufficient follow–up time was allowed for people to develop PPMS, since individuals with PPMS typically have a later disease onset.

We were fortunate to have access to three large Canadian cohorts of MS patients with a heterogeneous population, which lent added power to our study. This allowed us to create a large combined dataset that included MS patients from three provinces in Eastern, Central, and Western Canada. The cohorts were followed for up to 28 years of ascertainment and 4 decades of birth years. This allowed for the identification of potential heterogeneity between geographic regions and populations of Canada while the follow–up period allowed for the assessment of trends over a significant period of time.

While the three databases captured most MS patients, a limitation of this study is that they did not capture the whole MS population in their respective provinces. Although it is not possible to determine the exact coverage, previous studies have estimated that the BCMS database captures approximately 60-80% of MS patients in BC[16,23] and the NS database captures between 67-83% of MS patients in NS.[15] The proportion of cases captured in MB is expected to be comparable to NS and BC. It is possible that age at onset trends are different among patients that did not attend these clinics, although the impact of unequal observation times is expected to be the same. For future birth cohort studies, the inclusion of more recent generations and more data from other provinces (if available) would be optimal.

The databases in BC and NS were populated prospectively, while in MB, data were collected through a combination of chart reviews and prospective data collection. Clinical information in the MB charts

Table 2 | Mean age at onset for the complete and restricted cohorts, by province and birth year category

Birth Cohort	All provinces, complete cohort		Nova Scotia, complete cohort		Manitoba, complete cohort		British Columbia, complete cohort	
	Mean age at onset	95% C.I.	Mean age at onset	95% C.I.	Mean age at onset	95% C.I.	Mean age at onset	95% C.I.
1941-1945	36.9	36.3-37.7	38.4	36.9-39.8	39.0	36.3-41.8	36.3	35.5-37.1
1946-1950	35.7	35.1-36.1	35.8	34.7-36.9	38.2	36.4-39.9	32.0	34.6-35.8
1951-1955	33.6	33.2-34.1	34.2	33.3-35.2	35.3	34.0-36.5	33.1	32.5-33.6
1956-1960	32.1	31.7-32.5	33.1	32.3-34.0	33.5	32.3-34.6	31.2	30.7-31.7
1961-1965	30.1	29.8-30.5	31.5	30.8-32.2	31.6	30.6-32.6	28.9	28.4-29.4
1966-1970	28.0	27.6-28.4	29.4	28.7-30.2	29.4	28.5-30.4	26.7	26.2-27.2
ANOVA Results	$F_{7,9451}$=249.5; P<0.001		$F_{7,2609}$=59.8; P<0.001		$F_{7,1411}$=54.8; P<0.001		$F_{7,5415}$=156.5; P<0.001	
Birth Cohort	All provinces, complete cohort		Nova Scotia, complete cohort		Manitoba, complete cohort		British Columbia, complete cohort	
1941-1945	29.5	28.9-30.0	29.5	28.3-30.6	28.0	25.9-30.0	29.6	28.9-30.3
1946-1950	29.4	28.9-29.8	29.3	28.5-30.1	29.3	27.9-28.5	29.4	28.9-29.9
1951-1955	29.0	28.7-29.4	28.8	28.0-29.6	29.5	28.5-30.5	29.0	28.6-29.5
1956-1960	28.7	28.4-29.1	28.7	28.0-29.5	28.6	27.6-29.7	28.7	28.3-29.2
1961-1965	28.8	28.5-29.2	29.3	28.6-29.9	29.9	28.9-30.8	28.3	27.8-28.8
1966-1970	28.1	27.6-28.7	28.7	27.6-29.9	29.5	28.2-30.8	27.4	26.7-28.2
ANOVA Results	F5,5743=3.4; P=0.005		F5,1470=0.5; P=0.74		F5,722=0.9; P=0.45		F5,3539=5.6; P<0.001	

was collected at each clinic visit by the MS specialist neurologist (i.e. by a comparable method to the data collection methods in BC and NS). Therefore, we do not expect that differences in data collection methods influenced our findings and conclusions.

Due to the inevitable delay between MS symptom onset and the date of diagnosis, the onset date of MS symptoms is typically collected retrospectively by patient recall. The accuracy of this recall might be influenced by many factors, including the delay to medical recognition or diagnosis, and symptom severity at onset. This might also lead to apparent changes in age at onset over time.

We used a smaller birth year interval for the most recent (1966-1967) birth group in the restricted cohort analyses rather than the five-year interval used for the other groups. However, the 1966-1967 birth cohort still included 439 subjects, a number that was comparable to that in the 1941-1945 restricted cohort (557 subjects). Both of these smaller birth cohorts included sufficient patients, allowing adequate power to address the objectives of this study.

By using three MS cohorts from three different Canadian provinces, we have demonstrated how estimates of change in the age at MS symptom onset between birth year groups over time can be significantly inflated when observation time differed, or was not controlled for, between birth cohorts. Moreover, attempts to address this question with birth cohorts of varying observation time can introduce bias. It is therefore important to ensure comparable observation times and equal opportunity to develop symptoms when assessing trends in the clinical characteristics of MS.

Table 3 | Results of linear regression analyses to assess the relationship between age at onset and birth year

	Estimated β-value	95% CI for β		p-value
Complete cohort		Lower Bound	Upper Bound	
All provinces	-0.382	-0.400	-0.365	<0.0001
Nova Scotia	-0.364	-0.399	-0.330	<0.0001
Manitoba	-0.451	-0.497	-0.406	<0.0001
British Columbia	-0.396	-0.420	-0.373	<0.0001
Restricted cohort				
All provinces	-0.047	-0.070	-0.023	<0.0001
Nova Scotia	-0.016	-0.064	0.032	0.64
Manitoba	0.026	-0.045	0.097	0.31
British Columbia	-0.077	-0.106	-0.047	<0.0001

References

1. Ascherio A, Munger KL. Environmental risk factors for multiple sclerosis. Part I: The role of infection. *Ann Neurol.* 2007 Apr; 61(4):288-99.
2. Ascherio A, Munger KL. Environmental risk factors for multiple sclerosis. Part II: Noninfectious factors. *Ann Neurol.* 2007 Jun; 61(6):504-13.
3. Belbasis L, Bellou V, Evangelou E, Ioannidis JP, Tzoulaki I. Environmental risk factors and multiple sclerosis: An umbrella review of systematic reviews and meta–analyses. *Lancet Neurol.* 2015 Mar; 14(3):263-73.
4. Giovannoni G, Ebers G. Multiple sclerosis: The environment and causation. *Current Opin Neurol.* 2007 Jun; 20(3):261-8.
5. Romero-Pinel L, Martinez-Yelamos S, Gubieras L, *et al.* Anticipation of age at onset in familial multiple sclerosis. *Eur J Neurol.* 2010 Apr; 17(4):572-5.
6. Cocco E, Sardu S, Lai M, Spinnicci G, Contu P, Marrosu MG. Anticipation of age at onset in multiple sclerosis: A Sardinian cohort study. *Neurology.* 2004 May; 62(10):1794-8.
7. Koch-Henriksen N, Sorensen PS. The changing demographic pattern of multiple sclerosis epidemiology. *Lancet Neurol.* 2010; 9(5):520-32.
8. Celius EG, Smestad C. Change in sex ratio, disease course and age at diagnosis in Oslo MS patients through seven decades. *Acta Neurol Scand Suppl.* 2009; 189:27-9.
9. Niedziela N, Adamczyk-Sowa M, Pierzchala K. Epidemiology and clinical record of multiple sclerosis in selected countries: A systematic review. *Int J Neurosci.* 2014; 124(5):322-30.
10. Hassan-Smith G, Douglas MR. Epidemiology and diagnosis of multiple sclerosis. *Br J Hosp Med.* 2011 Oct; 72(10):M146-51
11. Tremlett H, Paty D, Devonshire V. Disability progression in MS is slower than previously reported. *Neurology.* 2006 Jan; 66:172-7.
12. Alonso-Magdalena L, Romero-Pinel L, Moral E, Carmona O, Gubieras L, Ramon JM, *et al.* Anticipation of age at onset in multiple sclerosis: methodologic pitfalls. *Acta Neurol Scand.* 2010 Jun; 121(6);426-8.
13. Lu E, Zhu F, Zhao Y, van der Kop M, Sadovnick A, Synnes A, *et al.* Birth outcomes of pregnancies fathered by men with multiple sclerosis. *Mult Scler.* 2014 Aug; 20(9):1260-4.
14. Kingwell E, Evans C, Zhu F, Oger J, Hashimoto S, Tremlett H. Assessment of cancer risk with beta-interferon treatment for multiple sclerosis. *J Neurol Neurosurg Psychiatry.* 2014 Oct; 85(10):1096-102.
15. Marrie RA, Fisk JD, Stadnyk KL, Yu BN, Tremlett H, Wolfson C, *et al.* The incidence and prevalence of multiple sclerosis in Nova Scotia, Canada. *Can J Neurol Sci.* 2013 Nov; 40(6):824-31.
16. Tremlett H, Zhao Y, Rieckmann P, Hutchinson M. New perspectives in the natural history of multiple sclerosis. *Neurology.* 2010 Jun; 74(24):2004-15.
17. Shirani A, Zhao Y, Karim ME, Evans C, Kingwell E, van der Kop ML, *et al.* Association between use of interferon beta and progression of disability in patients with relapsing–remitting multiple sclerosis. *JAMA.* 2012 Jul; 308(3):247-56.
18. Poser CM, Paty DW, Scheinberg L, McDonald WI, Davis FA, Ebers GC, *et al.* New diagnostic criteria for multiple sclerosis: Guidelines for research protocols. *Ann Neurol.* 1983 Mar; 13(3):227-31.
19. McDonald WI, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD, *et al.* Recommended diagnostic criteria for multiple sclerosis: Guidelines from the International Panel on the diagnosis of multiple sclerosis. *Ann Neurol.* 2001 Jul; 50(1):121-7.
20. Statistics Canada. 1996 Census: Ethnic origin, visible minorities [Internet]. Ottawa: Statistics Canada; 1998 [cited 2016 May 06]. Cat. No.: 93F0026XDB96000. Available from: http://www.statcan.gc.ca/daily-quotidien/980217/dq980217-eng.htm
21. Statistics Canada 2011 National Household Survey. Immigration and ethnocultural diversity in Canada [Internet]. Statistics Canada; 2013 [cited 2016 May 06]. Cat. No.: 99-010-X2011001. Available from: https://www12.statcan.gc.ca/nhs-enm/2011/as-sa/99-010-x/99-010-x2011001-eng.cfm
22. Sumelahti M-L, Holmberg MHA, Murtonen A, Huhtala H, Elovaara I. Increasing incidence in relapsing–remitting MS and high rates among young women in Finland: A thirty–year follow–up. *Mult Scler Int.* 2014 Oct; 186950.
23. McKay KA, Tremlett H, Zhu F, Kastrukoff L, Marrie RA, Kingwell E. A population–based study comparing multiple sclerosis clinic users and non–users in British Columbia, Canada. *Eur J Neurol.* 2016; 23(6):1093-100.