Temporal trends of disability progression in multiple sclerosis: findings from British Columbia, Canada (1975 –2009)

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Abstract

Background: Recent natural history studies suggest that multiple sclerosis (MS) is a more slowly progressing disease than previously thought. These observations are from studies separated by time, geography and methodological approach.
Objectives: We investigated whether MS disease progression has changed over time in British Columbia, Canada.
Methods: The British Columbia MS database was queried for relapsing-onset MS patients with symptom onset from 1975 to <1995, first assessed within 15 years from onset and with at least two Expanded Disability Status Scale (EDSS) scores. Latest follow-up was to 2009. Patients were grouped by 5-year onset intervals (1975 to <1980, 1980 to <1985, 1985 to <1990, 1990 to <1995). Outcome was defined as time to reach sustained and confirmed EDSS 6 within 15 years of disease duration. Kaplan–Meier analysis was used to compare: the proportion of patients reaching EDSS 6 (primary analysis) and the time to EDSS 6 (secondary analysis) across the time-period groups.
Results: A total of 2236 relapsing-onset MS patients (73.4% female; mean age at onset: 32.3 ± 8.8 years) were included. No significant temporal trend was found in the proportion of patients reaching EDSS 6 within 15 years from onset (28.5%, 26.4%, 27.7%, 22.3% for intervals 1975 to <1980, 1980 to <1985, 1985 to <1990, 1990 to <1995, respectively; $p = 0.09$) or in survival curves for time to reach the outcome ($p = 0.14$).
Conclusions: Rates of disease progression remained relatively stable over two decades of MS onset in British Columbia, Canada. Our results suggest that differences in disease progression findings between natural history studies may be related to factors other than time period.

Keywords
multiple sclerosis, disease progression, disability, time trends

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Introduction

Multiple sclerosis (MS) is the most common cause of neurological disability in young adults.[1] A general trend of a longer time to disability milestones has been reported from more recent natural history studies;[2–4] median survival times from onset to requiring a cane have increased from 15 to 20 years, as reported in earlier publications,[5–7] to 28–32 years in more recent reports.[2–4] This observation of a seemingly slower disease progression, however, is based on findings from heterogeneous studies differing in methodological approach, study population, and time period.[8]

Evaluating temporal trends of disability progression in MS is challenging, but has important implications from epidemiological and clinical perspectives. Environmental factors (which may change over time) are not only implicated in MS etiology, but also in disability progression.[9] Temporal trends in disability progression may also indicate changes in prognostic factors. Moreover, clinical trial design can be

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affected by such changes; an early termination of a phase III clinical trial occurred recently, partly due to the placebo group's unexpected slow progression,[10] which reflected contemporary disease progression reports rather than findings from the older study which was referenced for the trial design.[11] Finally, any temporal changes in natural history have important implications regarding the impact of the MS disease modifying drugs (DMDs), especially where a natural history comparison group is desired.

While several studies have assessed time trends in MS prevalence or incidence[12–14] and mortality,[15,16] long-term trends of MS disability progression have rarely been described. We examined whether disability progression has temporally changed in British Columbian MS patients.

Subjects and methods

Design and setting

We conducted a retrospective study with prospectively collected data from the longitudinal British Columbia Multiple Sclerosis (BCMS) database. Established in 1980, the database is estimated to capture 80% of the British Columbian MS population[17,18] and links the four MS clinics in the province of British Columbia (BC) during the study period (Vancouver, Victoria, Kelowna, and Prince George). The University of British Columbia's Clinical Research Ethics board approved the study.

Study population

We queried the BCMS database for relapsing-onset MS (R-MS) patients with symptom onset from 1975 to the end of 1994, first assessed in a BC MS clinic within 15 years from onset. We focused on this time period and 15-year cut-off to ensure sufficient follow-up time for all patients, to reduce the potential bias from extended referral delay, and to make the temporal groups comparable (see below under 'Outcome and cut-off time'). All patients were diagnosed with clinically or laboratory supported definite MS (Poser criteria).[19] The latest follow-up was to 2009. Those with fewer than two Expanded Disability Status Scale (EDSS) scores or with childhood-onset MS (onset age < 16 years) were excluded. Patients were divided into four time-period groups based on 5-year onset intervals (1975 to <1980, 1980 to <1985, 1985 to <1990, and 1990 to <1995).

Outcome and cut-off time

The outcome was time from onset to sustained and confirmed EDSS 6 within 15 years of disease duration (thus allowing comparable follow-up time between onset groups). An EDSS score of 6 indicates 'intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 m with or without resting'.[20] The criterion for 'sustained' disability progression was met when all subsequent EDSS scores were greater than or equal to the defined outcome (EDSS 6), and was 'confirmed' by a subsequent EDSS score ≥6 at least 150 days later. When the last EDSS score was ≥6, but was not sustained and confirmed, then the patient was right censored at the time when the preceding EDSS score less than 6 was obtained (thereby avoiding an over-estimation of the time to EDSS 6).

The 15-year cut-off was considered both in defining the outcome and as an inclusion criterion for the cohort selection: to allow valid equivalent comparisons between onset time periods (so that no single time period could have a longer follow-up time than another time period); to ensure sufficient opportunity for patients to reach the end point of interest (approximately 21% of our MS patients were expected to reach EDSS 6 within 15 years);[4] and to give patients ample opportunity for their MS to be recognized and to be referred to an MS clinic.

Statistical analyses

Our primary analysis was to compare the rates of progression within 15 years, defined as the proportion of patients reaching sustained and confirmed EDSS 6 within 15 years of symptom onset. The rates were estimated using the Kaplan–Meier method. Patients who had fewer than 15 years of follow-up and did not reach EDSS 6 were included as right censored. Those patients who had already reached EDSS 6 by first clinic visit (left censored) were also included by assuming they had reached EDSS 6 half way between onset and their first clinic assessment. As our comparison focused on the progression rate at year 15, the actual time of reaching EDSS 6 for the left censored patients has no or little effect on the estimated rates. We assessed a linear trend of the progression rates across the four onset periods using a Z statistic: $Z = \sum a_i p_i / \sqrt{\sum a_i s_i^2}$ where $i = 1, \ldots, 4$; p_i is the Kaplan–Meier estimate of the progression rate of the i^{th} group, s_i is the corresponding standard error, and $(a_1, \ldots, a_4) = (-3, -1, 1, 3)$ is a vector of weights constructed by an orthogonal linear contrast that is sensitive for detecting gradual changes.

As a secondary comparison, the Kaplan–Meier survival curves for time to reach EDSS 6 within 15 years disease duration were assessed using the log–rank (Mantel–Cox) test for linear trend with the same weights in the Z statistic. Left-censored patients were included as in the primary analysis. The independent effects of potential risk factors on time to reach sustained disability were examined using a multivariable Cox regression model, with sex, age at symptom onset, onset symptoms, and time period of MS onset included as categorical covariates. The proportional hazard assumption was assessed using log–log plots.

For all comparisons, the potential bias created by imputing the middle value from onset to first clinic assessment for left-censored patients was explored through a 'best and

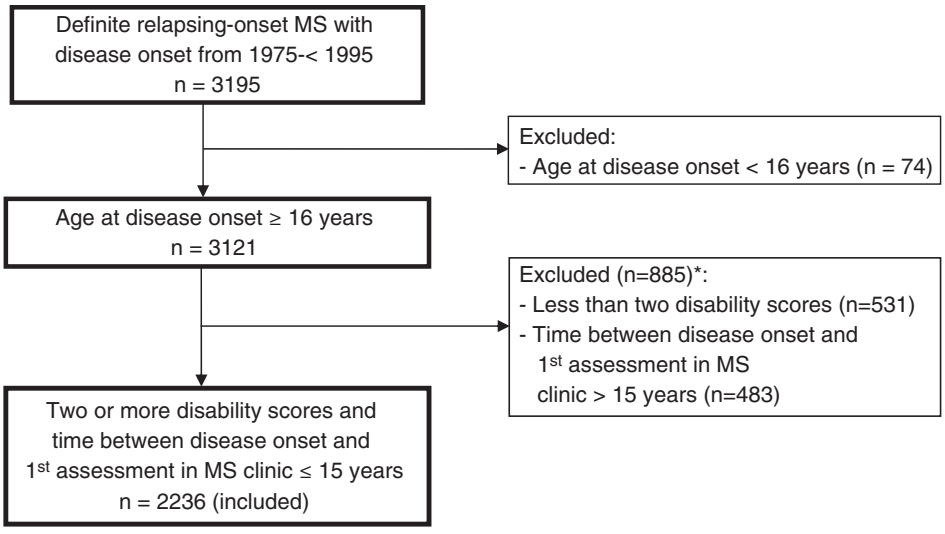


Figure 1. Selection of the study population from the British Columbia Multiple Sclerosis database.
* One hundred and twenty-nine patients had both fewer than two EDSS scores and a referral delay of greater than 15 years.

worst case scenario' sensitivity analysis. 'Best case scenario' assumed left-censored patients reached the outcome on their first clinic assessment; 'worst case scenario' assumed patients did so at MS onset. In a complementary analysis, DMD treatment was included as a categorical covariate ('ever vs. never treated') in the Cox model. Alternative approaches were considered, such as removing patients exposed to a DMD, or removing patients' data once a DMD was started ('right censoring'). However, as DMDs are prescribed to specific and selected patients, excluding such data could create bias.

As demographic changes over time can influence disease progression, we also examined any temporal changes in sex (using logistic regression) and age at MS onset (using one-way analysis of variance with polynomial linear contrasts).

Statistical analyses were performed using the Statistical Package for the Social Sciences version 16.0 (SPSS Inc., Chicago, Illinois, USA).

Results

Study cohort

A total of 2236 patients fulfilled the selection criteria on 1 May 2009 (Figure 1). Demographic characteristics of excluded patients as well as their distribution across the time-period intervals can be viewed on-line; the characteristics of those excluded because of a lack of data (<2 EDSS scores) were similar to those included, suggesting, although not proving that the possibility of bias from exclusion of these patients was slight (supplementary Table e-1, available on-line). The demographics and clinical characteristics of the 2236 included patients are described in Table 1. EDSS scores were assigned on average every 1.09 (±2.04) years. At the first disability assessment, 587 (26.3%) patients had already reached EDSS 3 (moderate disability), 147 (6.6%) EDSS 6 (required a cane), and 11 (0.5%) EDSS 8 (wheelchair bound).

During the study observation period, 23.8% of patients (Table 1) had been exposed to a DMD, cytotoxic immunosuppressant or other clinical trial drugs. The percentage of treated patients was 1.0%, 8.3%, 24.2%, and 43.4% for the earliest to the most recent time interval, respectively. However, the actual proportion of the observation time exposed to drug was only 7.0% overall, and 0.2%, 1.4%, 5.0%, and 16.0% for the earliest to most recent time-period group, respectively.

Temporal trends in the proportion of patients who progressed

Rates of progression to EDSS 6 within 15 years from disease onset fluctuated slightly over time, but no significant linear trend was evident ($p = 0.09$; Figure 2).

Temporal trends in survival curves

Kaplan–Meier survival curves for time to EDSS 6 from onset within 15 years disease duration are displayed in Figure 3. No significant difference in disease progression was observed over time (log–rank test for linear trend, $\chi^2 = 1.90$, $df = 1$, $p = 0.14$).

Sensitivity analysis

A sensitivity analysis based on 'best' and 'worst cases scenarios' for left-censored patients produced similar results for both the primary and the secondary comparison (supplementary Figures e-1 and e-2, available on-line).

Table 1. Demographic and clinical characteristics of the study population ($n = 2236$)

Characteristic	Value
Sex, *n* (%)	
Male	594 (26.6)
Female	1642 (73.4)
Age at MS onset (years)*	32.3 (±8.8); 31.4 [16–73]
n (%)	
<20	135 (6.0)
20 – <30	859 (38.4)
30 – <40	812 (36.3)
40 – <50	346 (15.5)
≥50	84 (3.8)
Year of MS onset, *n* (%)	
1975 – <1980	311 (13.9)
1980 – <1985	509 (22.8)
1985 – <1990	661 (29.6)
1990 – <1995	755 (33.8)
Onset symptoms†, *n* (%)	
Optic neuritis	386 (17.3)
Motor	359 (16.1)
Sensory	1166 (52.1)
Cerebellar, ataxia, or brainstem	349 (15.6)
Other‡	327 (14.6)
Age at first EDSS assessment (years)*	38.2 (±9.3); 37.3 [17.0–79.0]
Disease duration at first EDSS assessment (years)*	5.8 (±4.1); 5.4 [<1–14.9]
Disease duration at last follow-up (years)*	12.2 (±3.2); 13.6 [<1–15.0]
1975 – <1980	12.6 (±2.6)
1980 – <1985	12.0 (±3.4)
1985 – <1990	12.2 (±3.4)
1990 – <1995	12.0 (±3.2)
Ever treated with a DMD during the observation period, *n* (%)§	533 (23.8)

*Results presented as mean (±standard deviation) and median [range].
† Categories of onset symptoms are not mutually exclusive. Onset symptoms were unknown for 52 (2.3%) patients.
‡ Other symptoms included: bladder problems, symptoms of acute transverse myelitis, fatigue, and other non-specified symptoms.
§ Including beta-interferons, glatiramer acetate, natalizumab, cytotoxics and clinical trial drugs; 95% (507/533) of patients were exposed for longer than 3 months and 90% (480/533) for longer than 6 months.
EDSS: Expanded Disability Status Scale, DMD: disease modifying drug.

Multivariable Cox regression model

Findings were largely unchanged after adjustment for other patients characteristics; i.e. there was still no significant overall difference in disease progression across the time-period groups ($p = 0.20$, see Table 2). The most recent onset group (1990 to <1995) trended towards a slower disease progression, however this was marginal, with the 95% CI being close to 1. Of the other factors examined, male sex and an older onset age (≥50 years) were associated with more rapid progression to EDSS 6 (hazard ratio (HR) = 1.46, 95% CI: 1.21–1.77; HR = 2.94, 95% CI: 1.77–4.88, respectively; see Table 2). Onset symptoms were not strong predictors of progression, although the presence of sensory symptoms was associated with a marginally lower hazard of reaching EDSS 6 (HR = 0.75, 95% CI: 0.59–0.96).

Although our study was not designed to study the effectiveness of DMDs, inclusion of DMD treatment in the Cox model resulted in even smaller differences between HRs across the time-period groups (supplementary Table e-2).

Temporal trends in patient demographics

The female:male ratios for the earliest (1975 to <1980) to the most recent (1990 to <1995) interval of disease onset were 2.70:1, 2.51:1, 2.98:1, 2.79:1, respectively. Logistic regression analysis showed no significant trend in sex ratio over time ($\chi^2 = 1.72$, $df = 3$, $p = 0.63$). The mean onset age increased moderately (by approximately 1.5 years every 5 years), from the earliest to the latest onset group: 29.7(± 8.47), 30.9(± 8.55), 32.5(± 8.50), and 34.2(± 8.93) years ($F = 68.34$, $df = 1$, $p < 0.001$, one-way analysis of variance with orthogonal linear contrasts).

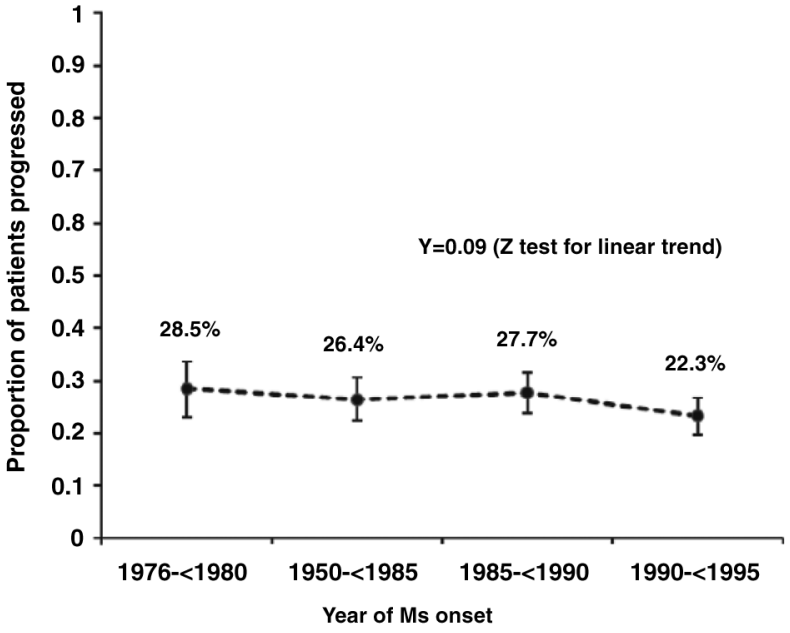
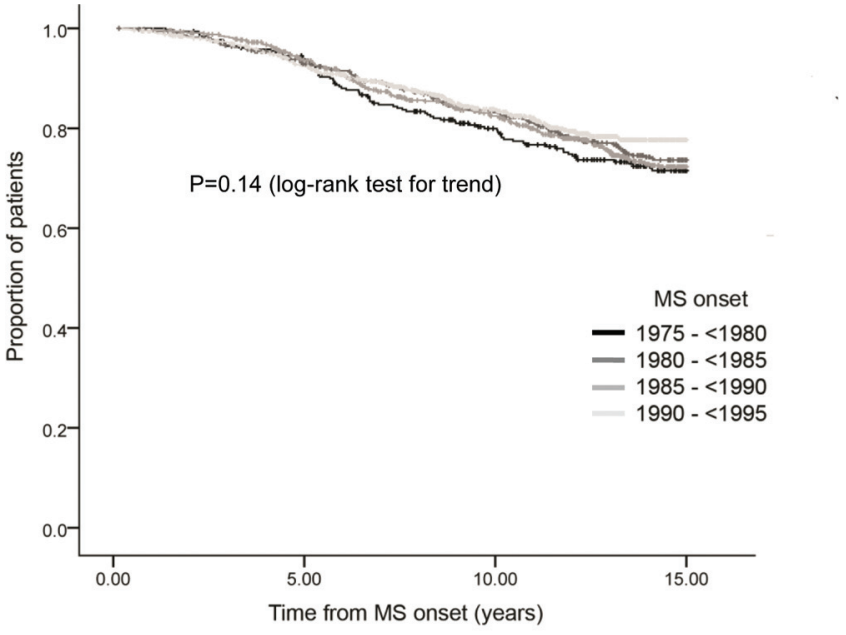


Figure 2. Proportions of patients reaching EDSS 6 within 15 years from disease onset, by 5-year onset intervals. The proportions were derived from Kaplan–Meier survival analysis. *n* = 2236. Error bars represent the 95% CIs.



Patients at risk of progressing to EDSS 6 at selected time points (years)

MS onset	0	5	10	15	Right-censored patients*
1975 - < 1980	311	289	222	119	228 (73.3%)
1980 - < 1985	509	449	355	179	392 (77.0%)
1985 - < 1990	661	574	435	161	509 (77.0%)
1990 - < 1995	755	653	447	87	618 (81.9%)

*Those who did not reach EDSS 6 during the follow-up period.

Figure 3. Survival curves of time to EDSS 6 within 15-years disease duration, by 5-year onset intervals. *n* = 2236.

Table 2. Multivariable Cox regression analysis of potential factors affecting time to reach EDSS 6 within 15 years from disease onset

Characteristic	No. of patients (n = 2235)*	Hazard ratio (95% CI)
Sex		
Female	1642	1
Male	594	1.46 (1.21–1.77)
Age at onset groups (years)		
<20	135	1
20–29	859	0.89 (0.60–1.32)
30–39	812	1.11 (0.75–1.64)
40–49	346	1.35 (0.88–2.07)
≥50	84	2.94 (1.77–4.88)
Initial symptoms		
Optic neuritis		
Absent	1850	1
Present	386	0.95 (0.70–1.28)
Motor		
Absent	1877	1
Present	359	1.22 (0.94–1.58)
Sensory		
Absent	1070	1
Present	1166	0.75 (0.59–0.96)
Cerebellear, ataxia or brainstem		
Absent	1887	1
Present	349	0.95 (0.72–1.25)
Other symptoms		
Absent	1909	1
Present	327	0.87 (0.67–1.14)
Year of disease onset		
1975 – <1980	311	1
1980 – <1985	509	0.87 (0.65–1.15)
1985 – <1990	661	0.95 (0.72–1.24)
1990 – <1995	755	0.77 (0.58–1.01)

*One patient who was censored before the earliest event was dropped by the Cox model. Left-censored patients (n = 147) were assumed to have reached the outcome (EDSS 6) midway between onset and first EDSS assessment and were included in the Cox model.

Discussion

We found no strong evidence to suggest a change in MS disease progression over time. Both the proportion of patients reaching sustained and confirmed EDSS 6 and the time to reach this disability milestone were relatively stable in patients with R-MS over two decades (1975 to <1995). To the best of our knowledge, no study to date has investigated time trends for MS disability progression from a large natural history cohort.

Our findings were largely unchanged when we controlled for potential confounders, including sex and onset age. We did find, however, as most other natural history studies have done, that an older age at onset and male sex were predictive of a more rapid progression (from disease onset).[8]

Our observation of a relatively stable trend in MS disease progression has several clinical and practical implications. Firstly, it indicates that our MS population in BC, Canada has been steady over two decades of MS onset in terms of disease progression. Secondly, it suggests that the differences in findings between natural history studies (at least from 1975 onwards) might be explained by variation in geographical location (e.g. environmental factors, latitude, ethnicity, or medical facilities), methodology (e.g. case ascertainment, retrospective vs. prospective data collection, type of disability scale, and definition of outcome)[8] or perhaps other unidentified factors. Thirdly, it supports the potential utilization of a historical control group as a valid comparison group to ascertain the effectiveness of DMDs on disease progression.

We were unable to examine lifestyle or environmental exposures in our cohort (e.g. smoking, vitamin D deficiency, and the Epstein–Barr virus),[9,21] which may have changed over time; decreases in smoking prevalence and serum levels of vitamin D have been reported.[22,23] It is difficult to predict how these changes might have influenced our findings. The potential for gene–environment interactions is a further complex consideration. Our finding therefore does not provide support either for or against the role of changing environmental factors in disease progression.

Despite the well-recognized shortcomings of the EDSS, it is still the most widely used rating scale for disability in MS[24] and EDSS 6 is an important and clinically relevant disability milestone. For this study, we chose a conservative and appropriate definition of sustained and confirmed EDSS 6 taking into account the possibility of fluctuations in EDSS after apparently confirmed progression.[25] The primary comparison was between the proportions of patients reaching the outcome within 15 years of symptom onset, across the time-period groups. This approach had several advantages, such as ensuring valid comparisons between onset time periods, as well as providing sufficient time to be diagnosed with MS and for patients to be followed up to assess the long-term disease progression. However, some patients with very benign MS and a longer referral delay (i.e. a longer delay between onset of symptoms and referral to a specialist for diagnosis) could have been missed. A previous study from our group indicates that the referral delay for R-MS patients is decreasing,[26] such that over time we may be capturing 'benign' patients earlier, especially in the more recent group. This could potentially account for the slightly lower progression rate in the 1990 to <1995 onset cohort. On the other hand, we could have missed patients who deteriorated very rapidly from onset of their MS in the earliest cohort (onset 1975 to <1980), if they had died or become institutionalized within 5 years or less from MS onset, i.e. before the first MS clinic opened in 1980. However, such severe disease is considered to be extremely rare, and therefore unlikely to have significantly impacted findings.

Patients who had already reached the EDSS outcome by their first clinic visit had little opportunity to impact on the estimated rates in our primary analysis (which focused on the proportion of patients reaching EDSS 6 at 15 years, rather than time to the outcome); this was a strength of the primary analysis. These patients also had little impact on the secondary analysis; regardless of whether the 'best' or 'worst' case scenario was applied, the findings were similar. Some other natural history studies have dealt with this issue by attempting to retrospectively estimate the time of reaching EDSS 6 through chart review or patient interview. This has its own set of limitations, being dependent on the physician's interview and history-taking skills, and patients' cognitive ability. Also, retrospectively teasing out the difference between a patient truly reaching 'sustained and confirmed EDSS 6' versus choosing to use a cane to walk can be challenging, leading to variability and a potential underestimation of 'time to EDSS 6.'

Natural history studies of MS ideally follow cohorts of untreated patients. The increasing use of DMDs for MS makes this progressively more challenging to achieve. The longevity of our database ensured that over 90% of the follow-up time was in DMD naïve patients. We also included DMD use in a multivariable Cox model and this did not change our main finding. Naturally, the impact of DMDs on disease progression is an important question which needs to be determined from well-designed drug effectiveness studies.

Our study has some limitations. About 20% of the BC MS population is not captured in our database, which given the absence of robust prevalence studies in BC since the mid 1980s[17,18] may have changed over time and this issue may affect the generalizability of our results. Furthermore, we could not explore changes in disease progression prior to 1975. Our study focused on those with R-MS (relapsing–remitting and secondary progressive MS); the approximately 10% of patients with primary progressive MS were excluded because this cohort was too small to examine trends over time. Finally, despite all our attempts to make the time-period groups comparable and perform a structured sensitivity analysis, we cannot exclude whether competing and/or combination effects of ascertainment, recruitment, environmental factors, and DMDs over time could have influenced our findings.

We did not observe any large shifts in patient demographics over time, although this was not the primary aim of the study. The sex ratio remained stable over both decades. Other studies (although not all) have reported an increasing female:male ratio in MS patients.[27] Some of these studies, however, refer back to data from the 1950s or earlier.[27] It remains possible that changes in the sex ratio occurred in our cohort prior to 1975. We also observed a marginal increase in onset age (averaging 1.5 years every 5 years). There are mixed findings in the literature; some report decreases (e.g. in a genetically distinct Sardinian cohort),[28] while others find no change over time.[29] Our observed increase in onset age would be consistent with a general increase in survival in the general population over time.[30]

In summary, while we cannot rule out the possibility that changes in disease progression occurred before 1975, our study shows that rates of disease progression remained relatively stable over two decades of MS onset in BC, Canada. It would be of interest to know if this has occurred in other MS populations. The relationship between MS progression and various geographical, environmental and methodological factors should be further evaluated. Accurate assessment of temporal trends in MS progression from geographically diverse cohorts would contribute to a better understanding of the natural history of MS and might have important implications for the role of environmental factors in the progression of MS.

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Conflict of interest statement

A.S. has received travel grants to present and attend conferences from the endMS Research and Training Network (2010), and the European Committee for Treatment and Research in Multiple Sclerosis (2010). E.K. has had travel and accommodation costs covered to present at and attend conferences from the endMS Research and Training Network (2008), the International Society for Pharmacoepidemiology (2010) and Bayer Schering Pharma (2010). P.R. serves on scientific advisory boards for Novartis and Merck Serono; has received speaker honoraria from Sanofi–Aventis, Bayer Schering Pharma, Biogen Idec, Merck Serono, Novartis, and Teva Pharmaceutical Industries Ltd. H.T. has received speaker honoraria and/or travel expenses to speak at conferences from: the Consortium of MS Centres, US National MS Society, Swiss Multiple Sclerosis Society, the University of British Columbia Multiple Sclerosis Research Program, Bayer Pharmaceuticals (2010, invited speaker, honoraria declined), Teva Pharmaceuticals (2011, invited speaker). Unless otherwise stated, all speaker honoraria are either donated to an MS charity or to an unrestricted grant for use by her research group.

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