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Clinical course of multiple sclerosis: A nationwide cohort study

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Abstract

Background: The course of multiple sclerosis (MS) has been studied in several cohorts; however, results have varied significantly.

Objective: To describe the clinical course of MS in a nationwide cohort of patients.

Method: Data from the Swedish MS register (SMSreg) were used to estimate the median time to the sustained Expanded Disability Status Scale (EDSS) scores 3.0, 4.0 and 6.0, onset of secondary progressive multiple sclerosis (SPMS) and death using Kaplan–Meier method. A possible effect of first-line treatments on age at EDSS 6.0 and SPMS was estimated.

Results: In all, 12,703 patients were included. Median ages at EDSS scores 3.0, 4.0 and 6.0 were 55.4 (95% confidence interval (CI): 54.8−55.8), 60.7 (95% CI: 60.1−61.2) and 64.3 (95% CI: 63.6−64.7), respectively. Median age at SPMS was 57.4 (95% CI: 56.9−57.9). The median age at the time of death was 80.5 (95% CI: 79.9−81.1). Males and progressive-onset patients showed higher risks of disability worsening. On average, treated patients gained 1.6 years (95% CI: 0.2−3) to EDSS 6.0 as a result of treatment.

Conclusion: Ages at disability milestones in this population-based cohort were higher than previously described in clinic- and regional-based samples. Nevertheless, MS patients die at younger age and live at an average almost 20 years with moderate and 30 years with severe disability.

Keywords: Multiple sclerosis, disease course, disability progression

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Introduction

The course and progression of multiple sclerosis (MS) vary strikingly between patients, and the future of an individual patient is difficult to predict.[1] The clinical course of MS has often been studied by estimating the time from birth and onset of the disease to the Expanded Disability Status Scale (EDSS) milestone scores 3.0, 4.0, 6.0 and 8.0 or conversion to secondary progressive multiple sclerosis (SPMS). Not surprisingly, and despite seemingly simple analytical prerequisites, results have varied between the best known 'natural course cohorts' such as the ones from Lyon in France, London Ontario, British Columbia in Canada and Gothenburg in Sweden. For example, the reported median time to EDSS score 6.0 from onset of MS has varied up to 15 years between studies.[2]

Since the mid-1990s, disease-modifying treatments (DMTs) have been available for the treatment of relapsing MS. Availability of DMTs may have impacted characteristics of today's MS populations through treatment effects and more importantly patients' behaviour as a result of treatment availability (e.g. over presentation of severe patients). At present, it is not entirely clear whether the characteristics and clinical course of today's MS patients presenting at MS clinics have changed due to changes in the management of the disease. Therefore, analysis of a contemporary population-based cohort can offer valuable knowledge.

The aim of this study was to use a population-based cohort of adequate coverage and follow-up to estimate the time to major MS disability and clinical milestones and all-cause mortality. It is applicable to today's MS patients' situation when a significant number of bout-onset patients have received DMTs.

Materials and methods

Patient population

Incidence and prevalence of MS in Sweden are estimated to be around 10.2 and 189 per 100,000, respectively, which is among the highest in the world.[3,4] In this work, we analysed data from patients registered in the Swedish MS Register (SMSreg).[5] SMSreg is a national quality register containing clinical and demographic data on about 17,600 MS patients (at the time of this study). The SMSreg is designed to assure quality health care for patients with MS and is used in almost all 64 Swedish neurology clinics. The register covers around 80% of all prevalent cases of MS in Sweden.[6]

Study design

We conducted a cohort analyses measuring the time from date of birth, disease onset and diagnosis to the date of several major disability and clinical course milestones and mortality.

Outcome measures

EDSS score milestones 3.0, 4.0 and 6.0. The EDSS score is the most-used method of quantifying disability in MS. The scale ranges from 0 to 10 in 0.5 unit increments. Scoring is performed by a neurologist and is based on the examination of eight functional systems.[7] Age at and time from onset and diagnosis of MS to sustained EDSS score milestones 3.0 (moderate disability but no impairment of walking), 4.0 (significant disability but able to walk without aid or rest for 500 m) and 6.0 (requires unilateral assistance to walk about 100 m with or without resting) were our milestones of interest with regard to EDSS score. An EDSS score was defined as sustained if there has been at least one more recorded EDSS score and no proceeding score was more than 0.5 score lower.

Onset of progressive MS. Year of transition to SPMS is estimated and recorded in SMSreg by a neurologist. Time from birth and disease onset to onset of SPMS (mid-year of registered year in SMSreg) were estimated using the Kaplan–Meier method.

All-cause mortality. Living status and date of death (if deceased) are yearly updated in SMSreg using statistics from the Swedish death register with total population coverage. We calculated the Kaplan–Meier estimates of age at death and years from disease onset to death. We also calculated age and sex standardised mortality ratios (SMRs) according to the 2010 mortality rates of the Swedish general population.

This study was approved by the Swedish regional ethical review board in Stockholm (EPN).

Statistical analysis

Data were summarised using descriptive statistics. The Kaplan–Meier method was used to estimate the median time from date of birth, disease onset and diagnosis to the outcome of interest. Log-rank tests and flexible parametric models[8] were used to compare the median times and hazards between sexes and patient groups based on MS phenotype at onset (bout onset vs progressive onset). We also investigated the geographical differences in the risk of reaching disability milestones between north (Norrland), middle (Svealand) and south of Sweden (Götaland).

To examine the impact of missing outcome dates on the estimations, we performed the sensitivity analysis used by Tremlett and colleagues.[9] Shortly, when time of EDSS score 6.0 was unknown, best-, worst- and middle-case scenarios assumed that patients have reached EDSS 6.0 at the time of first clinic visit, disease onset and time between disease onset and first clinic visit, respectively.

We estimated the average treatment effect in treated (ATET) on mean age at EDSS score 6.0 and conversion to SPMS using inverse-probability weighting with regression adjustment.[10,11] Outcome adjustment was made for sex, date of MS onset and date of birth. We model assignment to the treatment as a function of first recorded EDSS score, age at the first EDSS score, onset age and date of onset. Patients were categorised into two treatment groups. Untreated was defined as having been exposed to a first-line DMT (interferon beta 1a, interferon beta 1b and glatiramer acetate) for less than 6 months and treated was defined as at least 6 months of exposure to a first-line DMT. Neither of the groups had exposure to a second-line DMT. ATET gave us the estimated average years gained by the means of treatment to EDSS score 6.0 and conversion to SPMS. Since ATET is obtained from a treated population, the conditional independence and the sufficient overlap assumptions are less restrictive.

Except in the estimation of time to death, we only included patients with at least three neurology clinic visits to ensure sufficient specialist exposure and robust estimations. A sub-analysis of time to EDSS score 6.0 with no restriction was performed to ensure that no selection bias has been introduced to the main analyses by only including patients with minimum three clinic visits. Statistical analyses were performed using Stata 14.2.[12]

Results

By July 2015, 17,554 individuals with MS and available data on sex and date of birth were registered in SMSreg. In all, 12,703 patients had at least three recorded EDSS scores and were included in the analyses of time to EDSS score milestones and onset of SPMS. In this group, 71% were females. Mean age at the last clinic visit was 50 years (standard deviation (SD): 13) and mean age at the onset of MS was 33 (SD: 11). Duration of exposure to DMTs was unknown in 14.8% (1885) of patients and 13.8% (1751) had never been exposed to a DMT. Among those exposed, 84% (7692) had received at least one first-line DMT (interferon beta 1a, interferon beta 1b and glatiramer acetate) and 54.4% (4931) had been exposed to a second-line DMT (natalizumab, fingolimod and rituximab) (Table 1).

Table 1. Clinical and demographic characteristics of the 12,703 included patients.

Age at last clinic visit (mean (SD))	50 (13)
Age at onset (mean (SD))	33 (11)
Disease duration, years (mean (SD))	17 (11)
Active follow-up time,[a] years (median (IQR))	7 (4–10)
Female (% (*n*))	71 (9014)
Clinical phenotype at last clinic visit (%)	
Relapsing remitting	56.5 (7182)
Primary progressive	7.6 (971)
Secondary progressive	28.9 (3671)
Progressive relapsing	1.2 (159)
Unknown	5.7 (720)
Last recorded EDSS score (median (IQR))	3 (1.5–6)
Treatment	
Unknown DMT status (% (*n*))	14.8 (1885)
Known DMT status (% (*n*))	85.2 (10,817)
Never exposed to a DMT (% (*n*))	13.7 (1751)
Exposed to a first-line DMT (% (*n*))	84.8 (7692)
Duration on first-line DMTs, year (median (IQR))	4.5 (2–8)
Exposed to a second-line DMT (% (*n*))	54.4 (4931)
Duration on second-line DMTs, year (median (IQR))	2 (1–4)

EDSS: Expanded Disability Status Scale; IQR: interquartile range; SD: standard deviation; DMT: disease-modifying treatment.
[a]Active follow-up time represents time between first and last recorded EDSS score. First-line DMTs included interferon beta 1a, interferon beta 1b and glatiramer acetate. Second-line DMTs included natalizumab, fingolimod and rituximab.

Time to EDSS score milestones

Median age at sustained EDSS score 3.0 was 55.4 (54.8–55.8) which was reached in 19.8 (19.1–20.6) years after the disease onset and 14.9 (14.4–15.6) years after MS diagnosis. Median ages at sustained EDSS scores 4.0 and 6.0 were 60.7 (60.1–61.2) and 64.3 (63.6–64.7), respectively (Figure 1). Detailed Kaplan–Meier estimates of time to the EDSS score milestones are shown in Table 2. The three scenarios in the estimation of time to EDSS score 6.0 and inclusion of all patients with no minimum number of clinic visits yielded similar results comparable with the main analysis indicating minimum influence of missing outcome dates on the estimations and no selection bias.

Total population of Sweden was 9,851,017 in 2015. The majority of Swedes resided in the south in the province of Götaland (n = 4,703,283) followed by Svealand (Middle) (n = 3,981,535) and Norrland (North) (n = 1,166,199). The north-south gradient in population size was also seen in SMSreg with majority of the patient last resided in south of Sweden (Norrland = 1473, Svealand = 5339, Götaland = 5825 and 66 missing). In comparison with patients residing in Götaland, those living in Norrland and Svealand showed significantly higher risk of reaching EDSS score 3.0. Risk of EDSS score 4.0 was only elevated in patients living in Svealand and almost no difference in the risk of sustained EDSS score 6.0 was observed between geographical regions except an increased risk for patients in Svealand from the date of diagnosis (hazard ratio (HR): 1.11 (95% CI: 1.01–1.23) (Table 3).

Time to transition to SPMS

Of the 8526 bout-onset MS patients with full data (date of onset, latest phenotype, ⩾3 clinic visits and date of SPMS) 2732 (32%) had converted to SPMS. Median age at the transition to SPMS was 57.4 (95% CI: 56.9–57.9) years. From the disease onset and date of MS diagnosis, median times to the onset of SPMS were 23 (95% CI: 22.8–23.9) (Figure 1) and 19.9 (95% CI: 18.9–21.0) years, respectively. The median age at the onset of primary progressive multiple sclerosis (PPMS) was 43.6 (95% CI: 42.8–44.9) which was significantly younger than 47.5 (95% CI: 47.0–48.0) in SPMS patients (p < 0.001) (non-Kaplan–Meier estimate without consideration of those still relapsing-remitting multiple sclerosis (RRMS)). Men had 24% (95% CI: 14–35) higher risk of conversion from birth. From the disease onset, risk of conversion in men was 30% (95% CI: 20–41) higher than women. A significant geographical difference was observed in the risk of conversion to SPMS. Patients residing in north (Norrland) and centre of Sweden (Svealand) were at significantly higher risk of conversion to

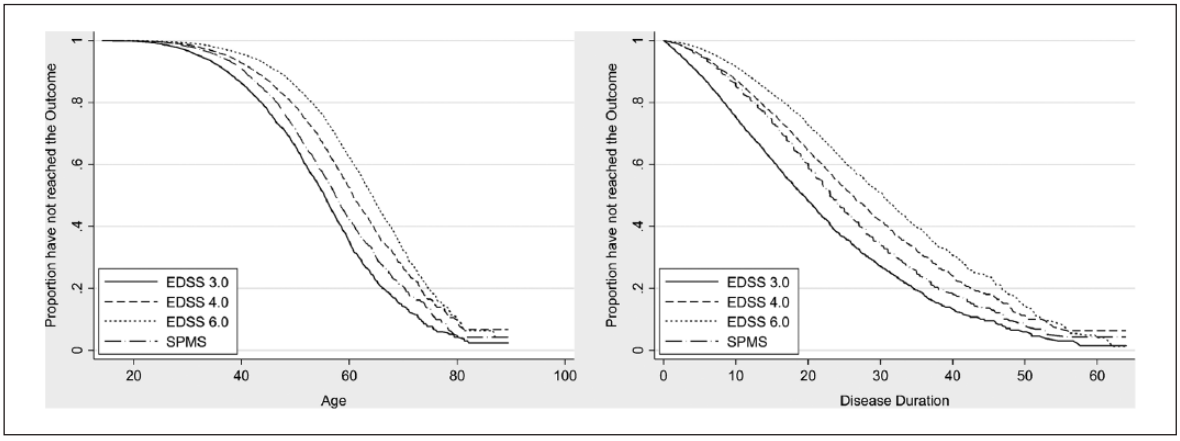

Figure 1. Kaplan–Meier curves of time from birth (left) and multiple sclerosis onset (right) to EDSS score milestones 3.0, 4.0, 6.0 and onset of secondary progressive multiple sclerosis.

SPMS compared to the patients living in the south (Götaland) (Table 3).

All-cause mortality

From the 15,952 patients with known date of MS onset at December 2015, 1335 had died. Median age at the time of death was 80.5 years (95% CI: 79.9–81.1). From the disease onset, the median time to death was 51.9 (95% CI: 50.5–53.6) years. Men were at 45% (95% CI: 29–63) higher risk of all-cause mortality compared with women. No increased risk was observed in PPMS patients (HR: 1.12, 95% CI: 0.98–1.29). Compared to the age- and sex-matched individuals in the Swedish general population, MS patients showed 2.02 times (95% CI: 1.91–2.13) increased risk of death. SMR was 2.35 (95% CI: 2.19–2.51) in females and 2.11 (95% CI: 1.93–2.30) in males. Table 4 summarises the times from birth and MS onset to death.

Treatment effect

We identified 3761 bout-onset patients matching the treatment criteria and available data. In total, 924 patients were categorised as untreated and 2837 patients as treated. Median time on treatment was 3.5 years (interquartile range: 6–9.5). The average age at sustained EDSS score 6.0 was 60 (95% CI: 59–61) in the treated group. The average age would have been 58.6 (95% CI: 57–59) if no patient had been treated. This gave us ATET of 1.6 years (95% CI: 0.2–3, $p = 0.024$) as result of exposure to first-line treatments. The ATET was not significant for the age at SPMS conversion (coefficient: −0.14, 95% CI: −1.7 to 1.43).

Discussion

In this nationwide cohort study, we reported one of the longest times to clinical course milestones and the highest life expectancy in patients with MS. In all, 50% of MS patients in Sweden reached EDSS scores 3.0, 4.0, 6.0 and SPMS 20, 26, 30 and 23 years after disease onset and at median ages of 55, 60, 64 and 57, respectively. We also report a gender difference in disability progression in MS with men at higher risk of reaching all disability milestones.

Age at and time from disease onset to EDSS score milestones in our study were substantially higher than those clinic-based observations from London, Ontario (Canada),[13] Lyon,[14] Rennes[15] and Lorraine[16] (France). However, our estimation of time from onset of MS to EDSS score 6.0 (30.4 years) is similar to the estimations from population-based cohorts in British Columbia (Canada) (27.9 years)[9] and Olmsted County (United States) (30 years (obtained from the Kaplan–Meier curves)).[17] Median time from onset of MS to onset of SPMS was 23 years in our population. This estimation is longer than 19.1 years in Lyon,[18] 20 years in Lorraine,[16] 11–15 years in London, Ontario, 14 years in Gothenburg (Sweden),[19] 19 years in Hordaland County[20] (Norway) and 21.4 years in British Columbia.[21] We also reported older age at conversion to SPMS than the estimation shown in British Columbia (57 vs 53.7).[21] Overall, transition to SPMS occurred between EDSS scores 3.0 and 4.0.

Sex and initial MS phenotype (relapsing vs progressive onset) showed significant effects on the risk of reaching almost all clinical course milestones and mortality except for age at EDSS score 3.0 which was similar between two initial phenotypes. We found

Table 2. Kaplan–Meier estimates of time from birth, disease onset and MS diagnosis to EDSS score milestones 3.0, 4.0 and 6.0.

	Median time from birth (years)		Median time from disease onset (years)		Median time from diagnosis (years)	
	Total number (% reached)	Median age (95% CI)	Total number (% reached)	Time (95% CI)	Total number (% reached)	Time (95% CI)
EDSS score 3.0						
All	7864 (40.1%)	55.4 (54.8−55.8)	7579 (40.3%)	19.8 (19.1−20.6)	6854 (37.5%)	14.9 (14.4−15.6)
Sex						
Female	5712 (39%)	55.9 (55.4−56.5)	5496 (39.2%)	20.8 (20.1−21.5)	5001 (35%)	15.5 (14.9−16.2)
Male	2152 (43.1%)	53.9 (52.9−54.8)	2083 (43.2%)	17.9 (16.8−18.4)	1853 (39.3%)	13 (12.1−14.0)
Onset phenotype						
Bout onset	7270 (38.3%)	55.3 (54.8−55.8)	7032 (38.4%)	20.8 (20.1−21.4)	6463 (36.2%)	15.5 (14.9−16.1)
Progressive onset	308 (85%)	54.8 (53.4−55.8)	295 (85.7%)	7.8 (6.6−8.6)	210 (79%)	3.9 (3.1−5.0)
EDSS score 4.0						
All	8453 (28%)	60.7 (60.1−61.2)	8156 (28.1%)	26.2 (25.3−26.7)	7548 (26.7%)	19.9 (19.9−21.0)
Sex						
Female	6108 (26.5%)	61.7 (60.7−62.4)	5883 (26.7%)	27.9 (26.4−28.7)	5449 (25.5%)	21.2 (20.0−22.6)
Male	2345 (31.7%)	58.3 (57.5−59.2)	2273 (32%)	22.6 (21.5−24.3)	2099 (31.1%)	17.1 (15.7−18.3)
Onset phenotype						
Bout onset	7760 (26.0%)	60.9 (60.3−61.7)	7513 (26.1%)	27.4 (26.3−28.3)	7023 (24.8%)	20.9 (19.8−22)
Progressive onset	387 (67.7%)	57.9 (56.4−59.7)	373 (67.8%)	11.7 (10.4−12.5)	322 (64.6%)	5.5 (4.6−6.3)
EDSS score 6.0						
All	9800 (25.1%)	64.3 (63.6−64.7)	9457 (25.2%)	30.4 (29.4−31.1)	8672 (23.4%)	23.1 (22.2−24.1)
Sex						
Female	7038 (23.6%)	64.8 (64.2−65.5)	6781 (23.8%)	31.7 (30.5−32.6)	6212 (21.9%)	24.7 (23.2−25.8)
Male	2762 (28.8%)	62.8 (61.3−63.6)	2676 (28.9%)	26.7 (25.3−28.3)	2460 (27.1%)	20.3 (19.0−21.8)
Onset phenotype						
Bout onset	8828 (22.7%)	65.0 (64.3−65.7)	8547 (22.4%)	31.8 (30.7−32.6)	7925 (20.9%)	24.6 (23.4−25.8)
Progressive onset	632 (64.4%)	60.3 (59.2−61.3)	612 (65%)	13.9 (12.6−14.8)	518 (60.8%)	8.6 (7.7−9.3)
Scenarios[a]						
Worst	10,393 (29.3%)	62.9 (62.3−63.5)	10,050 (29.7%)	28.7 (27.8−29.6)	8706 (23.7%)	23.1 (22.1−24.0)
Middle case	10,393 (29.4%)	62.6 (62.1−63.1)	10,050 (29.7%)	27.7 (26.6−28.4)	9052 (26.6%)	21.4 (20.7−22.3)
Best	10,415 (29.5%)	62.5 (62.1−63.0)	10,050 (29.7%)	27.9 (27.3−28.7)	9127 (27.2%)	21.2 (20.5−21.9)
Any number of clinic visits[b]	13,368 (23.1%)	65.6 (65.1−66.1)	12,703 (23.3%)	31.3 (30.5−32.2)	11,257 (21.8%)	23.3 (22.4−24.1)

MS: multiple sclerosis; EDSS: Expanded Disability Scale Status; CI: confidence interval.
[a]Scenarios simulated the situation where those with first recorded EDSS more than 6.0 were assumed to have reached the EDSS score 6.0 at the time of disease onset (worst), middle point between onset and first clinic visit (middle case) and at the time of EDSS record (best).
[b]No restriction in the number of clinic visits.

unfavourable clinical course in men which was reported previously by Confavreux and Vukusic.[14] and was regardless of follow-up scale (age or disease duration). However, male MS patients died at lower rates than females when compared to the general population. We also observed a significant regional difference in the risk of disability worsening. Patients residing in the south of Sweden did generally better (i.e. 2 years longer time to EDSS score 3.0) compared to those living in the centre or north. However, the difference weakened by increase in the follow-up time. Such differences in the risk of short-term outcomes (EDSS 3.0 and conversion to SPMS) can possibly be the result of regional differences in patients' management and access to care (e.g. distance to MS specialist clinics, etc.) in different regions of Sweden in the early stages of MS, but can theoretically depend on environmental factors or even in differences in the use of the EDSS Scale.

While our overall estimation of time from MS onset to EDSS score 6.0 (30.4 (95% CI: 29.4–31.1) years)

Table 3. Hazard of reaching EDSS score milestones 3.0, 4.0 and 6.0 and conversion to SPMS from birth, disease onset and MS diagnosis.

	Hazard ratio from birth (95% CI)	Hazard ratio from disease onset (95% CI)	Hazard ratio from diagnosis (95% CI)
EDSS score 3.0			
Sex			
Female	–	–	–
Male	1.20 (1.11−1.30)	1.22 (1.12−1.32)	1.18 (1.08−1.29)
Onset phenotype			
Bout onset	–	–	–
Progressive onset	1.12 (0.98−1.27)	3.33 (2.92−3.79)	3.62 (3.09−4.26)
Province			
Götaland	–	–	–
Svealand	1.16 (1.07−1.25)	1.20 (1.11−1.30)	1.25 (1.15−1.36)
Norrland	1.31 (1.17−1.46)	1.22 (1.08−1.37)	1.21 (1.07−1.38)
EDSS score 4.0			
Sex			
Female	–	–	–
Male	1.27 (1.16−1.39)	1.27 (1.15−1.39)	1.27 (1.16−1.40)
Onset phenotype			
Bout onset	–	–	–
Progressive onset	1.28 (1.12−1.46)	3.86 (3.37−4.41)	4.69 (4.05−5.43)
Province			
Götaland	–	–	–
Svealand	1.19 (1.09−1.30)	1.23 (1.13−1.35)	1.31 (1.19−1.44)
Norrland	1.11 (0.97−1.28)	1.03 (0.89−1.18)	1.12 (0.97−1.30)
EDSS score 6.0			
Sex			
Female	–	–	–
Male	1.22 (1.11−1.33)	1.21 (1.11−1.32)	1.25 (1.14−1.38)
Onset phenotype			
Bout onset	–	–	–
Progressive onset	1.46 (1.31−1.63)	4.27 (3.82−4.77)	4.66 (4.12−5.27)
Province			
Götaland	–	–	–
Svealand	1.05 (0.96−1.14)	1.07 (0.98−1.16)	1.11 (1.01−1.23)
Norrland	0.97 (0.85−1.11)	0.92 (0.80−1.05)	0.97 (0.84−1.12)
Conversion to secondary progressive			
Sex			
Female	–	–	–
Male	1.24 (1.14−1.35)	1.30 (1.20−1.41)	1.34 (1.21−1.47)
Province			
Götaland	–	–	–
Svealand	1.26 (1.16−1.37)	1.30 (1.19−1.41)	1.40 (1.28−1.54)
Norrland	1.29 (1.14−1.47)	1.27 (1.12−1.44)	1.23 (1.06−1.43)

EDSS: Expanded Disability Status Scale; MS: multiple sclerosis; SPMS: secondary progressive multiple sclerosis; CI: confidence interval.
Hazard ratio from one multivariate flexible parametric model.

was longer than 27.9 years reported by Tremlett and colleagues,[9] the categorised estimations based on onset phenotypes were strikingly similar (13.9 (95% CI: 12.6–14.8) vs 13.3 (95% CI: 11–15.5) in PPMS and 31.7 (95% CI: 30.5–32.6) vs 30.3 (95% CI: 28.6–32) in bout-onset patients). Therefore, the difference

Table 4. Hazard ratios and Kaplan–Meier estimates of median time to death from birth and disease onset.

	Total number (number died)	Median age (95% CI), years	Hazard ratio (95% CI)	Median time from disease onset (95% CI), years	Hazard ratio (95% CI)
All	15,952 (1335)	80.5 (79.9−81.1)		51.9 (50.5−53.6)	
Sex					
Female	11,214 (842)	81.4 (80.5−82.1)	–	53.6 (51.5−55.5)	–
Male	4738 (493)	78.9 (77.7−79.9)	1.45 (1.29−1.63)	48.3 (46.6−50.4)	1.44 (1.28−1.62)
Initial phenotype					
Bout onset	13,667 (975)	80.5 (79.9−81.4)	–	53.0 (51.5−55.3)	–
Progressive onset	1386 (265)	79.9 (77.6−81.1)	1.12 (0.98−1.29)	37.9 (35.8−44.0)	2.96 (2.58−3.41)

CI: confidence interval.

in the overall estimations between the two populations can be attributed to difference in the percentage of PPMS patients (8% in Sweden vs 12% in Canada). The discrepancy seen between our estimations and the other previous reports can be explained by differences in the population characteristics (percentage of progressive patients) and the studies' methodological approaches such as inclusion and exclusion criteria, definition of sustained EDSS score, sampling strategies and more importantly the nature of the cohorts (population-based vs clinic-based).

The main strength of our study is the use of a nationwide cohort. In comparison to regional and clinic-based studies, our data are more likely to capture MS patients with a wider disability range. However, it is still possible that some very severe patients have died or have not been captured by the register. This may result in overestimation of time to disability milestones in our historic cohorts (as more benign patients were likely to be alive at the time of data collection) but is unlikely to influence the overall estimations. Majority of MS patients in Sweden are of White European descent; hence, our results are more generalisable to this group of patients.

Here, we showed one of the highest survivals reported in MS; however, this was still significantly shorter than the survival of Swedish general population (SMR: 2.02). Our reported overall and sex-specific SMRs are in line with the previously reported SMRs from other countries.[22]

Although the majority of the patients in our sample had been exposed to at least a first-line DMT, the stratified estimations of time from disease onset to EDSS score 6.0 in our sample was almost comparable with the estimation obtained from the mainly untreated patient population of British Columbia (31.7 vs 30.3 in bout-onset patients).[9] On average, our treated patients gained extra 1.6 years to EDSS score 6.0 due to exposure to first-line DMTs. This might explain the 1.4 years difference between the two populations. However, time to conversion to SPMS was not influenced by exposure to treatments and the average time gained to EDSS score 6.0 was only marginally significant. Overall, the evaluation of long-term effectiveness of DMTs merits further investigations (which is out of the scope of this paper) and caution must be taken when drug effectiveness is being explored in lack of randomisation.

Our research highlights the importance of population-based research for more consistent and unbiased description of MS clinical course. Our work also highlights the significant social and economic burden of MS to the society, even two decades into the DMT era. It is clear that the DMTs were unsatisfactory in preventing eventual disability, due to either lack of effectiveness or unfavourable timing.

Overall, age at major disability milestones in MS in this nationwide cohort was significantly older than previous clinical- and regional-based reports. Societal and economic consequences of MS is immense as MS patients not only die at younger age but also live almost 20 years with moderate and 30 years with severe impairment and disability.

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Author contribution

A.M. designed the study, analysed and interpreted data, and wrote and revised the manuscript. O.B. interpreted data and revised the manuscript. J.H. designed the study, interpreted data and revised the manuscript.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship and/or publication of this article: A.M. and O.B. report no conflicts of interest. J.H. received honoraria for serving on advisory boards for Biogen, Sanofi-Genzyme and Novartis and speaker's fees from Biogen, Merck-Serono, Bayer-Schering, Teva and Sanofi-Genzyme. He has served as PI for projects sponsored by, or received unrestricted research support from, Biogen, Merck-Serono, TEVA, Novartis, Sanofi-Genzyme and Bayer-Schering.

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