Original article

Effectiveness of first generation disease-modifying therapy to prevent conversion to secondary progressive multiple sclerosis

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A R T I C L E   I N F O

A B S T R A C T

Background: The use of disease-modifying therapies (DMTs) in multiple sclerosis (MS) has been associated with reduced relapse rates and accumulation of disability. However, studies examining impact of DMT on risk of transition to secondary progressive MS (SPMS) leveraging population-based nationwide data are still rare. Here, we determine the population incidence of conversion to SPMS using two consecutive nation-wide cohorts, one immediately before and one after the introduction of DMT in Sweden.

Methods: We included two consecutive population cohorts of relapsing-remitting MS (RRMS) from the Swedish national MS register for the periods 1975–1994 ($n = 2161$), before DMT availability, and 1995–2011 ($n = 3510$), in which DMTs, mainly first generation DMT (injectables), became available and eventually were used by 70% of patients. We explored the risk of transition to SPMS as a calendar year function encompassing the two cohorts. In addition, we determined the incidence of transition to SPMS through age strata below and above 50 years in untreated and treated patient subgroups.

Results: The risk of conversion to SPMS (adjusted for current age, current time since onset, calendar year and sex) was significantly lower in the second compared with the first population cohort (hazard ratio 0.58; CI 0.48, 0.70). The risk of SPMS conversion per calendar year decreased by 2.6% annually ($p < 0.001$) after 1995. The risk of SPMS conversion increased with age until age 50. Thereafter, it was unchanged or decreased among those with early MS onset age (<35 years), but continued to increase with onset at higher age, with similar trends in treated and untreated subgroups.

Conclusion: The incidence of SPMS conversion significantly decreased at the population level after introduction of first generation DMTs by 1995. DMT efficiency was confirmed by a downward turn of the annual trajectory of the risk of SPMS conversion after 1995. An onset age determined pattern of variable SPMS incidence in higher age appeared in both treated and untreated strata. While first generation DMT delayed conversion to SPMS, their long-term effect was only moderate.

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1. Introduction

Several centres have observed a milder long-term course of multiple sclerosis (MS) over the last decades (Kister et al., 2012), (Beiki et al., 2019). Although the cause of this change is complex, including improved diagnostic techniques, modified diagnostic criteria, and changed demographics, the disease-modifying therapies (DMTs), introduced in Sweden 1995 (Sorensen et al., 2020), are considered to have impact on MS course. However, the evidence based on different criteria of long-term outcomes associated with first generation DMT (injectables) is inconsistent (Shirani et al., 2012). Conversion to SPMS is a key determinant of long-term disease evolution and prognosis (Scalfari et al., 2013). Most observational follow-up studies with at least 5 years of follow-up showed delay of conversion to SPMS after treatment with first generation DMT (Bergamaschi et al., 2016; Trojano et al., 2007; Tedeholm et al., 2007; Drulovic et al., 2013; Signori et al., 2016; Zhang et al., 2015). Investigators were increasingly aware of several inherent biases in observational studies, the most detrimental of which probably is indication bias, which means that patients with more severe disease move into the treated subgroup, confounding indicators of effectiveness (Sormani and Bruzzi, 2015)' (Kalincik and Butzkueven, 2016). Methods used to manage indication bias in observational studies include regression analyses with validated predictors (Tedeholm et al., 2013), or propensity score analysis (Trojano et al., 2007)' (He et al., 2020). If predictors are not available, an alternative design may be based on two successive population cohorts, one right before the introduction of DMT became available and one immediately following with DMT in general use (Veugelers et al., 2009). The SPMS incidence in the defined population is a sum of treated and untreated patients' SPMS incidences, so the total population-based incidence is expected to evade indication bias, although it may be affected by other bias. We here compare the risk of transition to SPMS in two consecutive population cohorts, including the age segment after 50 years which was generally excluded from trials (Vollmer et al., 2021), one immediately before DMT became available in Sweden, and one right after the introduction of first generation DMT.

2. Materials and methods

2.1. Study design

We herein (A) compare the incidence of transition to SPMS in two consecutive population materials, an untreated cohort from 1975 to 1994 and a partially DMT treated cohort from 1995 to 2011. The first cohort included only DMT untreated patients, and the second included all DMT treated and untreated patients with onset in this and previous cohorts. (B) Covering the same periods, we study the calendar year incidence of transition to SPMS annually from 1950 to 2011. Furthermore, we (C) study the incidence of transition to SPMS in DMT treated and untreated subgroups defined by onset 1950–1994 or 1995–2011 (incidence cohorts) and with individual age below or above 50 and (D) compare subgroups only defined by DMT treatment and adjusted for current age, time since onset and current calendar year.

2.2. Patient materials

Before the DMT era, the therapeutic tradition in Sweden was conservative. Except for sporadic use of azathioprine and monthly pulsed infusions of methylprednisolone, MS patients received no long-term immunosuppressive treatment prior to 1995, the year we terminated the DMT untreated cohort. For our partially treated cohort we were faced with a choice between a long follow-up vs a homogenous first generation DMT treated material; as a compromise we terminated the cohort at December 31st 2011, when second-generation DMTs started to come into wider use. Although natalizumab (Miller et al., 2003) was approved in 2006, its use was initially limited (10% of time on therapy until 2012; Supplementary Table 1). For 1950–2011, Swedish National

MS contained 17,971 patients (Fig. 1) who had provided consent for inclusion (www.neuroreg.se). The data extraction 2017 encompassed 12,246 patients with either RRMS or SPMS and with disease onset before 2012, of whom 10,492 had at least one visit with information on treatment status. To achieve uniform data quality, we restricted the cohort to patients from the 12 largest Swedish MS centres, with data from more than half of the patient population of the Swedish national register. Ultimately, we imported data from 6500 patients with onset during 1950–2011 from the Swedish MS register on August 30, 2017. We used the Swedish national MS register's SPMS criterion of an insidious increase in neurological deficit, typically initiated or dominated by a pyramidal syndrome, which is compatible with the Lublin and Reingold 1996 consensus definition of SPMS (Lublin and Reingold, 1996). The active centres checked data for quality, reducing the rate of missing data on the year of transition to SPMS to 1.3%. There was consensus among participating centres that the uncertainty of retrospective estimates of the year of onset of incipient progression in the national register amounts to a few years. We included individual data on sex, date of birth, age, date of MS onset, date of each visit, date when treatment was started, type of DMT, all DMT periods, interval from disease onset to start of first DMT, and year of transition from RRMS to SPMS. From the imported data we defined the following cohorts:

- Two population cohorts, 1975–1994 resp. 1995–2011.
- An incidence cohort with onset 1950–1994, untreated, censored December 31, 1994
- An incidence cohort with onset 1950–1994, untreated*), censored at treatment or December 31, 2011.
- An incidence cohort with onset 1995–2011, untreated*), censored at treatment or December 31, 2011.
- An incidence cohort with onset 1995–2011, DMT treated, censored December 31, 2011. *) despite DMT available for MS patients from 1995

The study was approved by the Research Ethics Committee of Gothenburg (Dnr 545–16, August 30, 2016) and by the Research Board of the Swedish National MS Register (Dnr 44).

2.3. Statistical methods

To estimate the instantaneous hazard function (HF) for the transition from RRMS to SPMS, we used a modified Poisson regression model (Albertsson-Wikland et al., 2016; Breslow and Day, 1987; Skoog et al., 2014). We assessed the relationship between the risk of SPMS and sex, current time since disease onset, current age, and current calendar year. The observation period for each patient was divided into 1-month intervals. Outcome was transition from RRMS to SPMS per individual. The time at risk was censored at the year of conversion to SPMS or date of last visit. The Poisson variable is continuously updated and provides a momentary risk, allowing us to include current age in addition to time since onset, calendar year and risk of SPMS in the model. The meaning of momentary risk is more evident from our previous study using Poisson regression in a web-based predictor estimating the current risk of SPMS at any time during RRMS (Skoog et al., 2019).

2.3.1. Comparing population cohorts (substudy A)

Some patients with onset during 1975–1994 started DMT later, during 1995–2011. When comparing the SPMS risk in the MS population living during 1995–2011 vs living during 1975–94 independent of their onset time, the modified Poisson regression model described above was used, resulting in a HR with 95% confidence interval. The HR were also adjusted for current age, current time since onset, current calendar year and sex (Table 2a and b).

2.3.2. Risk of transition to SPMS in relation to calendar year (substudy B)

All patients, irrespective of onset year, age and treatment,

contributed to a HF describing the incidence of transition from RRMS to SPMS at the current calendar year. The HF of SPMS was linear in the two variables time since onset and current age. Current calendar years were treated as piece-wise continuous linear variables with a breakpoint at the calendar years of 1980 and 1995. This HF was used to calculate the HR describing the increase or decline with one year of change in current calendar year with 95% CI. The risk of SPMS was also investigated with spline functions with current calendar year as continuous variable using breakpoints in current calendar year. Breakpoints for current calendar year were 1975, 1990, and 2005. HF was used to calculate the incidence of SPMS with 95% CIs with sex, time since onset, current age, and current calendar year as covariates.

2.3.3. Risk of SPMS relative to age and age at onset (substudy C)

Separate models were developed for individuals with onset during 1950–1994 and 1995–2011 and by intervals of age at onset, and by therapy (Tables 3-4). When applying the model to untreated individuals,

the observation time was censored at first medication intake (first or second generation DMT). When including a treated individual, the observation time started at the first medication. Thus, one individual could contribute to the model for both untreated and treated individuals with observation time before and after treatment. The HF of SPMS was linear in the two variables time since onset and current age. Current age was treated as piece-wise continuous linear variables with a breakpoint at the age of 50 years (Table 4). Among patients with onset during 1995–2011, those with an age of onset of <35 years generally did not reach 50 years of age because of the short follow-up to the end of 2011. Consequently, 30 and 40 years of age were substituted for 50 years as the breakpoints in these groups. Hazard ratios (HRs) to describe increase or decrease with age were calculated from HF. Two-sided p values were used for all analyses, with $p < 0.05$ considered significant.

The risk of SPMS was also investigated with spline functions in current age as continuous variables using breakpoints (Figs. 2-3). The splines were second order functions between the breakpoints and linear
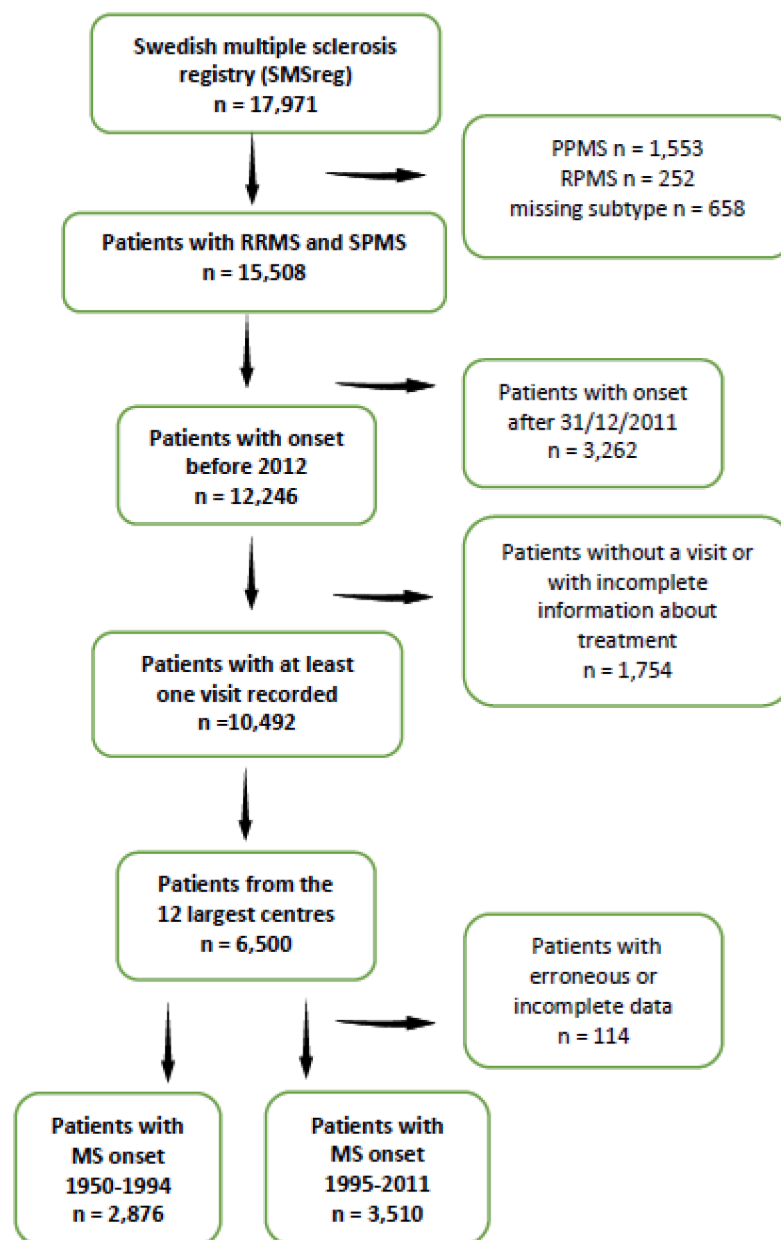

Fig. 1. Flowchart of patient selection for the present study. The material is derived from the Swedish MS register and includes patients with RRMS onset during 1950–2011.

functions at the tails, resulting in a smooth curve. Available breakpoints for Figs. 2 and 3 were age 25, 35, 45, and 55. Breakpoints (knots) define different regions (or partitions) for age. For some subgroups the data do not cover all breakpoints. Then the breakpoints for current age were determined based on the range of data (Supplementary Table 2). HF was used to calculate the incidence of SPMS with 95% confidence intervals (CIs) for different analyses (Figs. 2–3, significance values shown), with sex, time since onset, current age, and current calendar year as covariates.

2.3.4. Risk of transition to secondary progression in relation to treatment (substudy D)

To study the overall effect of treatment on the risk of SPMS we used the variable "treatment" as a time-dependent covariate, adjusted for current age, time since onset and current calendar year.

3. Results

3.1. Test of risk of transition from RRMS to SPMS between the first and second population cohort (substudy A)

HR for the difference in risk of transition to SPMS between population Cohort 1 (all participants living through the calendar years 1975–1994) and the population Cohort 2 (all participants living through the calendar years 1995–2011) was 1.18 unadjusted, and 0.58 adjusted for current age, current time since onset, current calendar year and sex (Table 2). The large difference between unadjusted and adjusted values mainly depends on adjustment for current age and calendar year.

3.2. Risk of transition to SPMS relative to calendar year (substudy B)

The risk of transition to SPMS was calculated as a function of calendar year 1950–2011 and adjusted for current time since onset, current age, and sex. The risk of SPMS in untreated patients showed a tendency to increase by 3.0% per year during 1980–1995 (HR 1.030, 95% CI: 1.016–1.043, $p < 0.001$). On the contrary, the risk diminished by 2.6% annually after 1995 (HR 0.975, 95% CI: 0.966–0.984, $p < 0.001$; Fig. 4).

3.3. Lifetime risk of SPMS (trend before and after 50 years of age) (substudy C)

3.3.1. Risk of SPMS before and after age 50 in the incidence cohort with onset 1950–1994, censored December 31, 1994, untreated

In this subgroup the risk of conversion to SPMS increased significantly with current age by 6%–9% annually among those < 50 years of age ($p < 0.004$). The risk decreased significantly after 50 years of age in the subgroup with youngest age at onset (< 25 years, $p = 0.02$), with no significant change with age in the subgroups with older age at onset ($\geq$ 25 years; Table 4, representative example with confounders locked at the indicated values in Fig. 2a).

Table 2

a. SPMS incidence in Cohort 1 and 2.

Subgroup	n	Number of SP	Total follow up time (years)	SP incidence per 100 (95% CI)
Onset 1950–1994, censored at Dec 1994	2876	793	31,946	2.5 (2.3, 2.7)
Onset 1975–1994, censored at Dec 1994**	2161	408	16,384	2.5 (2.3, 2.7)
Onset 1950–1994. Only time from 1995 and later. Censored at Dec 2011	2078	1008	22,075	4.6 (4.3, 4.9)
Onset 1975–1994. Only time from 1995 and later. Censored at Dec 2011	1750	819	19,172	4.3 (4.0, 4.6)
Onset 1995–2011. Censored at last visit before Dec 2011	3510	460	24,250	1.9 (1.7, 2.1)
Onset 1950–1994. Only time from 1995 and later. Censored at last visit before Dec 2011 and Onset 1995–2011. Censored at last visit before Dec 2011	5588	1468	46,326	3.2 (3.0, 3.3)
Onset 1975–1994. Only time from 1995 and later. Censored at last visit before Dec 2011 and Onset 1995–2011. Censored at last visit before Dec 2011***	5260	1279	43,423	2.9 (2.8, 3.1)

*Individuals with onset earlier than 1975 were excluded. Onset from 1950 was used in Tables 1, 3 and 4. **identical to Cohort 1. ***identical to Cohort 2.

b. Hazard ratio (HR) and 95% CI for test of SPMS incidence between cohorts and subgroups.

Cohort and subgroups	Vs. Cohort and subgroups	HR not adjusted for any variable*	HR adjusted for current age, current time since onset, current calendar year and sex
onset 1975–1994, censored at Dec 1994*	Onset 1975–1994. Only time from 1995 and later. Censored at Dec 2011. and Onset 1995–2011. Censored at Dec 2011	**1.18 (1.06, 1.32)**	**0.58 (0.48, 0.70)****

*Individuals with onset earlier than 1975 were excluded.
**) difference between unadjusted and adjusted mainly depends on adjustment of current age and calendar year.

3.3.2. Risk of SPMS before and after age 50 in the incidence cohort with onset 1950–1994, censored at treatment or 2011, untreated but with DMT available from 1995

The risk of conversion to SPMS increased also in this subgroup significantly with current age by 5%–9% annually before the age of 50 ($p < 0.001$). The risk for SPMS after 50 years of age decreased 4% per year for those with MS onset at age < 25 years ($p = 0.074$) or 25–35 years ($p = 0.051$; Table 4, representative example with confounders locked at the indicated values in Fig. 2b).

Table 1

Registry-based patient data.

Characteristics	Cohort 1 onset 1950–1994 (N = 2876)				Cohort 2 onset 1995–2011 (N = 3510)			
	N	Mean	SD	Range	N	Mean	SD	Range
Age at onset, years		29.9	9.0	8.8–64.1		33.2	10.4	6.8–72.0
Calendar year of onset		1982		1950–1994		2002		1995–2011
Time to last recorded visit, years		26.7	9.8	1.1–61.5		7.5	4.5	0.0–16.9
Gender, female n (%)	2122 (73.8%)				2499 (71.2%)			
Transitioned to SPMS	1801 (62.6%)				460 (13.1%)			
Time to SPMS or censoring, years		18.8	9.7	0.0–61.5		6.9	4.3	0.0–16.9
Treated patients	1038 (36.1%)				2682 (76.4%)			
Time to treatment, years		14.4	7.7	1.0–47.0		2.8	2.9	0.0–15.6

Table 3
SPMS incidence in three cohorts, unadjusted.

Age at onset	<25 years	25–35 years	>35 years
Incidence per 100 person-years (untreated period) 1950–94	2.3 (2.1–2.5)	3.0 (2.7–3.2)	4.3 (3.9–4.8)
Incidence per 100 person-years (untreated period) 1995–2011	0.4 (0.2 0.7)	0.9 (0.7–1.3)	2.6 (2.2–3.1)
Incidence per 100 person-years (treated period) 1995–2011	1.2 (0.8–1.6)	1.5 (1.2-1.9)	4.1 (3.5–4.7)

3.3.3. Risk of SPMS before and after age 50 (or substituted by age 30 or 40 due to insufficient follow-up time to age 50 with early onset) in the incidence cohort with onset 1995–2011, untreated but with DMT treatment available

In this subgroup, conversion to SPMS risk increased with current age before the age breakpoints of 30–50 years ($p < 0.044$). Thereafter, the yearly risk for SPMS increased after age 50 with current age for those with onset ≥ 35 years of age, with no significant change after the breakpoint for those who were <35 years of age at onset ($p < 0.001$; Table 4, representative example with confounders locked at the indicated values in Fig. 3a).

3.3.4. Risk of SPMS before and after age 50 (or substituted by age 30 or 40 due to insufficient follow-up time to age 50 with early onset) in an incidence cohort with onset 1995–2011, DMT treated

In this subgroup (where a majority initiated DMT), we observed a yearly increased risk of transition to SPMS with current age before 50 years of age ($p < 0.05$). After 50 years of age, we observed a continuous increase in the risk of SPMS in those with age of onset ≥35 years ($p < 0.0069$) and no significant change after the breakpoint with younger age at onset (Table 4, representative example with confounders locked at the indicated values in Fig. 3b).

3.4. Risk of transition to SPMS in contemporary DMT treated (1995–2011) vs. untreated patients (substudy D)

Treatment with DMTs, when analysed as a time-dependent covariate, adjusted for current age, time since onset and current calendar year, was associated with an increased risk of transition to SPMS in both Cohort 1 (after 1995) (HR 1.37, 95% CI: 1.20–1.56, $p < 0.001$) and Cohort 2 (HR 1.45, 95% CI: 1.16–1.80, $p < 0.001$). The HR decreased with longer latency to start of treatment, and the higher incidence in treated periods was consistent in each of the age at onset groups (<25, 25–35, >35 years).

4. Discussion

We here demonstrate that the incidence of transition from RRMS to SPMS was significantly lower in a 1995–2011 population cohort, right after the introduction of disease-modifying therapy (DMT) in Sweden 1995, than in the immediately preceding 1975–1994 untreated cohort. The 1995–2011 RRMS patients had a treatment option, mainly with first generation DMT (injectables), and were gradually treated up to more than 70%. The annual incidence of SPMS demonstrated a sharp reduction around 1995, the year when the first DMT was approved, after adjusting for factors influencing the calendar year incidence. A similar incidence of SPMS in treated and untreated subgroups before and after age 50 may be due to indication bias, which probably also explains the paradoxical result of DMT treatment by direct comparison of treated vs untreated patients, despite adjusting for time since onset. Recommendations followed by most neurologists in Sweden from 1995 restricted the use of DMT to active disease, probably reinforcing indication bias. In order to evade indication bias (Sormani and Bruzzi, 2015) (Kalincik and Butzkueven, 2016), we used a calendar year-based design of comparing two consecutive populations, the first untreated and the next including both untreated patients and patients starting DMT. With this

Table 4
Risk factors for hazard function for SPMS incidence [*].

Onset 1950–1994, untreated, censored Dec 1994,	HR for one year of increase in current age before age 50		HR for one year of increase in current age after age 50	
Onset age	HR (95% CI)	Two-sided *p*	HR (95% CI)	Two-sided *p*
All	1.06 (1.05, 1.07)	<0.001	0.98 (0.96, 1.01)	0.17
<25	1.06 (1.02, 1.10)	0.0036	0.87 (0.78, 0.98)	0.020
25–35	1.08 (1.04, 1.12)	<0.001	0.95 (0.88, 1.02)	0.13
≥35	1.09 (1.04, 1.14)	<0.001	0.99 (0.95, 1.03)	>0.30
Onset 1950–1994, untreated, censored at first DMT or last visit before 2012,	HR for one year of increase in current age before age 50		HR for one year of increase in current age after age 50	
Onset age	HR (95% CI)	Two-sided *p*	HR (95% CI)	Two-sided *p*
All	1.06 (1.06, 1.07)	<0.001	0.99 (0.98, 1.01)	>0.30
<25	1.05 (1.02, 1.09)	<0.001	0.96 (0.92, 1.00)	0.074
25–35	1.07 (1.04, 1.10)	<0.001	0.96 (0.93, 1.00)	0.051
≥35	1.09 (1.05, 1.13)	<0.001	1.01 (0.99, 1.04)	0.21
Onset 1995–2011, untreated periods,	HR for one year of increase in current age before age 50		HR for one year of increase in current age after age 50	
Onset age	HR (95% CI)	Two-sided *p*	HR (95% CI)	Two-sided *p*
All	1.09 (1.06, 1.11)	<0.001	1.10 (1.06, 1.13)	<0.001
≥35	1.14 (1.07, 1.22)	<0.001	1.10 (1.06, 1.13)	<0.001
Onset 1995–2011, untreated periods, younger [**]	HR for one year of increase in current age before breakpoint		HR for one year of increase in current age after breakpoint	
Onset age	HR (95% CI)	Two-sided *p*	HR (95% CI)	Two-sided *p*
<25, breakpoint 30	1.35 (1.02, 1.78)	0.035	0.69 (0.27, 1.74)	>0.30
25–35, breakpoint 40	1.14 (1.00, 1.29)	0.044	1.17 (0.87, 1.56)	>0.30
Onset 1995–2011, treated periods,	HR for one year of increase in current age before age 50		HR for one year of increase in current age after age 50	
Onset age	HR (95% CI)	Two-sided *p*	HR (95% CI)	Two-sided *p*
All	1.07 (1.06, 1.09)	<0.001	1.06 (1.03, 1.09)	<0.001
≥35	1.10 (1.03, 1.16)	0.0019	1.05 (1.01, 1.09)	0.0069
Onset 1995–2011, treated periods, younger [**]	HR for one year of increase in current age before breakpoint in age		HR for one year of increase in current age after breakpoint in age	
Onset age	HR (95% CI)	Two-sided *p*	HR (95% CI)	Two-sided *p*
<25, breakpoint 30	1.05 (0.93, 1.19)	>0.30	0.99 (0.80, 1.23)	>0.30
25–35, breakpoint 40	1.17 (1.05, 1.31)	0.034	0.92 (0.76, 1.11)	>0.30

[*] Piece-wise linear model with breakpoints, adjusted for current time from onset, calendar year, and sex.
[**] Rationale for substituted breakpoints at 30 and 40 years of age, see text.

population-based design, the overall SPMS incidence should be less influenced by preferential movement of severe cases to the treated subgroup. However, the comparisons between two consecutive populations cohorts may be influenced by other biases, notably competing risks. Exogenous risk factors for MS possibly influencing the SPMS incidence such as low vitamin D levels or smoking (Manouchehrinia
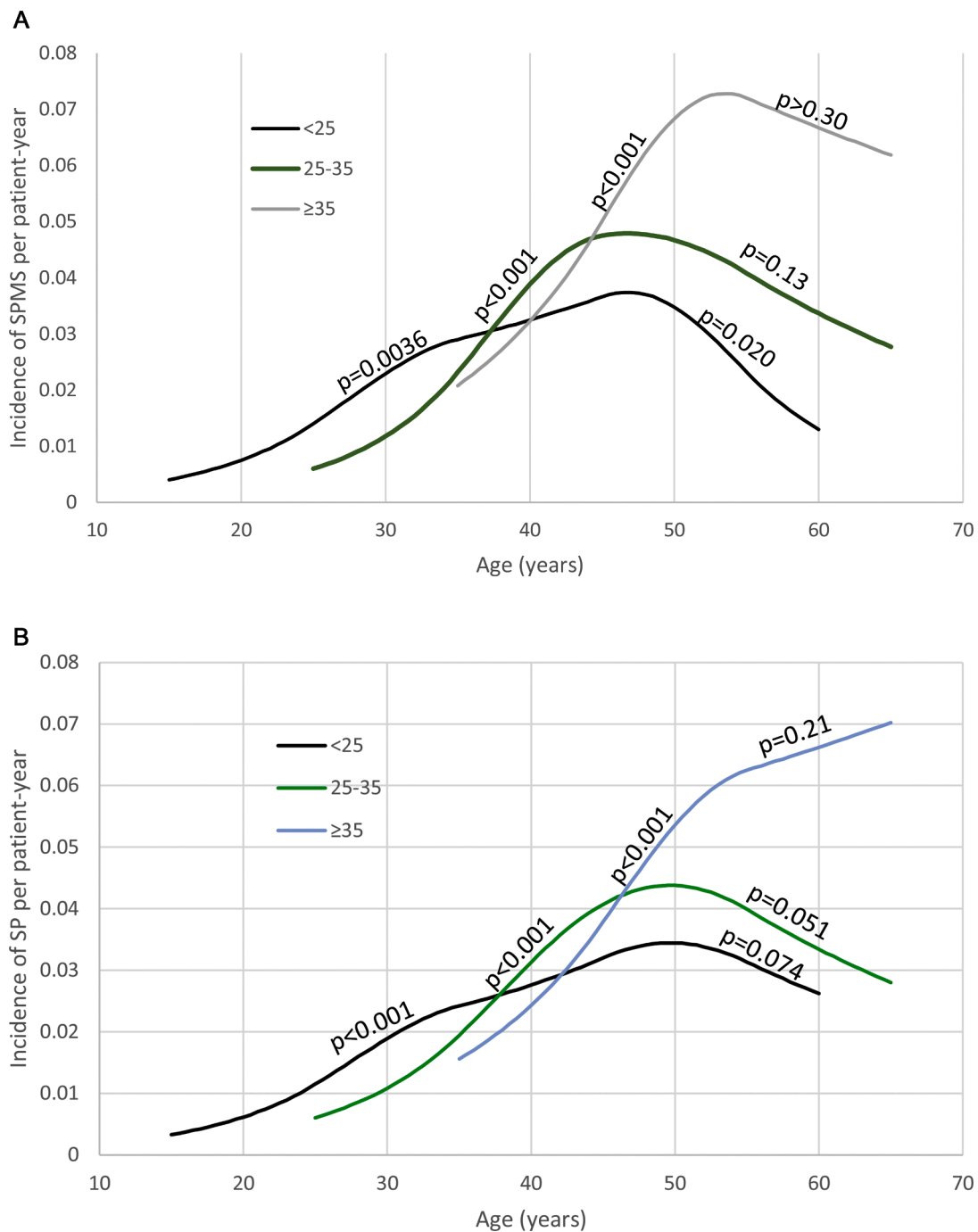
Fig. 2. 2a. Hazard function for SPMS in patients with onset during 1950–1994 and censoring in Dec 1994 in three age at onset groups. The incidence of SPMS is a function of current age and adjusted for time from onset, calendar year, and gender. The figure shows a representative example of a man for whom time after onset is fixed to 5 years and the calendar year to 1990. 2b. Group 1b Hazard function for SPMS in untreated patients with onset during 1950–1994 and censoring at first treatment. The incidence of SPMS is a function of current age and adjusted for time from onset, calendar year, and gender. The figure shows a representative example of a man for whom time after onset is fixed to 5 years and the calendar year to 1990.

et al., 2014) are not expected to elicit a significant change in the SPMS risk trajectory during a few years. More relevant, the McDonald diagnostic criteria first published 2001 (McDonald et al., 2001) may have reduced the subsequent apparent SPMS risk. However, we contend that the introduction of DMT from 1995 was a major contributor to the downturn of the SPMS incidence trajectory after 1995. A further type of probable confounding in the present study is survivorship bias, here apparently lowering the incidence in the first part of the 1950–95 cohort, as severe cases with onset from 1950 into the 1980s were likely lost when patients died or moved to nursing homes. Unfortunately, the

present material extending over decades lacks data on predictors essential for useful regression or propensity score methods (Gout, 2008).

The population-based design using a common parameter from an untreated and a subsequent treated population was previously used in a Canadian disability progression study demonstrating a moderate long-term effect of introduction of first generation DMT (Veugelers et al., 2009). A similarly designed study used two cohorts with contemporary treated vs. historical untreated controls, and concluded that biases producing exaggerated outcomes with historical controls would equate biases producing underestimated outcomes with contemporary controls
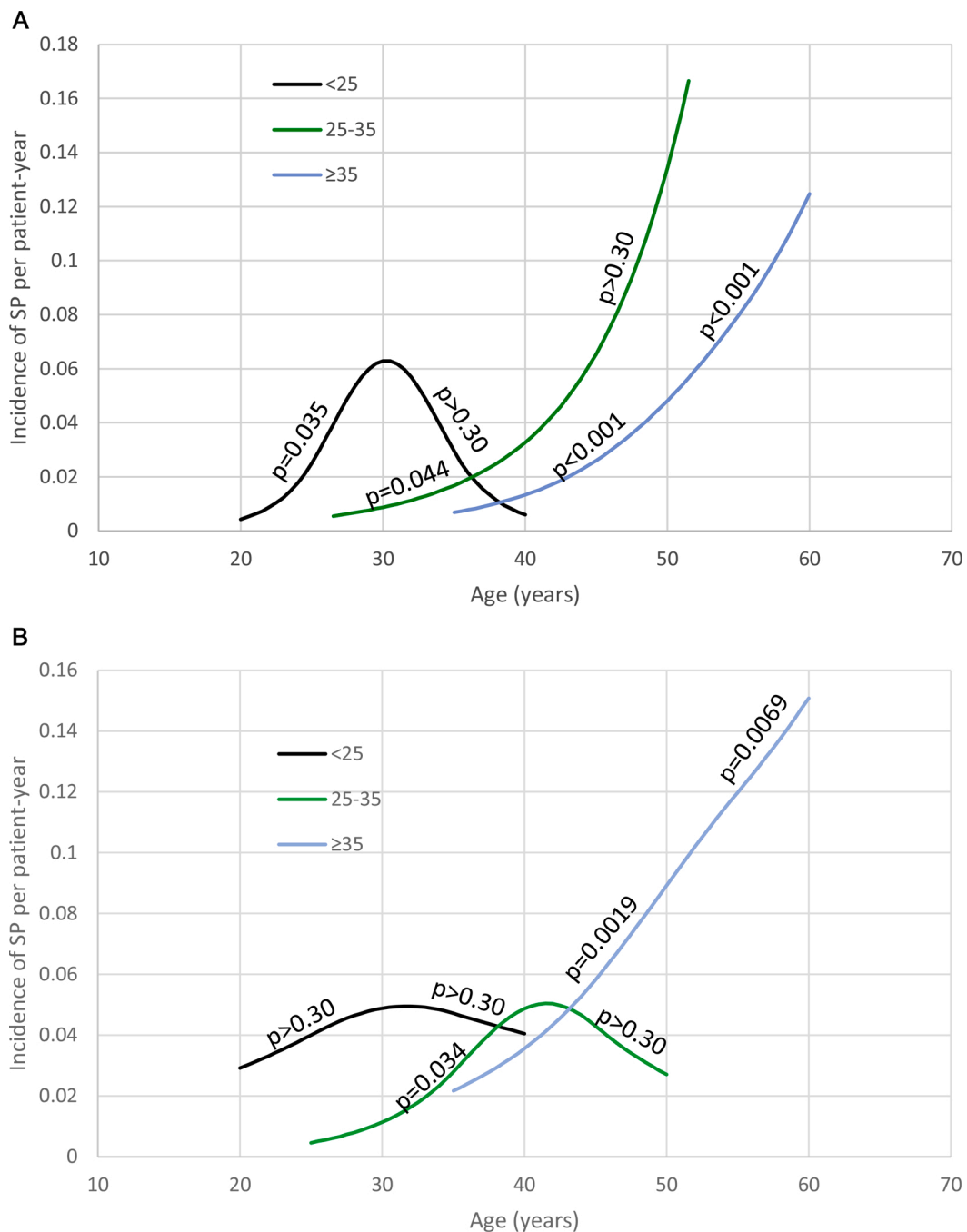
Fig. 3. 3a. Hazard function for SPMS in patients with onset during 1995–2011 and censoring at first treatment in three age at onset groups. The incidence of SPMS is a function of current age and adjusted for time from onset, calendar year, and gender. The figure shows a representative example of a man for whom time after onset is fixed to 5 years and the calendar year to 2000. 3b. Hazard function for SPMS in patients with onset during 1995–2011 and censoring at 2011, with only treated periods included. The incidence of SPMS is a function of current age adjusted for time from onset, calendar year, and gender. The figure shows a representative example of a man for whom time after onset is fixed to 5 years and the calendar year to 2000.

(Shirani et al., 2012). We suggest that indication bias and competing risks had opposing effects in the present study. A population-based study with similar aim as the present demonstrated a sharp increase in the age at disability milestones in a cohort diagnosed after 2000, 5 years after the introduction of DMTs, and a further, sharper positive change in this parameter attributed to the introduction of second-generation DMTs (Capra et al., 2017).

In the 1950–1995 cohort we observed an increasing risk of conversion to SPMS during the first decades of their disease, followed by decades with the risk leveling out or decreasing, which probably indicates

the presence of a neurodegenerative response with induction in a window of early MS-related inflammatory focal lesions, analogous to reported MRI and neuropathology data in the early vs. later stages of MS (Frischer et al., 2009). Age-related degeneration may contribute to the increased risk of transition to SPMS with higher age at onset. The occurrence of a middle-age maximum in cases with a younger age of onset argues against the idea of MS as a primary degenerative disorder, in which a relentless tendency for conversion to the SPMS phenotype with increasing age would be expected. Although the present age-dependent outcomes before and after age 50 were similar in the
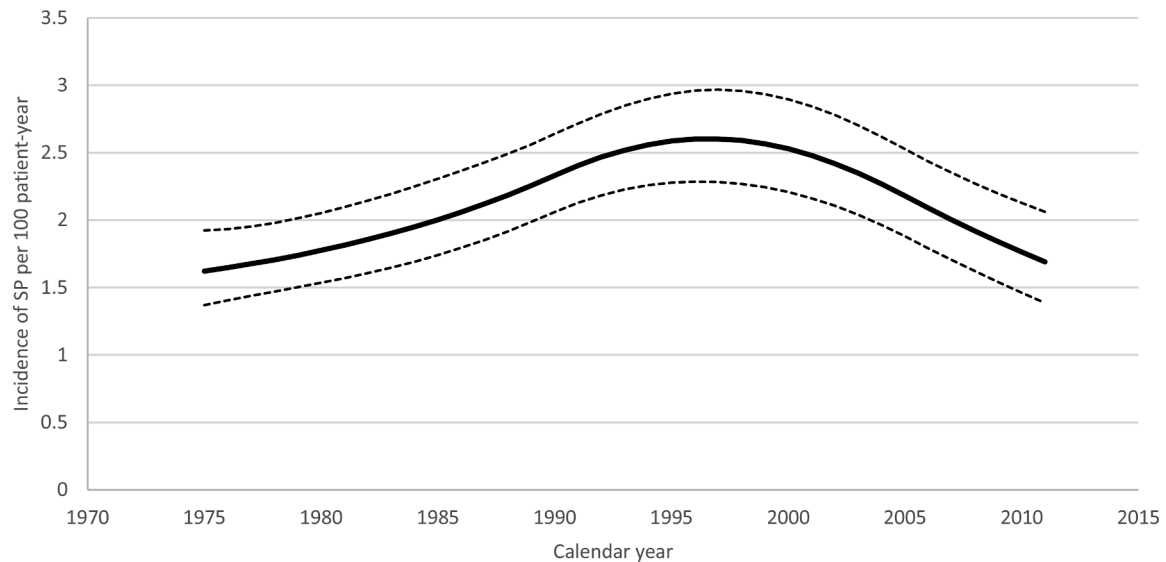
Fig. 4. Incidence of SPMS as a function of calendar year per 100 person-years. Total material, untreated and treated cases. The incidence of SPMS is a function of the current calendar year adjusted for time from onset, current age, and sex. The figure shows a representative example of a man for whom time after onset was fixed to 5 years and the current age 35 years. The overall shape of the curve is representative of curves with other values for the three adjustment variables.

treated and untreated strata, possibly due to indication bias, the middle-age maximum of risk of conversion to SPMS suggests that anti-inflammatory therapy may reduce the risk of SPMS if instituted in the early phases of MS. However, the residual risk of conversion to SPMS does not abate after age 50, indicating that trials on DMT discontinuation in this age group could use SPMS, in addition to markers of current activity, as a meaningful outcome.

The present demonstrates, in agreement with a majority of variously designed long-term follow up studies (Goodin et al., 2012), that first generation DMT have a long-term moderate efficacy, such as the DMT-induced 4 to 7 years delay of SPMS conversion demonstrated in registry studies from Italy and Sweden (Trojano et al., 2007)ʼ (Tedeholm et al., 2013). First generation DMT (injectables) are still used by approximately 7% of MS patients in Sweden, with a trend towards abandoning these DMT, particularly for escalation therapy in younger patients (VAP, www.neuroreg.se). While matched studies showed superior efficacy of specific second generation DMT over first generation (injectables) (Brown et al., 2019), further parallel studies at the population level using the present calendar year based design might explore an associated overall reduction of SPMS incidence and a possible delay of its age maximum.

5. Conclusion

Altogether, the efficacy of first generation DMT (injectables) to decrease the SPMS incidence is robust at the population level, and detectable despite complex confounders at the individual level, however their efficacy is moderate.

CRediT authorship contribution statement

H Tedeholm: Conceptualization, Formal analysis, Writing – original draft. **F Piehl:** Data curation, Writing – review & editing. **J Lycke:** Resources, Data curation, Writing – review & editing. **J Link:** Formal analysis. **L Stawiarz:** Formal analysis. **J Burman:** Data curation. **P de Flon:** Data curation. **K Fink:** Data curation. **M Gunnarsson:** Data curation. **J Mellergård:** Data curation. **P Nilsson:** Data curation. **P Sundström:** Data curation, Writing – review & editing. **A Svenningsson:** Data curation, Writing – review & editing. **H Johansson:** Formal analysis, Writing – original draft. **O Andersen:** Conceptualization, Project administration, Resources, Writing – original draft.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2022.104220.

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