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Glossary:
MS = multiple sclerosis;
RRMS = relapsing-remitting MS;
SPMS = secondary progressive MS;
SPMS-N = SPMS with no superimposed relapse activity;
SPMS-A = SPMS with superimposed relapse activity;
PPMS = primary progressive MS;
PPMS-N = PPMS with no superimposed relapse activity;
PPMS-A = PPMS with superimposed relapse activity;
EDSS = Expanded Disability Status Scale;
DMT = disease-modifying therapy;
IST = immunosuppressant therapy;
ASCT = autologous stem-cell transplant;
CI = confidence interval;
HR = hazard ratio.

Abstract

Background. Some studies comparing primary and secondary progressive multiple sclerosis (PPMS, SPMS) report similar ages at onset of the progressive phase, and similar rates of subsequent disability accrual. Others report later onset and/or faster accrual in SPMS. Comparisons have been complicated by regional cohort effects, phenotypic differences in sex ratio and management, and variable diagnostic criteria for SPMS.

Methods. We compared disability accrual in PPMS and operationally-diagnosed SPMS in the international, clinic-based MSBase cohort. Inclusion required PPMS or SPMS with onset at age ≥18 years since 1995. We estimated Andersen-Gill hazard ratios for disability accrual on the Expanded Disability Status Scale (EDSS), adjusted for sex, age, baseline disability, EDSS score frequency, and drug therapies, with center and patient as random effects. We also estimated ages at onset of the progressive phase (Kaplan-Meier) and at EDSS milestones (Turnbull). Analyses were replicated with physician-diagnosed SPMS.

Results. Included patients comprised 1872 with PPMS (47% male; 50% with activity) and 2575 with SPMS (32% male; 40% with activity). Relative to PPMS, SPMS had older age at onset of the progressive phase (median 46.7 years [95% confidence interval 46.2–47.3] versus 43.9 [43.3–44.4]; $P<.001$), greater baseline disability, slower disability accrual (hazard ratio 0.86 [0.78–0.94]; $P<.001$), and similar age at wheelchair dependence.

Conclusions. We demonstrate later onset of the progressive phase and slower disability accrual in SPMS versus PPMS. This may balance greater baseline disability in SPMS, yielding convergent disability trajectories across phenotypes. The different rates of disability accrual should be considered before amalgamating PPMS and SPMS in clinical trials.

Key messages

What is already known on this topic

Some studies comparing PPMS and SPMS report similar ages at onset of the progressive phase and similar rates of disability accrual, while others report later onset and/or faster accrual in SPMS. Comparisons have been complicated by regional cohort effects, phenotypic differences in sex ratio and management, and variable diagnostic criteria for SPMS.

What this study adds

We compared disability accrual in PPMS and SPMS in the international MSBase cohort, using multivariable survival models, with SPMS diagnosed operationally. Relative to PPMS, patients with SPMS have greater baseline disability at onset of the progressive phase; however, we show that patients with SPMS enter their progressive phase at older ages and experience slower disability accrual thereafter. This may yield similar ages at wheelchair dependence across phenotypes.

How this study might affect research, practice, or policy

Our results indicate that disability accrual is slower in SPMS than in PPMS. Caution is warranted about combining the two phenotypes in clinical trials, even as their long-term prognosis may be similar.

Introduction

Over 80% of patients with multiple sclerosis (MS) first present with relapsing-remitting MS (RRMS), in which episodic relapses produce varying degrees of sustained disability. Most convert, after a median 15–20 years, to secondary progressive MS (SPMS),[1–3] defined by continuous disability accrual (the "progressive phase") with or without superimposed relapses ("activity").[4] In contrast, ~15% of patients with MS have primary progressive MS (PPMS), with the progressive phase apparent from clinical onset.

Several geographically determined cohort studies have compared disability trajectories in PPMS and SPMS, using nonparametric estimates of time to milestones on the Expanded Disability Status Scale (EDSS).[5] Most concluded that regardless of phenotype, the progressive phase had median onset during the fifth decade of life, and stereotyped disability accrual above EDSS 4.[6–12] Many authors (not all)[13] have therefore argued that although SPMS begins with baseline disability established during the relapsing-remitting phase, PPMS and SPMS ultimately converge on a partially age-dependent disability trajectory.[2,7–12,14,15]

However, whereas several studies found that PPMS and SPMS had similar ages at onset of the progressive phase,[2,9,10,12] and similar rates of disability accrual thereafter,[9,12] others found SPMS had later onset[16,17] or faster disability accrual.[8,18] The possibility that SPMS displays both greater baseline disability and faster ongoing disability accrual conflicts with a model in which long-term outcomes converge across phenotypes.

Past comparisons of PPMS and SPMS have been complicated by regional cohort effects; phenotypic differences in sex ratio[19] and clinical management; and poorly standardized diagnosis of SPMS.[20,21] Here, we compare disability accrual among patients with PPMS and SPMS in the international MSBase cohort, using multivariable survival models, and applying operationalized diagnostic criteria for SPMS.[22] We also estimate ages at onset of the progressive phase and at EDSS milestones in each phenotype; assess mean disability trajectories; and compare subgroups of each phenotype with and without activity.

Methods

Participants

Patient records were extracted from MSBase on January 7, 2020. MSBase is an international, clinic-based multiple sclerosis registry,[23] approved by the Melbourne Health Human Research Ethics Committee (2006.044) and includes records entered prospectively since July 1, 2004, in addition to retrospectively added records. Participants gave written informed consent as per the MSBase and local regulations. Data quality and generalizability procedures were applied before inclusion screening (**supplementary methods 1.1**).

Patients with PPMS were identified by physician diagnosis, with onset defined as the date of first symptoms. Patients with SPMS were identified operationally (among patients with initial RRMS), using the previously validated Lorscheider criteria.[22] These require an EDSS increase of at least 1.5, 1.0, or 0.5 point(s) from baseline(s) 0, 1.0–5.5, and ≥ 6, respectively; confirmation over ≥ 90 days of the EDSS increase and leading functional system score; and a minimum EDSS score of 4 and pyramidal functional system score of 2 at onset. Only EDSS scores > 30 days after the onset of any preceding relapse ("outside relapse") are used to identify and confirm EDSS increases.

Study eligibility required PPMS or SPMS with onset at age ≥ 18 years since January 1, 1995, and at least three EDSS scores[5]—including a final "confirmatory score" ≥ 180 days after the second and outside relapse. For patients with SPMS, eligibility further required initial records during RRMS, including an EDSS score ≤ 3; this ensured diagnosis at the earliest qualifying date under the Lorscheider criteria. Eligible patients were generally included from the date of their first EDSS score in the progressive phase; if this score occurred during relapse and the first subsequent score outside relapse was lower, the patient was included from the date of the latter. Patients were censored on the date of their final score ≥ 180 days prior to the final confirmatory score.

Patients were considered to have superimposed activity (PPMS-A, SPMS-A) if any relapse was documented during the progressive phase (prospectively or retrospectively, including any diagnosis of "progressive-relapsing MS"); otherwise, patients were considered to have no relapse activity (PPMS-N, SPMS-N). Relapses are defined in MSBase protocols by new or exacerbated symptoms persisting ≥ 24 hours, absent concurrent illness, and beginning > 30 days after onset of any prior relapse.

Outcomes

The primary outcome was disability accrual during the progressive phase. Disability accrual events were defined by an EDSS score increase of at least 1.5, 1.0, or 0.5 point(s) from baseline(s) 0, 1.0–

5.5, and ≥ 6 respectively,[24] with the increase confirmed ≥ 180 days later outside relapse, and sustained throughout follow-up. Each event established a new EDSS baseline, defined as the lowest score on or after that date. Periods between baselines were termed "epochs".

The secondary outcome was age at confirmed EDSS ≥ 7 (wheelchair dependence), defined by the first EDSS score ≥ 7 with no subsequent score < 7 and a confirmatory score ≥ 7 recorded ≥ 180 days later outside relapse. For patients observed from a confirmed score ≥ 7, EDSS ≥ 7 was considered attained in the interval between MS onset (inclusive) and the first available EDSS score (exclusive).

Population mean EDSS scores by age, in two-year intervals, were calculated for each phenotype ("mean EDSS trajectories"). For these calculations, if a patient had multiple scores within a two-year interval, the median was taken as the patient's score for that interval.

Statistical analysis

Disability accrual in PPMS and SPMS was visualized using Nelson-Aalen cumulative hazard functions, and compared formally using Andersen-Gill adjusted hazard ratios (HR).

All Andersen-Gill models included random-effects terms for treating center and for patient identity (nested within treating center). The initial model, estimating the total effect of phenotype (PPMS or SPMS), included terms for sex and for age at the start of each epoch. The "complete" model (**supplementary methods 1.2–1.3**) added terms for EDSS score at the start of each epoch; the proportion of each epoch receiving disease-modifying therapy (DMT) and immunosuppressant therapy (agents listed in **table 1**); and the annualized frequency of EDSS scores during each epoch ("EDSS score frequency"). Next, a phenotype–activity interaction was added; based on the result, the "complete" model was re-assessed with phenotype comprising PPMS-N, PPMS-A, SPMS-N, and SPMS-A. Finally, to assess whether hazard ratios for DMT differed between phenotypes, models were constructed separately for PPMS and SPMS, with or without an activity–DMT interaction. Ties were handled using the Efron approximation. The proportional hazards assumption was assessed using Schoenfeld residuals (visual and formal evaluation).

For each phenotype, age-based survival functions for onset of the progressive phase were estimated using the Kaplan-Meier estimator, and compared using the log-rank test. Age-based survival functions for EDSS ≥ 7 were estimated using the Turnbull estimator (to accommodate interval-censored observations), and compared using a generalized log-rank test.[25] Median ages at onset of the progressive phase and at confirmed EDSS ≥ 4, ≥ 6, and ≥ 7 were likewise estimated using the Turnbull estimator, for the full dataset (1995–2020; all patients) and for three constituent time periods (1995–2003, 2004–2011, 2012–2020); analyses for each period included only patients

diagnosed with PPMS or SPMS within the period, and only EDSS scores recorded before the end of the period.

Five sensitivity analyses were performed. The first required onset of PPMS or SPMS since July 1, 2004 (the start of prospective data collection in MSBase). The second examined only the longest period (if any) in each patient's progressive phase during which at least one EDSS score was recorded every 15 months (457 days). The third defined disability accrual and EDSS ≥ 7 to require confirmation over ≥ 365 days, reducing the possibility that "confirmed" EDSS increases might subsequently reverse.[24,26] The fourth obtained period-specific hazard ratios 0–5, 5–10, and 10–15 years from onset of the progressive phase. The fifth assessed disability accrual from EDSS 4–5 rather than from onset of the progressive phase (and, accordingly, restricted analysis to EDSS scores ≥ 4, and to patients with an initial score in the progressive phase ≤ 5).

Finally, all analyses were repeated comparing PPMS with SPMS identified by physician diagnosis (since January 1, 1995), rather than operationalized criteria.

To assess whether the effect of phenotype (PPMS or SPMS) on disability accrual was mediated by DMT exposure and EDSS score frequency, a mediation analysis was performed using a broadly applicable natural effects estimation procedure (**supplementary methods 1.4**).[27,28] Mediation analysis assumes control for exposure–outcome, mediator–outcome, and exposure–mediator confounding, and the absence of mediator–outcome confounders affected by the exposure.

Analyses were performed in R 4.0.0 (packages 'survival' 3.1-12, 'coxme' 2.2-16, 'lme4' 1.1-26, 'glrt' 2.0, 'survminer' 0.4.8).

Results

Main analyses

1872 patients with PPMS (47% male; 50% PPMS-A) and 2575 with operationally diagnosed SPMS (32% male; 40% SPMS-A) were included in the main analyses, drawn from 107 centers in 33 countries (**figure 1**; **supplementary figure 1.1**; **supplementary table 1.1**). Among patients with operationally diagnosed SPMS, 1134 (44%) were physician-diagnosed by the end of follow-up. Patient characteristics are summarized in **table 1** (for relapse characteristics, see **supplementary table 1.2**).

Table 1. Clinical characteristics of included patients

Patient characteristics	PPMS (all)	PPMS-N	PPMS-A	SPMS (all)	SPMS-N	SPMS-A
Patients	**1872**	935	937	**2575**	1541	1034
Sex, male (%)	**878 (47)**	442 (47)	436 (47)	**836 (32)**	513 (33)	323 (31)
Age, MS onset	**43.5 ± 10.5**	45.6 ± 9.8	41.5 ± 10.7	**32.3 ± 10.2**	33.2 ± 10.5	31.0 ± 9.6
Age, progressive phase	**43.5 ± 10.5**	45.6 ± 9.8	41.5 ± 10.7	**47.0 ± 10.1**	48.7 ± 10.3	44.5 ± 9.4
Age, inclusion	**48.7 ± 10.8**	50.7 ± 10.1	46.7 ± 11.2	**47.0 ± 10.1**	48.7 ± 10.3	44.5 ± 9.4
Time, MS onset to inclusion; years	**4.1 [2.0–7.3]**	4.1 [2.1–7.3]	4.1 [1.9–7.3]	**13.5 [8.2–19.7]**	14.3 [8.8–20.8]	12.4 [7.3–18.2]
Time, follow-up; years	**4.2 [1.9–7.9]**	3.8 [1.7–7.5]	4.4 [2.1–8.2]	**3.7 [1.6–6.8]**	2.7 [1.2–5.4]	5.3 [2.8–8.6]
EDSS score frequency, annualized	**1.53 [1.00–2.28]**	1.37 [0.92–2.10]	1.68 [1.12–2.44]	**1.79 [1.20–2.56]**	1.69 [1.09–2.30]	1.90 [1.38–2.94]
Disability at inclusion; EDSS	**4.0 [3.0–6.0]**	4.0 [3.0–6.0]	4.0 [3.0–6.0]	**4.5 [4.0–6.0]**	4.5 [4.0–6.0]	4.5 [4.0–5.5]
Disability at censoring; EDSS	**6.0 [4.5–6.5]**	6.0 [4.5–6.5]	6.0 [4.0–6.5]	**6.0 [4.5–6.5]**	5.5 [4.0–6.5]	6.0 [5.0–6.5]
Disability increase, annualized; EDSS	**0.15 [0.00–0.38]**	0.15 [0.00–0.37]	0.15 [0.00–0.39]	**0.00 [0.00–0.22]**	0.00 [0.00–0.22]	0.06 [0.00–0.22]
Deaths recorded, from any cause (%)	**59 (3)**	33 (4)	26 (3)	**71 (3)**	45 (3)	26 (3)
Relapses during follow-up						
Patients (%)	**336 (18)**	0 (0)	336 (36)	**948 (37)**	0 (0)	948 (92)
Annualized relapse rate	**0.26 [0.14–0.48]**	NA	0.26 [0.14–0.48]	**0.34 [0.19–0.60]**	NA	0.34 [0.19–0.60]
Cerebrospinal fluid oligoclonal bands; patients (%)						
Present	**1149 (61)**	546 (58)	603 (64)	**1496 (58)**	833 (54)	663 (64)
Absent	**89 (5)**	46 (5)	43 (5)	**86 (3)**	52 (3)	34 (3)
Not assessed	**634 (34)**	343 (37)	291 (31)	**993 (39)**	656 (43)	337 (33)
Disease-modifying therapy, proportion of follow-up receiving treatment; patients (%)						
0%	**1104 (59)**	652 (70)	452 (48)	**541 (21)**	395 (26)	146 (14)
> 0–25%	**221 (12)**	105 (11)	116 (12)	**204 (8)**	111 (7)	93 (9)
> 25–50%	**144 (8)**	46 (5)	98 (10)	**184 (7)**	87 (6)	97 (9)
> 50–75%	**106 (6)**	36 (4)	70 (7)	**185 (7)**	80 (5)	105 (10)
> 75%	**297 (16)**	96 (10)	201 (21)	**1461 (57)**	868 (56)	593 (57)
Disease-modifying therapy, exposure to specific agents during follow-up; patients (%)						
Interferon beta	**318 (17)**	85 (9)	233 (25)	**1014 (39)**	517 (34)	497 (48)
Glatiramer acetate	**154 (8)**	46 (5)	108 (12)	**412 (16)**	194 (13)	218 (21)
Fingolimod	**118 (6)**	39 (4)	79 (8)	**510 (20)**	225 (15)	285 (28)
Teriflunomide	**28 (1)**	7 (1)	21 (2)	**141 (5)**	78 (5)	63 (6)

Dimethyl fumarate	**24 (1)**	8 (1)	16 (2)	**166 (6)**	89 (6)	77 (7)
Cladribine	**2 (0)**	0 (0)	2 (0)	**13 (1)**	6 (0)	7 (1)
Mitoxantrone	**91 (5)**	29 (3)	62 (7)	**129 (5)**	57 (4)	72 (7)
Natalizumab	**83 (4)**	27 (3)	56 (6)	**443 (17)**	216 (14)	227 (22)
Alemtuzumab	**12 (1)**	3 (0)	9 (1)	**55 (2)**	24 (2)	31 (3)
Daclizumab	**1 (0)**	0 (0)	1 (0)	**3 (0)**	2 (0)	1 (0)
Rituximab	**62 (3)**	16 (2)	46 (5)	**52 (2)**	28 (2)	24 (2)
Ocrelizumab	**169 (9)**	90 (10)	79 (8)	**78 (3)**	51 (3)	27 (3)
Siponimod	**0 (0)**	0 (0)	0 (0)	**2 (0)**	2 (0)	0 (0)
ASCT	**4 (0)**	0 (0)	4 (0)	**9 (0)**	4 (0)	5 (0)
Immunosuppressant therapy, exposure to specific agents during follow-up; patients (%)						
Azathioprine	**233 (12)**	61 (7)	172 (18)	**231 (9)**	94 (6)	137 (13)
Methotrexate	**121 (6)**	41 (4)	80 (9)	**105 (4)**	36 (2)	69 (7)
Cyclophosphamide	**94 (5)**	26 (3)	68 (7)	**90 (3)**	31 (2)	59 (6)
Mycophenolate mofetil	**5 (0)**	2 (0)	3 (0)	**1 (0)**	1 (0)	0 (0)
Pregnancy during follow-up						
Patients (%)	**15 (1)**	2 (0)	13 (1)	**32 (1)**	13 (1)	19 (2)

Table 1. Clinical characteristics of included patients (continued)

Values are number (%), mean ± standard deviation, or median [interquartile range]. Patients classified as having PPMS-A include all eligible patients with a recorded diagnosis of progressive-relapsing MS (n = 540 patients; 58%). Patients classified as having SPMS under the operationalized diagnostic criteria include 1134 patients (44%) with SPMS under physician diagnosis. Annualized relapse rate is calculated for the subset of patients with one or more relapses during follow-up.

Abbreviations: EDSS = Expanded Disability Status Scale; ASCT = autologous stem-cell transplant, assumed effective for 5 years.

The Kaplan-Meier median age at onset of the progressive phase was younger in PPMS (43.9; 95% confidence interval [CI] = 43.3–44.4) versus SPMS (46.7; 95% CI = 46.2–47.3) ($P < .001$), and in the subgroup of each phenotype with activity (PPMS-A, SPMS-A) versus those without ($P < .001$ in both PPMS and SPMS) (**table 2**).

Table 2. Ages at onset of the progressive phase and at confirmed EDSS ≥ 7

Phenotype	All patients	Female	Male
Age at onset of the progressive phase (median), years (95% CI)			
PPMS	**43.9 (43.3–44.4)**	**44.4 (43.8–45.2)**	**43.0 (42.3–44.0)**
PPMS-N	46.0 (45.2–46.8)	46.5 (45.3–47.7)	45.5 (44.5–46.7)
PPMS-A	41.9 (40.7–42.6)	42.8 (42.0–43.7)	40.0 (38.6–41.8)

SPMS	**46.7 (46.2–47.3)**	**47.3 (46.6–47.8)**	**45.6 (44.9–46.7)**
SPMS-N	48.3 (47.7–49.0)	49.3 (48.3–50.2)	46.7 (45.6–48.0)
SPMS-A	44.1 (43.1–44.8)	44.2 (43.2–45.0)	43.0 (42.1–45.5)
Age at confirmed EDSS ≥ 7 (25th percentile), years (95% CI)			
PPMS	**60.3 (58.8–62.5)**	**63.4 (60.5–66.2)**	**58.1 (56.6–60.1)**
PPMS-N	62.5 (60.1–65.8)	66.0 (62.5–68.7)	60.1 (57.3–62.7)
PPMS-A	57.6 (55.4–60.9)	60.9 (56.3–65.3)	55.8 (52.8–58.6)
SPMS	**62.2 (60.2–64.0)**	**63.2 (62.1–66.0)**	**58.3 (56.5–62.3)**
SPMS-N	63.6 (62.1–66.9)	63.6 (62.1–67.1)	64.7 (60.4–70.8)
SPMS-A	58.2 (57.0–62.1)	63.2 (60.7–70.0)	55.4 (50.8–57.8)

Ages at onset of the progressive phase (Kaplan-Meier estimator; log-rank test) were younger in PPMS versus SPMS ($P < .001$), in subgroups with activity (-A) versus those without (-N) ($P < .001$ in both PPMS and SPMS), and in males versus females ($P = .22$ in PPMS, $P = .01$ in SPMS). Ages at confirmed EDSS ≥ 7 (Turnbull estimator; generalized log-rank test) were similar in SPMS and PPMS ($P = .06$; among females, $P = .45$; among males, $P = .44$; among patients with activity, $P = .22$; without activity, $P = .38$), but younger in patients with activity than in those without (PPMS-A vs. PPMS-N, $P = .002$; SPMS-A vs. SPMS-N, $P = .007$).

Abbreviations: CI = confidence interval; EDSS = Expanded Disability Status Scale.

The hazard of disability accrual was lower in SPMS versus PPMS—whether based on unadjusted Nelson-Aalen cumulative hazards (**figure 2A**); the Andersen-Gill model adjusted for sex and age (HR = 0.75; 95% CI = 0.70–0.81; $P < .001$; **supplementary table 1.3**); or the complete Andersen-Gill model further adjusted for baseline EDSS score, DMT and immunosuppressant therapy, and EDSS score frequency (HR = 0.86; 95% CI = 0.78–0.94; $P < .001$; **table 3**). The proportional hazards assumption was violated for EDSS score frequency; correction did not alter findings (**supplementary table 1.4**).

Table 3. Andersen-Gill models for hazard of confirmed disability accrual

Variable	Hazard ratio (95% CI)	*P*
Model comparing SPMS to PPMS (reference)		
Phenotype, SPMS	0.86 (0.78–0.94)	< .001

Sex, male	1.17 (1.09–1.25)	< .001
Age, at start of epoch	1.00 (0.99–1.00)	.28
EDSS baseline, at start of epoch	0.92 (0.90–0.95)	< .001
DMT, % of epoch on treatment (25% increments)	0.97 (0.94–0.99)	.004
IST, % of epoch on treatment (25% increments)	0.96 (0.92–0.99)	.01
EDSS score frequency, annualized, during epoch	1.14 (1.13–1.16)	< .001
Model comparing PPMS-A, SPMS-N, and SPMS-A to PPMS-N (reference)		
Phenotype		
PPMS-A	0.98 (0.89–1.09)	.75
SPMS-N	0.94 (0.84–1.06)	.34
SPMS-A	0.78 (0.69–0.88)	< .001
Sex, male	1.17 (1.09–1.25)	< .001
Age, at start of epoch	1.00 (0.99–1.00)	.13
EDSS baseline, at start of epoch	0.92 (0.90–0.94)	< .001
DMT, % of epoch on treatment (25% increments)	0.97 (0.95–0.99)	.006
IST, % of epoch on treatment (25% increments)	0.96 (0.92–0.99)	.01
EDSS score frequency, annualized, during epoch	1.15 (1.13–1.16)	< .001

Treating center and patient identity were modelled as random effects, with identity nested within center. The proportional hazards assumption was violated for EDSS score frequency.

Abbreviations: CI = confidence interval; EDSS = Expanded Disability Status Scale; DMT = disease-modifying therapy; IST = immunosuppressant therapy.

In the Andersen-Gill model adding a phenotype–activity interaction, disability accrual was not associated with phenotype (SPMS versus PPMS; HR = 0.94; 95% CI = 0.84–1.06; P = .34) or activity (present versus absent; HR = 0.98; 95% CI = 0.89–1.09; P = .75), but an interaction was observed between SPMS and activity (HR = 0.84; 95% CI = 0.73–0.96; P = .01). We therefore modified the complete model to estimate hazards of disability accrual in activity subgroups. Relative to PPMS-N, hazard was comparable in PPMS-A and SPMS-N, but lower in SPMS-A (HR

= 0.78; 95% CI = 0.69–0.88; $P < .001$; **table 3**; cf. unadjusted comparison, **figure 2B**). Analyses stratified by phenotype yielded no evidence of interactions between DMT and activity (PPMS, $P = .60$; SPMS, $P = .13$; **supplementary tables 1.5–1.6**).

Turnbull estimates for ages at EDSS ≥ 7 were similar in PPMS (25th percentile = 60.3 years; 95% CI = 58.8–62.5) and SPMS (25th percentile = 62.2 years; 95% CI = 60.2–64.0) ($P = .06$; among females, $P = .45$; males, $P = .44$). However, ages at EDSS ≥ 7 were younger in patients with relapse activity versus those without (PPMS-A versus PPMS-N, $P = .002$; SPMS-A versus SPMS-N, $P = .007$; **figure 3**), consistent with the earlier onset of the progressive phase in those with activity. Turnbull estimates for median ages demonstrated that whereas EDSS ≥ 4 was reached at younger ages in SPMS versus PPMS (and often prior to SPMS onset, as expected), ages at EDSS ≥ 6 and ≥ 7 became more similar across phenotypes (**table 4**). Therefore, the time between EDSS milestones was longer in SPMS (particularly SPMS-A), reflecting slower disability accrual in this phenotype versus PPMS. Across phenotypes, ages at onset of the progressive phase and at each EDSS milestone were older in later time periods.

Table 4. Ages at onset of the progressive phase and at confirmed EDSS scores, by time period

	Median age at progressive multiple sclerosis milestones, years (95% CI)			
	Onset	**EDSS ≥ 4**	**EDSS ≥ 6**	**EDSS ≥ 7**
Complete dataset (1995–2020)				
PPMS ($n = 1872$)	**43.9 (43.3–44.4)**	**50.4 (49.6–51.1)**	**56.9 (55.8–57.4)**	**72.8 (70.8–76.4)**
PPMS-N ($n = 935$)	46.0 (45.2–46.8)	51.9 (50.8–53.2)	57.5 (56.9–59.0)	75.4 (71.0–NA)
PPMS-A ($n = 937$)	41.9 (40.7–42.6)	47.7 (46.2–49.6)	54.8 (53.6–56.6)	70.8 (68.9–NA)
SPMS ($n = 2575$)	**46.7 (46.2–47.3)**	**46.1 (45.5–46.6)**	**55.4 (54.6–56.5)**	**76.0 (74.9–NA)**
SPMS-N ($n = 1541$)	48.3 (47.7–49.0)	47.6 (47.1–48.3)	57.8 (56.3–58.9)	76.0 (75.4–NA)
SPMS-A ($n = 1034$)	44.1 (43.1–44.8)	43.5 (42.9–44.3)	53.0 (52.0–54.1)	76.1 (70.0–NA)
1995–2003				
PPMS ($n = 125$)	**41.9 (39.3–44.9)**	**47.0 (45.8–50.9)**	**51.9 (50.0–55.2)**	**60.6 (56.0–65.0)**
PPMS-N ($n = 56$)	44.5 (41.5–48.7)	50.7 (47.9–53.5)	54.3 (51.0–57.5)	62.2 (56.0–68.5)
PPMS-A ($n = 69$)	41.0 (37.5–43.7)	44.4 (43.3–50.8)	47.6 (46.2–54.5)	58.8 (55.0–65.4)
SPMS ($n = 121$)	**43.0 (41.4–46.3)**	**42.9 (40.5–44.9)**	**47.4 (45.6–50.4)**	**57.4 (55.7–63.8)**
SPMS-N ($n = 48$)	45.5 (42.6–51.5)	44.5 (42.0–51.5)	48.8 (44.5–52.8)	57.4 (53.1–72.6)
SPMS-A ($n = 73$)	42.1 (39.8–44.9)	41.8 (39.8–44.5)	47.1 (45.1–51.5)	58.0 (56.3–NA)
2004–2011				
PPMS ($n = 266$)	**44.4 (43.3–45.9)**	**49.3 (46.6–50.8)**	**53.4 (52.2–56.9)**	**65.1 (62.4–NA)**
PPMS-N ($n = 132$)	46.5 (44.5–48.3)	50.5 (48.3–52.5)	54.8 (52.4–57.3)	67.5 (60.0–NA)
PPMS-A ($n = 134$)	42.8 (40.6–44.5)	46.4 (45.1–49.7)	53.0 (50.2–59.0)	65.1 (62.4–NA)

SPMS (*n* = 687)	**45.2 (44.2–46.0)**	**44.7 (43.8–45.6)**	**51.6 (49.7–52.5)**	**65.0 (62.1–68.4)**
SPMS-N (*n* = 329)	46.6 (45.7–48.2)	46.3 (45.3–47.6)	52.3 (50.6–54.6)	67.4 (63.6–71.4)
SPMS-A (*n* = 358)	43.3 (42.3–44.8)	43.0 (42.0–44.4)	49.8 (48.3–52.2)	61.3 (58.5–68.9)
2012–2020 (ending January 7, 2020)				
PPMS (*n* = 250)	**47.6 (45.9–49.8)**	**54.2 (52.6–59.1)**	**63.3 (61.1–70.6)**	**80.8 (NA–NA)**
PPMS-N (*n* = 129)	48.3 (47.2–51.5)	57.8 (52.6–60.8)	64.8 (60.8–NA)	NA (71.9–NA)
PPMS-A (*n* = 121)	45.5 (42.8–50.2)	54.2 (50.3–58.7)	62.3 (58.8–NA)	80.8 (NA–NA)
SPMS (*n* = 1353)	**47.9 (47.3–48.5)**	**47.2 (46.3–47.7)**	**59.5 (58.2–60.6)**	**NA (76.0–NA)**
SPMS-N (*n* = 950)	49.0 (48.2–49.9)	48.4 (47.5–49.1)	60.5 (59.5–63.6)	NA (76.0–NA)
SPMS-A (*n* = 403)	44.7 (43.2–46.7)	44.1 (42.9–45.6)	55.5 (54.4–58.0)	71.8 (71.8–NA)

Table 4. Ages at onset of the progressive phase and at confirmed EDSS scores, by time period (continued)

Median ages at onset of the progressive phase (Kaplan-Meier estimator) and at confirmed EDSS scores ≥ 4, 6, and 7 (Turnbull estimator), for the complete dataset and for three constituent time periods. Analyses for each time period include only those patients with onset of PPMS or (operationally diagnosed) SPMS during that period, and only EDSS scores recorded by the end of that period (such that the combined number of patients across the three periods is less than the total number of patients in the complete dataset). Note that in some cases data were insufficient for complete Turnbull estimates of the median ages at EDSS ≥ 6 or 7.

Abbreviations: CI = confidence interval; EDSS = Expanded Disability Status Scale.

When mean EDSS trajectories were assessed using only EDSS scores recorded during the progressive phase, patients with SPMS had higher scores at younger ages but flatter slopes over time versus those with PPMS (**figure 4A**). When trajectories were assessed including scores during RRMS, patients with RRMS-SPMS had steeper slopes at younger ages versus those with PPMS (**figure 4B**). These observations are consistent with a model in which the earlier onset of disability accrual in the RRMS–SPMS phenotype is balanced by faster disability accrual in PPMS, such that disability trajectories of the two phenotypes ultimately converge.

Sensitivity and mediation analyses

The sensitivity analyses corroborated the above findings; results are summarized in **supplementary tables 1.7–1.8**.

The analyses with SPMS defined by physician diagnosis (n = 4610 SPMS; 32% male; 50% SPMS-A) are presented in **supplementary material section 2**. Results corroborated those from the main analyses with respect to age at onset (Kaplan-Meier median for SPMS = 46.3 years; 95% CI =

45.8–46.7); hazard of disability accrual in SPMS versus PPMS (HR = 0.89; 95% CI = 0.83–0.95; $P < .001$; complete model); ages at EDSS milestones; and mean EDSS trajectories. However, the adjusted hazard of disability accrual was lower in both SPMS-A (HR = 0.85; 95% CI = 0.78–0.93; $P < .001$) and SPMS-N (HR = 0.86; 95% CI = 0.79–0.94; $P = .001$) versus PPMS-N. Additionally, EDSS ≥ 7 was reached at younger ages in SPMS (25th percentile = 54.4 years; 95% CI = 53.7–55.2) versus PPMS ($P < .001$), although still to a lesser extent than EDSS ≥ 4. Among patients with physician-diagnosed SPMS, 2458 (53%) met the operationalized diagnostic criteria.

Mediation analysis indicated that the causal effect of phenotype on disability accrual comprises only small indirect effects via DMT exposure (in 25% increments; HR = 1.02; 95% CI = 0.97–1.07) and EDSS score frequency (annualized; HR = 1.01; 95% CI = 1.00–1.02), and a substantial "direct" effect via other pathways (SPMS versus PPMS; HR = 0.78; 95% CI = 0.70–0.86).

Discussion

In this observational study comparing 1872 patients with PPMS and 2575 with operationally diagnosed SPMS from the MSBase cohort, SPMS had an older median age at onset by 3 years (46.7 versus 43.9), and a 14% lower hazard of disability accrual (adjusted for sex, age, baseline disability, disease-modifying and immunosuppressant therapy, and EDSS score frequency). However, patients who reached wheelchair dependence did so at similar ages in PPMS and SPMS. These results were robust in sensitivity analyses, in particular when including only patients with regular follow-up; when requiring confirmation of disability accrual events over at least one year; and when restricting analysis to EDSS scores ≥ 4 for both PPMS and SPMS. The older onset and lower hazard of disability accrual in SPMS were also demonstrated when SPMS was identified by physician diagnosis rather than operationalized criteria. Mediation analysis demonstrated that the lower hazard in SPMS versus PPMS was not reducible to differences in DMT exposure or EDSS score frequency between the two phenotypes.

Later onset of SPMS versus PPMS

Whether onset of the progressive phase occurs at older ages in SPMS versus PPMS remains contested.[2,16] We observe older median age at onset of SPMS versus PPMS by approximately 2–4 years, whether SPMS onset is identified by operationalized or physician diagnosis. This may reflect increasing use of high-efficacy DMT during RRMS, which defers conversion to SPMS.[29,30] However—consistent with some prior studies,[31] but not others[32]—we find that PPMS and SPMS show similar secular trends toward older ages at onset and at EDSS milestones, suggesting contributing factors beyond DMT uptake.

Slower disability accrual in SPMS versus PPMS; similar long-term trajectories

Modern cohort studies comparing PPMS and SPMS have reported either similar rates of disability accrual in the two phenotypes,[9,16] or faster accrual in SPMS.[8,18] These analyses used unadjusted life-table or Kaplan-Meier estimates of intervals between milestones (onset of the progressive phase; EDSS 4, 6, 7, or 8). In contrast, we observe slower disability accrual in SPMS. Our analyses used multivariable proportional hazards models, allowing adjustment for phenotypic differences in baseline disability, sex, age, and clinical management, without restriction to a single EDSS interval. It is possible that disability accrual in our SPMS cohort was tempered by DMT[18]—particularly in SPMS-A, where inflammation is treatable.[33] However, our mediation analysis suggests this explanation is insufficient, as do the secular trends noted above.

Our results cohere with the view that disability trajectories in RRMS-SPMS and PPMS ultimately converge as patients age[2,7–12,14]—perhaps reflecting a shift in pathology from focal inflammation

to diffuse neurodegeneration in the progressive phase,[34] accompanied by declining neurologic repair and compensation mechanisms.[35] Whereas disability accrual in RRMS-SPMS begins at RRMS onset (mean age 32.3 years in our SPMS cohort), accrual in PPMS typically begins a decade later (mean age 43.5 years). This delayed presentation in PPMS may be counterbalanced by younger onset of the progressive phase and faster disability accrual relative to SPMS, yielding convergence of long-term disability trajectories across phenotypes.

Supporting this interpretation, patients with PPMS and operationally diagnosed SPMS reached EDSS ≥ 6 and EDSS ≥ 7 (wheelchair dependence) at similar ages, despite the younger ages at EDSS ≥ 4 in the SPMS cohort. Likewise, mean EDSS trajectories for the two phenotypes converged with age (whether SPMS was diagnosed operationally or by physicians). However, patients with SPMS under physician diagnosis reached EDSS ≥ 7 younger than those with PPMS, as observed in some earlier cohorts.[7,8]

Patients with and without activity

In both PPMS and SPMS, patients with superimposed activity had younger onset of the progressive phase than those without, consistent with age-related declines in MS activity[18,36] and prior findings for PPMS.[8] Using operationalized diagnosis, SPMS-A had slower disability accrual versus PPMS-N, whereas SPMS-N did not. This may reflect a genuine phenotypic difference (e.g., SPMS-A may typically involve milder "progressive" pathology than other phenotypes). However, using physician diagnosis, both SPMS-N and SPMS-A had slower disability accrual versus PPMS-N.

Limitations

It remains difficult to precisely diagnose the onset of progressive MS.[35] Here, we have addressed the particular challenge of identifying the transition from RRMS to SPMS by using operationalized diagnosis, while also demonstrating consistent results under physician diagnosis. However, both methods of diagnosing SPMS are imperfect, as is physician diagnosis of PPMS. Importantly, our finding of slower disability accrual in SPMS is replicated in the estimates of median ages at EDSS milestones, and in the sensitivity analysis modelling accrual from EDSS 4–5 rather than from onset of the progressive phase. These two analyses depend on correct inclusion of patients with PPMS and SPMS, but not on precise identification of dates of onset.

Our main analyses using operationalized diagnosis of conversion from RRMS to SPMS required initial EDSS scores ≤ 3 during RRMS, with follow-up commencing at SPMS onset. This has several implications. First, many patients in our SPMS cohort lack a physician diagnosis, potentially because operationalized diagnosis detects SPMS earlier.[22] Second, the early progressive phase is preferentially sampled in SPMS. Third, the requirement for initial records from the

relapsing-remitting phase for patients with SPMS may have upwardly biased our estimated ages at onset and at EDSS milestones in this phenotype. Fourth, operationalized criteria for SPMS are not yet widely applied in clinical trials, which may limit generalizability of our findings. These concerns are addressed by the sensitivity analysis assessing disability accrual from EDSS 4–5, and by the analyses using physician-diagnosed SPMS. (For physician-diagnosed SPMS, ages at onset may be biased upward by diagnostic delay[20,21]; conversely, ages at onset and/or at EDSS milestones may be biased downward by preferential recognition of SPMS in patients with more aggressive disease.)

Our Kaplan-Meier analyses of ages at onset are right-truncated (restricted to individuals who experienced the outcome), so likely yielded net underestimates. This proved necessary in comparing PPMS and SPMS: whereas more accurate estimates of SPMS onset are obtained by including patients with unconverted RRMS in the risk set,[16] the equivalent is not feasible for PPMS given its covert prodromal pathology.[2,37]

Identification of patients with activity is complicated by variability in diagnosing relapse; unrecorded relapses; censoring before a patient's first superimposed relapse; and DMT-induced relapse suppression. We therefore assigned "active" status inclusively, if any relapse was recorded during the progressive phase. PPMS-A cohorts may also include cases of misclassified RRMS—although notably, we observe similar hazards of disability accrual in PPMS-A and PPMS-N.

The presented analyses did not differentiate disability accrual events by the magnitude of qualifying EDSS increases. This may yield a detection bias, understating disability accrual in patients who experienced rapid or repeated worsening between clinical visits. However, under both operationalized and physician diagnosis of SPMS, the median annualized frequency of EDSS scores was greater in SPMS versus PPMS (**table 1; supplementary table 2.2**). Moreover, epochs with an EDSS increase at least twice threshold were less common in both operationally diagnosed SPMS (7.5% of epochs in both SPMS-N and SPMS-A) and physician-diagnosed SPMS (11.1% in both SPMS-N and SPMS-A) versus PPMS (13.3% of epochs; PPMS-N, 13.1%; PPMS-A, 13.4%). Therefore, our finding of slower disability accrual in SPMS versus PPMS likely does not result from a preferential failure to capture accrual between visits in SPMS.

The current phenotypic classification[4] distinguishing RRMS, PPMS, and SPMS itself warrants examination,[35] given recent demonstrations of progression independent of activity during RRMS,[38–40] and evidence that the recognized phenotypes share the same underlying pathologies.[34] Nonetheless, our results suggest that the distinction between PPMS and SPMS captures clinically salient differences in disability accrual.

Clinic-based observational registry data are subject to selection biases, confounding, and incomplete records.[41] Here, data limitations precluded analyses of imaging records, and of death

as a competing risk. Additionally, although the EDSS remains widely used in both observational studies and clinical trials, it suffers from poor intra- and inter-rater reliability at low scores; poor responsiveness to upper-limb and cognitive impairments; and non-linearity.[24] In future studies, magnetic resonance imaging may help to identify prodromal MS pathology,[21] refine phenotypic classifications,[42] and provide paraclinical outcomes.[43]

Conclusion

We show that relative to PPMS, the progressive phase in SPMS begins at older ages, but with greater baseline disability due to the preceding relapsing-remitting phase. Patients with SPMS then experience slower disability accrual than those with PPMS, ultimately yielding convergent disability trajectories, with similar ages at more severe disability milestones in the two phenotypes. One should exercise caution about amalgamating PPMS and SPMS in clinical trials, and consider the difference in disability trajectories when comparing disability outcomes. At the same time, the convergence of disability trajectories in PPMS and SPMS coheres with the view that MS pathology interacts with normal central nervous system aging to drive similar long-term outcomes across phenotypes.

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Competing interests

Dr Roos served on scientific advisory boards for Novartis and Merck, and received conference travel support and/or speaker honoraria from Roche, Novartis, Biogen, Teva, Sanofi Genzyme, and Merck. Dr Nguyen received grants from MS Research Australia; grants, personal fees, and nonfinancial support from Biogen; grants and personal fees from Merck Serono; personal fees from Teva and Novartis; and nonfinancial support from Roche and Sanofi Genzyme. Dr Izquierdo received speaking honoraria from Biogen, Novartis, Sanofi, Merck, Roche, Almirall, and Teva. Dr Eichau received speaker honoraria and consultant fees from Biogen Idec, Novartis, Merck, Bayer, Sanofi Genzyme, Roche, and Teva. Dr Patti received speaker honoraria and advisory board fees from Almirall, Bayer, Biogen, Celgene, Merck, Novartis, Roche, Sanofi Genzyme, and Teva, and research funding from Biogen, Merck, FISM (Fondazione Italiana Sclerosi Multipla), Reload Onlus Association, and the University of Catania. Dr Horáková received speaker honoraria and consulting fees from Biogen, Merck, Teva, Roche, Sanofi Genzyme, and Novartis, and support for research activities from Biogen and the Czech Ministry of Education (project PROGRES Q27/LF1). Dr Havrdová received honoraria or research support from Biogen, Merck Serono, Novartis, Roche, and Teva; has been a member of advisory boards for Actelion, Biogen, Celgene, Merck Serono, Novartis, and Sanofi Genzyme; and received research support from the Czech Ministry of Education (project PROGRES Q27/LF1). Dr Girard received consulting fees from Teva Canada Innovation, Biogen, Novartis, and Sanofi Genzyme; lecture payments from Teva Canada Innovation, Novartis, and EMD; and research support from the Canadian Institutes of Health Research. Dr Duquette served on editorial boards for, and has been supported to attend meetings by, EMD, Biogen, Novartis, Genzyme, and Teva Neuroscience; he holds grants from the Canadian Institutes of Health Research and the MS Society of Canada, and received funding for investigator-initiated trials from Biogen, Novartis, and Genzyme. Dr Grand'Maison received honoraria or research funding from Biogen, Genzyme, Novartis, Teva Neurosciences, Mitsubishi, and ONO Pharmaceuticals. Dr Lugaresi received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities from Biogen, Merck Serono, Mylan, Novartis, Roche, Sanofi Genzyme, and Teva; her institutions have received research grants from Novartis (in the past 4 years). Dr Grammond served on advisory boards for Novartis, EMD Serono, Roche, Biogen Idec, Sanofi Genzyme, and Pendopharm; received grant support from Genzyme and Roche; and received research grants for his institution from Biogen Idec, Sanofi Genzyme, and EMD Serono. Dr Amato received honoraria as a consultant on scientific advisory boards for Biogen, Bayer Schering, Merck, Teva, and Sanofi-Aventis, and received research grants by Biogen, Bayer Schering, Merck, Teva, and Novartis. Dr Sola served on scientific advisory boards for Biogen Idec and Teva; received funding for travel and speaker honoraria from Biogen Idec, Merck, Teva, Sanofi Genzyme, Novartis, and Bayer; and received research grants for her institution from Bayer, Biogen, Merck, Novartis, Sanofi, and Teva. Dr Ferraro received travel grants and/or speaker honoraria from Merck, Teva, Novartis, Biogen, and Sanofi Genzyme. Dr Buzzard received honoraria and consulting fees from Biogen, Teva, Novartis, Sanofi Genzyme, Roche, Merck, CSL, and Grifols. Dr Lechner-Scott received travel compensation from Novartis, Biogen, Roche, and Merck; her institution received honoraria for talks and advisory board commitments, as well as research grants from Biogen, Merck, Roche, Teva, and Novartis. Dr Alroughani received honoraria as a speaker and for serving on scientific advisory boards from Bayer, Biogen, GSK, Merck, Novartis, Roche, and Sanofi Genzyme. Dr Boz received conference travel support from Biogen, Novartis, Bayer Schering, Merck, and Teva, and participated in clinical trials by Sanofi-Aventis, Roche, and Novartis. Dr van Pesch received travel grants from Merck, Biogen, Sanofi, Celgene, Almirall, and Roche; his institution received research grants and consultancy fees from Roche, Biogen, Sanofi, Celgene, Merck, and Novartis Pharma. Dr Terzi received travel grants from Novartis, Bayer Schering, Merck, and Teva, and participated in clinical trials by Sanofi-Aventis, Roche, and Novartis. Dr Maimone received speaker honoraria for advisory board service and travel grants from Almirall, Biogen, Merck, Novartis, Roche, Sanofi Genzyme, and Teva. Dr Ramo-Tello received research funding, compensation for travel, or speaker honoraria from Biogen, Novartis, Genzyme, and Almirall. Dr Spitaleri received honoraria as a consultant on scientific advisory boards from Bayer Schering, Novartis, and Sanofi-Aventis, and compensation for travel from Novartis, Biogen, Sanofi-

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Patient consent for publication

Not required.

Ethics approval

MSBase is registered with WHO ICTRP (anzctr.org.au identifier ACTRN12605000455662). MSBase is approved by the Melbourne Health Human Research Ethics Committee (reference 2006.044), and by ethics committees of participating centers as required by local laws and regulations.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

Data from each center contributing to MSBase are available at the discretion of the associated MSBase Principal Investigator(s). See https://www.msbase.org.

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Figure legends & tables

Figure 1. Flow diagram of patient inclusion

52062 patients with RRMS, and not meeting the operationalized diagnostic criteria for SPMS, were excluded.

Figure 2. Nelson-Aalen cumulative hazard curves for confirmed disability accrual

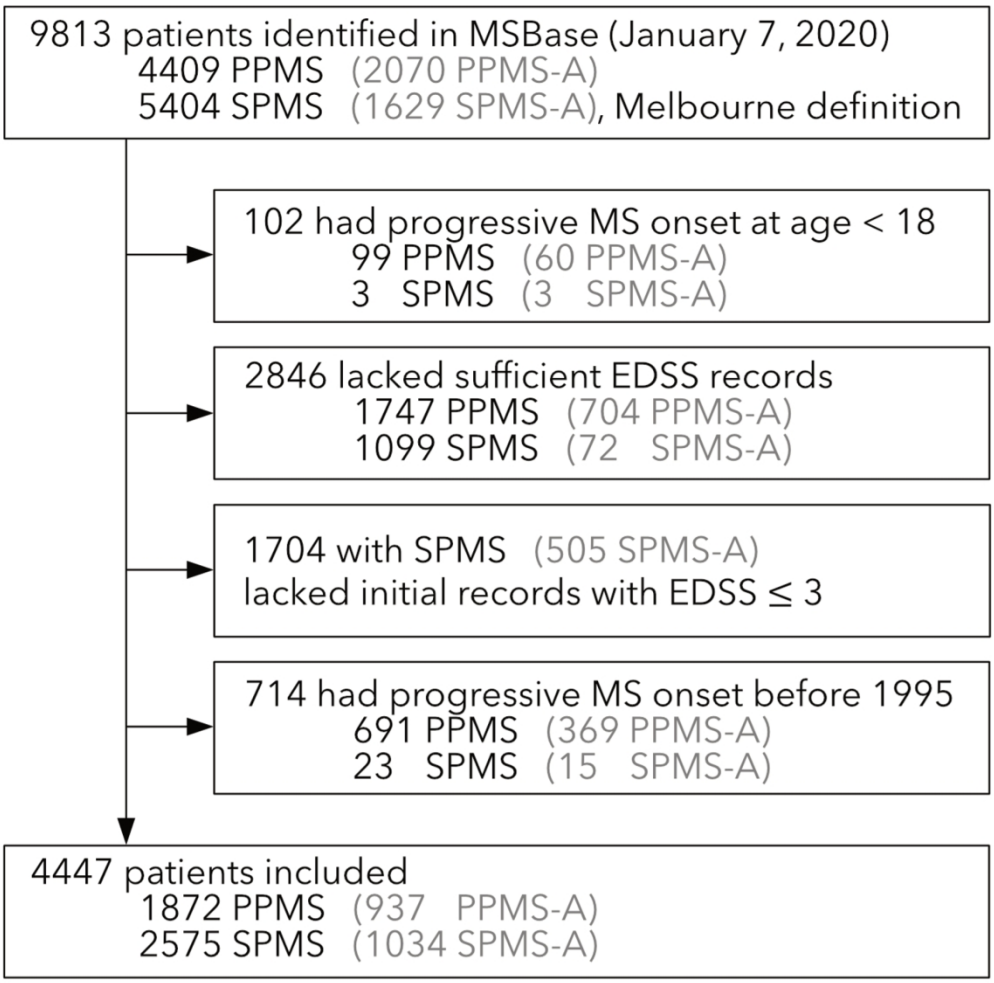
(**A**) PPMS and SPMS. (**B**) PPMS-N, PPMS-A, SPMS-N, and SPMS-A. The cumulative hazard indicates the expected number of confirmed disability accrual events for a patient observed for a given duration of time. Shaded regions indicate 95% confidence intervals. A-G HR = adjusted hazard ratio obtained with Andersen-Gill models (see **table 3**); CI = confidence interval.

Figure 3. Turnbull survival curves for confirmed EDSS ≥ 7 (wheelchair dependence)

(**A**) PPMS and SPMS. (**B**) PPMS-N, PPMS-A, SPMS-N, and SPMS-A. Patients who entered observation having already reached confirmed EDSS ≥ 7 are analyzed as interval-censored observations, with EDSS ≥ 7 reached in the interval (date of MS onset, date of first observation] (n = 37 PPMS-N, 43 PPMS-A; none with SPMS). Among patients with SPMS, 84 reached EDSS ≥ 7 at the date of onset of the progressive phase (60 SPMS-N, 24 SPMS-A); 24 reached EDSS ≥ 7 prior to the progressive phase (16 SPMS-N, 8 SPMS-A). *P* values (generalized log-rank tests): SPMS versus PPMS, *P* = .06; SPMS-N versus PPMS-N, *P* = .38; SPMS-A versus PPMS-A, *P* = .22; PPMS-A versus PPMS-N, *P* = .002; SPMS-A versus SPMS-N, *P* = .007. Values in the risk table indicate the number of patients at risk at each age; the number of interval-censored patients with an interval including that age (square brackets); and the cumulative number of patients having reached EDSS ≥ 7 at that age (curved brackets). Shaded regions indicate 95% confidence intervals. EDSS = Expanded Disability Status Scale.

Figure 4. Mean EDSS trajectories in PPMS-N, PPMS-A, SPMS-N, and SPMS-A

(**A**) Including only study-eligible EDSS scores, starting from onset of the progressive phase. (**B**) Including all available EDSS scores, starting from MS onset (including RRMS). Mean scores are plotted for each 2-year age interval, for groups with 10 or more patients contributing data in that interval. Error bars indicate 95% confidence intervals. EDSS = Expanded Disability Status Scale.



Flow diagram of patient inclusion
52062 patients with RRMS, and not meeting the operationalized diagnostic criteria for SPMS, were excluded.

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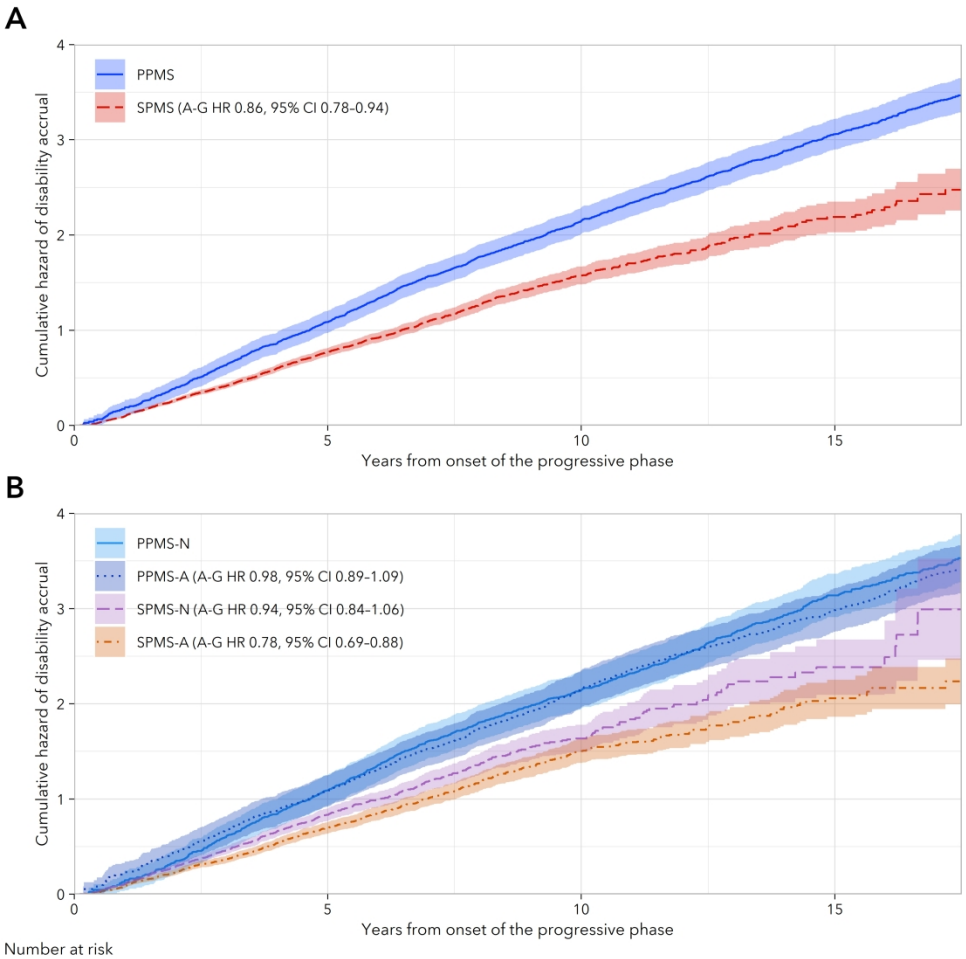

Number at risk

PPMS-N	24	260	384	375	315	262	163	91
PPMS-A	14	278	409	411	339	269	184	115
SPMS-N	1541	808	420	194	92	40	17	7
SPMS-A	1033	807	547	338	190	86	33	15

Cumulative exits (events)

PPMS-N	0 (0)	38 (67)	164 (274)	336 (505)	486 (657)	607 (800)	740 (904)	834 (956)
PPMS-A	0 (0)	30 (88)	139 (274)	299 (494)	448 (697)	598 (834)	719 (919)	808 (984)
SPMS-N	0 (0)	733 (420)	1121 (694)	1347 (823)	1449 (875)	1501 (903)	1524 (912)	1534 (917)
SPMS-A	0 (0)	227 (291)	487 (548)	696 (714)	844 (823)	948 (856)	1001 (874)	1019 (878)

Nelson–Aalen cumulative hazard curves for confirmed disability accrual
(A) PPMS and SPMS. (B) PPMS-N, PPMS-A, SPMS-N, and SPMS-A. The cumulative hazard indicates the expected number of confirmed disability accrual events for a patient observed for a given duration of time. Shaded regions indicate 95% confidence intervals. A¬–G HR = adjusted hazard ratio obtained with Andersen–Gill models (see table 3); CI = confidence interval.

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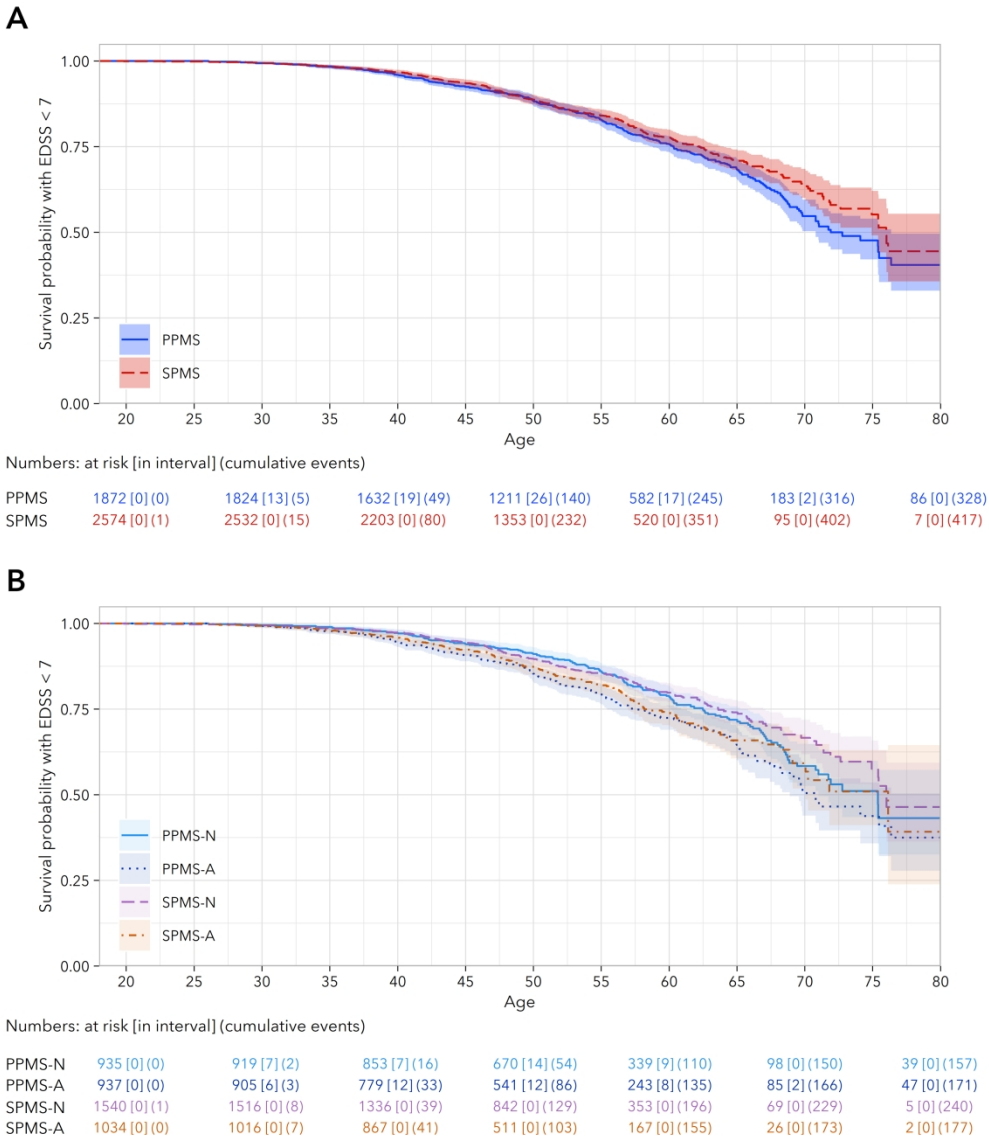

Turnbull survival curves for confirmed EDSS ≥ 7 (wheelchair dependence)
(A) PPMS and SPMS. (B) PPMS-N, PPMS-A, SPMS-N, and SPMS-A. Patients who entered observation having already reached confirmed EDSS ≥ 7 are analyzed as interval-censored observations, with EDSS ≥ 7 reached in the interval (date of MS onset, date of first observation] (n = 37 PPMS-N, 43 PPMS-A; none with SPMS). Among patients with SPMS, 84 reached EDSS ≥ 7 at the date of onset of the progressive phase (60 SPMS-N, 24 SPMS-A); 24 reached EDSS ≥ 7 prior to the progressive phase (16 SPMS-N, 8 SPMS-A). P values (generalized log-rank tests): SPMS versus PPMS, P = .06; SPMS-N versus PPMS-N, P = .38; SPMS-A versus PPMS-A, P = .22; PPMS-A versus PPMS-N, P = .002; SPMS-A versus SPMS-N, P = .007. Values in the risk table indicate the number of patients at risk at each age; the number of interval-censored patients with an interval including that age (square brackets); and the cumulative number of patients having reached EDSS ≥ 7 at that age (curved brackets). Shaded regions indicate 95% confidence intervals. EDSS = Expanded Disability Status Scale.

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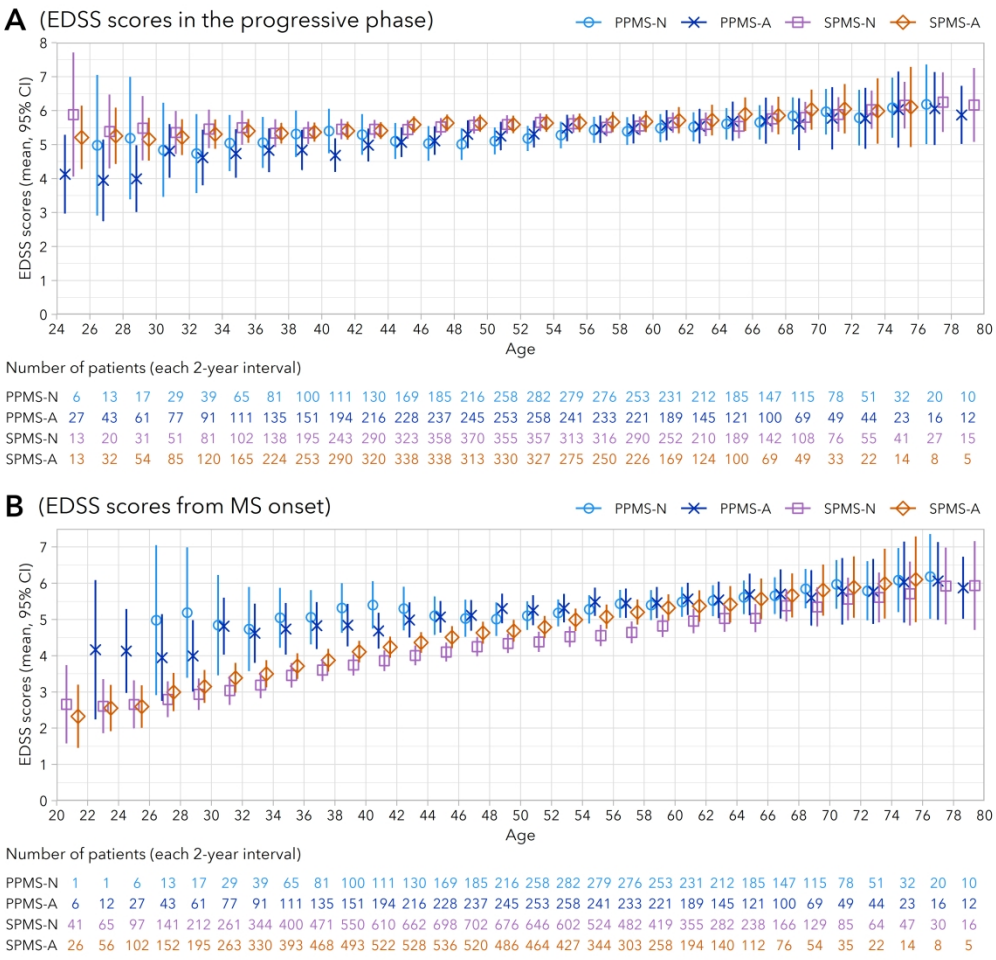

Mean EDSS trajectories in PPMS-N, PPMS-A, SPMS-N, and SPMS-A
(A) Including only study-eligible EDSS scores, starting from onset of the progressive phase. (B) Including all available EDSS scores, starting from MS onset (including RRMS). Mean scores are plotted for each 2-year age interval, for groups with 10 or more patients contributing data in that interval. Error bars indicate 95% confidence intervals. EDSS = Expanded Disability Status Scale.

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Supplement 1. Supplementary material for the main analyses

Harding-Forrester S, Roos I, Nguyen A-L, et al. Disability accrual in primary and secondary progressive multiple sclerosis.

Abbreviations

MS = multiple sclerosis

PPMS = primary progressive MS; PPMS-N = PPMS with no superimposed relapse activity; PPMS-A = PPMS with superimposed relapse activity

RRMS = relapsing-remitting MS

SPMS = secondary progressive MS; SPMS-N = SPMS with no superimposed relapse activity; SPMS-A = SPMS with superimposed relapse activity

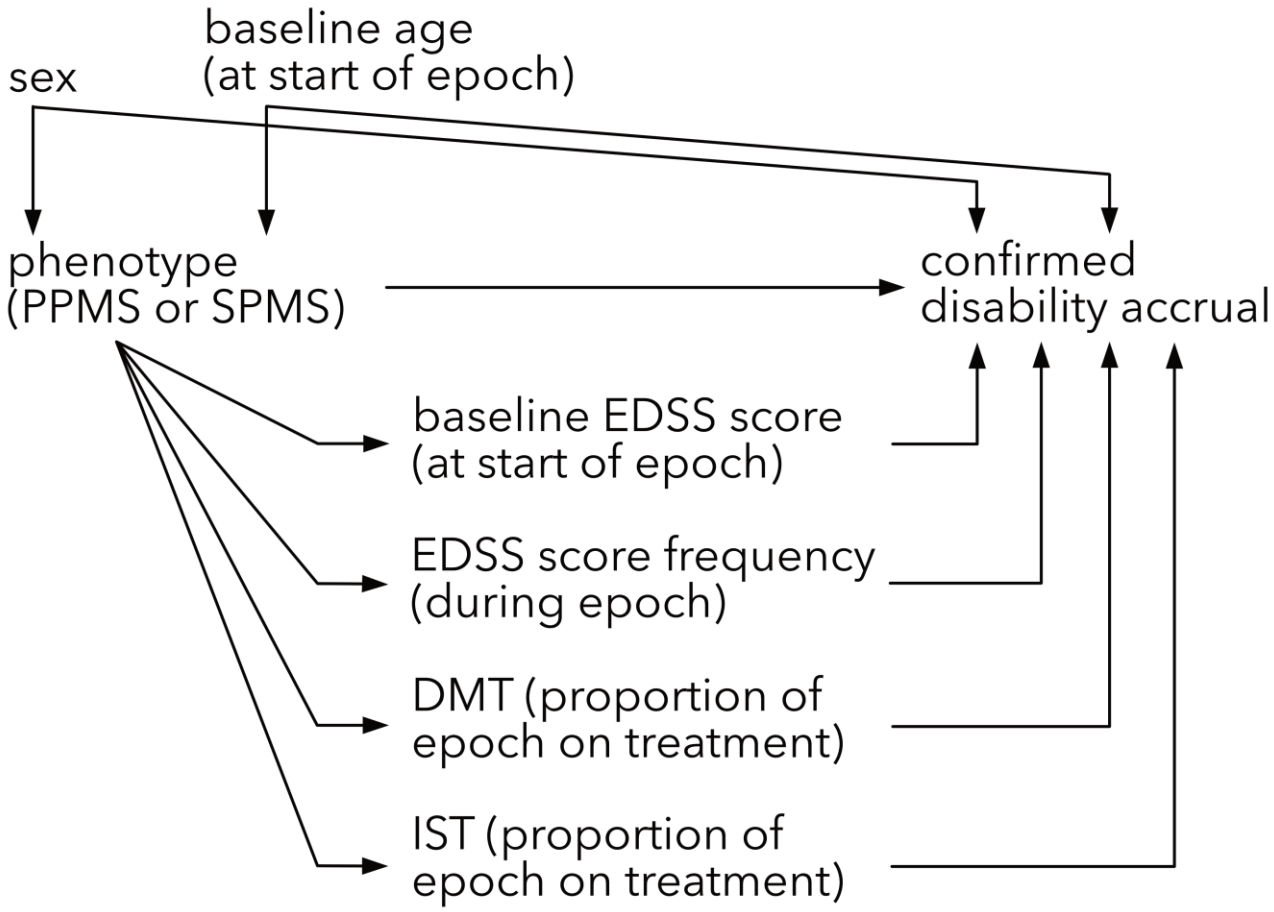
Supplementary methods 1.1.
Data quality procedure

Data quality procedure for MSBase data
Duplicate patient records were removed.
Centers with < 10 patient records were excluded.
Patients with missing date of birth were excluded.
MS onset dates after the data extraction date were removed.
Patients with missing date of the first clinical presentation of MS were excluded.
The dates of MS onset and of the first recorded MS course (e.g., primary progressive MS; clinically isolated syndrome) were aligned.
Patients with age at MS onset outside the range 0–100 years were excluded.
A logical sequence of MS courses was assured (e.g., clinically isolated syndrome, then relapsing-remitting MS, then secondary progressive MS).
Visit entries with a missing visit date, or with a recorded visit date before the recorded date of MS onset or after the data extraction date, were removed.
EDSS scores outside the range of possible EDSS values were removed.
Duplicate visit entries were merged.
MS relapses with missing onset date, or with a recorded onset date after the data extraction date, were removed.
Duplicate MS relapse entries were merged.
Relapses occurring within 30 days of each other were merged.
Visits preceded by relapses were identified, and time from the last relapse was calculated for each visit.
Therapies were labelled as discontinued or continuing.
Therapies with erroneous date entries were removed (e.g., treatment commencement date after treatment termination date; treatment commencement date after the data extraction date; commencement of disease-modifying therapy before the year 1980).
MS disease-modifying therapies were identified and labelled.
Duplicate treatment entries were removed.
Where multiple disease-modifying therapies were recorded simultaneously, the termination date of the previous therapy was imputed as the commencement date of the following therapy.

"Data extraction date" refers to the date of data extraction from MSBase (January 7, 2020).

Abbreviations: EDSS = Expanded Disability Status Scale.

Supplementary methods 1.2.
Directed acyclic graph:
Association of disability accrual and progressive MS phenotype



Random effects included in the models (treating center and patient identity) are not shown.
EDSS = Expanded Disability Status Scale; DMT = disease-modifying therapy; IST = immunosuppressant therapy.

Supplementary methods 1.3.
Formulation of the Andersen-Gill model for hazard of confirmed disability accrual

Each patient is represented as a series of observations in successive time intervals:
(start of follow-up, first event], (first event, second event], …. , (kth event, end of follow-up].

The intensity process $\lambda_{ijk}(t)$ driving confirmed disability accrual, for observation epoch k in patient j at center i, is:

$$\lambda_{ijk}(t) = Y_{ijk}(t)\,\lambda_0(t)\,\exp\{\,\beta_1\text{phenotype}_{ij} + \beta_2\text{sex}_{ij} +$$

$$\beta_3\text{age}_{ijk}(t) + \beta_4\text{EDSS}_{ijk}(t) + \beta_5\text{DMT}_{ijk}(t) + \beta_6\text{IST}_{ijk}(t) + \beta_7\text{freq}_{ijk}(t) +$$

$$b_1\text{center}_i + b_2\text{patient}_{ij}\,\}$$

with terms defined as:

Term	Definition
$Y_{ikj}(t)$	At-risk indicator: $Y_{ijk}(t) = 1$ during follow-up, 0 after end of follow-up
$\lambda_0(t)$	Baseline hazard (non-parametric, non-negative, time-dependent)
Independent variables, constant	
phenotype_{ij}	Progressive MS phenotype—*either*: PPMS (reference) or SPMS, *or* PPMS-N (reference), PPMS-A, SPMS-N, or SPMS-A
sex_{ij}	Female (reference) or male
Independent variables, time-dependent	
$\text{age}_{ijk}(t)$	Age in years at the start of the current epoch
$\text{EDSS}_{ijk}(t)$	EDSS score at the start of the current epoch
$\text{DMT}_{ijk}(t)$	Proportion of time on disease-modifying therapy during the current epoch
$\text{IST}_{ijk}(t)$	Proportion of time on immunosuppressant therapy during the current epoch
$\text{freq}_{ijk}(t)$	Frequency of EDSS scores during the current epoch
Random effects	
center_i	Treating center, with Gaussian distribution: $b_1 \sim G(0, \sum\theta)$
patient_{ij}	Patient identity, with Gaussian distribution: $b_2 \sim G(0, \sum\eta)$

Abbreviations: EDSS = Expanded Disability Status Scale.

Supplementary methods 1.4.
Mediation analysis

In a proportional hazards model with a common outcome, the hazard ratio after adjustment for mediators may not accurately estimate the causal direct effect of the exposure of interest.[1] To assess whether the effect of phenotype (PPMS or SPMS) on disability accrual was mediated by DMT exposure and EDSS score frequency, a mediation analysis was performed using a broadly applicable natural effects estimation procedure.[2,3] The proportion of time receiving DMT and the annualized frequency of EDSS scores were treated as mediators *M* within each epoch, with phenotype (SPMS versus PPMS) as the exposure *A*; sex and age at the start of each epoch as covariates *C*; and treating center and patient identity (nested within treating center) as random effects *Z*. Given $x = 2$ levels of the exposure and $k = 2$ mediators, a counterfactually augmented dataset was constructed from the observed data, with k auxiliary exposure variables and x^k copies of each observation epoch. The auxiliary exposure variables were assigned counterfactual values of the exposure in all possible combinations. Linear regression models were fitted for each mediator, conditional on the exposure and covariates, and were used to compute a weight for each observation i in the augmented dataset:

$$w_i = \prod_{k=1}^{K} \frac{\Pr\left(M^k = M_i^k | A = A_i^k, C = C_i, Z = Z_i\right)}{\Pr\left(M^k = M_i^k | A = A_i, C = C_i, Z = Z_i\right)}$$

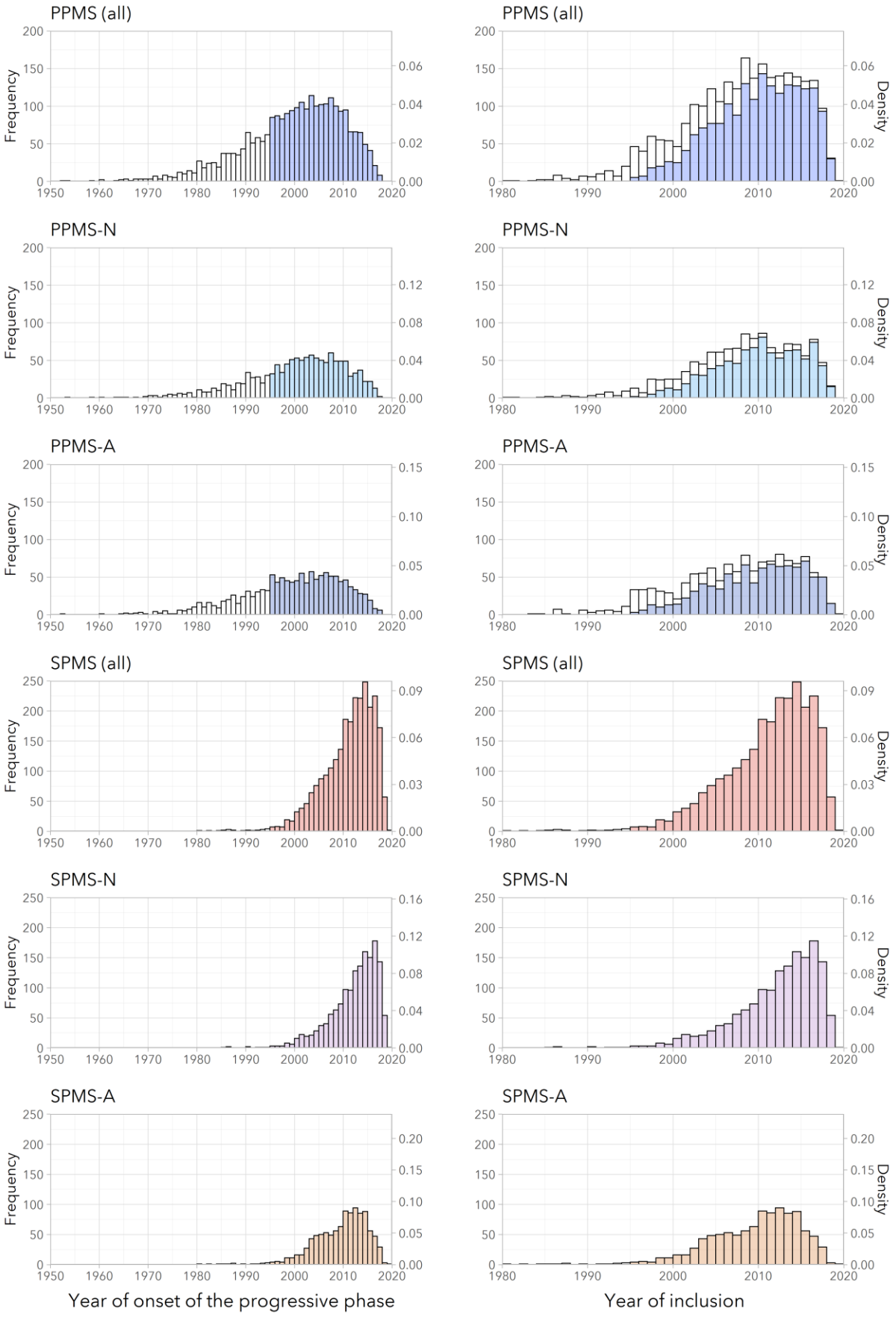
A weighted Andersen-Gill model was then fitted to the augmented dataset, conditional on the true and auxiliary exposure variables, covariates, and random effects (but not on the mediators). This yielded estimates of the natural direct effect from the true-exposure coefficient, and of the natural indirect effect via each mediator from the coefficient for its corresponding auxiliary exposure variable. Standard errors were estimated by bootstrapping (1000 resamples of complete patient records).

Mediation analysis assumes adequate control for exposure–outcome, mediator–outcome, and exposure–mediator confounding, and the absence of mediator–outcome confounders affected by the exposure.[1–3]

References

1. VanderWeele TJ. Mediation analysis: A practitioner's guide. *Annu Rev Public Health*. 2016;37:17–32.
2. Lange T, Vansteelandt S, Bekaert M. A simple unified approach for estimating natural direct and indirect effects. *Am J Epidemiol*. 2012;176(3):190–195.
3. Lange T, Rasmussen M, Thygesen LC. Assessing natural direct and indirect effects through multiple pathways. *Am J Epidemiol*. 2014;179(4):513–518.

Supplementary figure 1.1.
Dates of onset of the progressive phase and of inclusion



White regions in histogram bars indicate patients excluded by the requirement for onset of the progressive phase since January 1, 1995, who would otherwise have been included.

Supplementary table 1.1.
Included patients and treating centers, by country

Country	Centers	Patients (n)				
		Total	PPMS-N	PPMS-A	SPMS-N	SPMS-A
IT	11	**1115**	146	235	383	351
CA	6	**605**	178	44	291	92
ES	10	**602**	216	60	175	151
AU	19	**477**	127	100	180	70
TR	7	**384**	36	113	124	111
CZ	2	**332**	5	89	107	131
NL	5	**233**	83	51	65	34
BE	4	**136**	51	32	35	18
PT	2	**71**	11	18	25	17
KW	1	**69**	7	32	28	2
CH	3	**64**	0	42	21	1
US	1	**52**	13	9	24	6
LB	1	**44**	3	23	16	2
TN	1	**44**	1	17	8	18
AR	5	**42**	8	8	19	7
IR	2	**38**	11	27	0	0
GB	3	**26**	14	1	8	3
CU	1	**25**	6	4	12	3
BR	3	**15**	8	3	3	1
SA	1	**12**	2	8	1	1
EG	2	**12**	0	10	0	2
HU	4	**9**	0	2	6	1
OM	2	**9**	0	3	4	2
IL	1	**6**	0	0	1	5
DK	1	**5**	1	1	0	3
IN	2	**4**	1	2	1	0
RO	1	**4**	0	1	3	0
IE	1	**3**	3	0	0	0
GR	1	**2**	1	0	0	1
MT	1	**2**	1	1	0	0
MY	1	**2**	2	0	0	0
MK	1	**2**	0	0	1	1
NZ	1	**1**	0	1	0	0
Total	**107**	**4447**	**935**	**937**	**1541**	**1034**

Each country is indicated by its ISO 3166-1 alpha-2 code.

Supplementary table 1.2.
Relapse characteristics of included patients

	PPMS-A (n = 937 patients)	**SPMS-A** (n = 1034 patients)
Patient characteristics		
Patients with relapse during follow-up; No. (%)	336 (36)	948 (92)
Annualized relapse rate; median [IQR]	0.26 [0.14–0.48]	0.34 [0.19–0.60]
Relapse characteristics (across patients)		
Relapses recorded	743	2117
Relapses with phenotype(s) recorded; No. (% of all relapses)	610 (82)	1759 (83)
Relapse phenotypes; number of relapses (% of relapses with phenotype(s) recorded)		
Pyramidal	450 (74)	1212 (69)
Sensory	206 (34)	575 (33)
Cerebellar	95 (16)	216 (12)
Brainstem	76 (12)	273 (16)
Bowel/Bladder	46 (8)	104 (6)
Visual	56 (9)	107 (6)
Neuropsychology	16 (3)	26 (1)

Annualized relapse rate is calculated for the subset of patients with one or more relapses during follow-up.

Abbreviations: No. = number; IQR = interquartile range.

Supplementary table 1.3.
Andersen-Gill model for hazard of confirmed disability accrual, adjusted for sex and age

Variable	Hazard ratio (95% CI)	*P*
Phenotype, SPMS	0.75 (0.70–0.81)	< .001
Sex, male	1.16 (1.09–1.24)	< .001
Age, at start of epoch	1.00 (0.99–1.00)	.11

Treating center and patient identity were modelled as random effects, with identity nested within center.

Abbreviations: CI = confidence interval.

Supplementary table 1.4.
Andersen-Gill model for hazard of confirmed disability accrual, corrected for proportional hazards violation (EDSS score frequency)

Variable	Hazard ratio (95% CI)	*P*	Schoenfeld residuals *P*
Phenotype, SPMS	0.82 (0.75–0.89)	< .001	.61
3Sex, male	1.19 (1.12–1.28)	< .001	.92
Age, at start of epoch	1.00 (1.00–1.00)	.99	.87
EDSS baseline, at start of epoch	0.96 (0.94–0.99)	.001	.65
DMT, % of epoch on treatment†	0.95 (0.93–0.98)	< .001	.64
IST, % of epoch on treatment†	0.93 (0.90–0.96)	< .001	.19
EDSS score frequency (weeks from onset of the progressive phase)			
0–4 weeks	2.41 (1.84–3.17)	< .001	.14
> 4–8 weeks	1.70 (1.55–1.86)	< .001	
> 8–24 weeks	1.35 (1.29–1.42)	< .001	
> 24 weeks	1.12 (1.10–1.13)	< .001	

The proportional hazards violation for EDSS score frequency was corrected by including a time-dependent coefficient for this covariate, specified by a step function. To facilitate inclusion of time-stratified coefficients, this model omits random effects, and accounts for within-patient correlations by including patient identity as a cluster term to obtain robust variances. For comparison, for the model in the main text comparing SPMS to PPMS without proportional hazards correction (**table 3**), Schoenfeld residuals *P* values are: phenotype, .61; sex, .96; age, .64; EDSS baseline, .68; DMT, .74; IST, .19; EDSS score frequency, < .001.

Abbreviations: CI = confidence interval; EDSS = Expanded Disability Status Scale;
DMT = disease-modifying therapy; IST = immunosuppressant therapy.

† 25% increments.

Supplementary table 1.5.
Andersen-Gill model for hazard of confirmed disability accrual, stratified by phenotype

Variable	PPMS		SPMS	
	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
Sex, male	1.21 (1.10–1.33)	< .001	1.12 (1.01–1.24)	.04
Age, at start of epoch	1.00 (1.00–1.00)	.97	1.00 (0.99–1.00)	.07
EDSS baseline, at start of epoch	0.92 (0.89–0.94)	< .001	0.94 (0.90–0.99)	.01
DMT, % of epoch on treatment†	0.97 (0.94–1.01)	.10	0.98 (0.95–1.01)	.21
IST, % of epoch on treatment†	0.91 (0.87–0.96)	< .001	1.00 (0.95–1.06)	.95
EDSS score freq., during epoch	1.15 (1.13–1.17)	< .001	1.15 (1.12–1.19)	< .001

Treating center and patient identity were modelled as random effects, with identity nested within center.
The proportional hazards assumption was violated for EDSS score frequency.

Abbreviations: CI = confidence interval; EDSS = Expanded Disability Status Scale;
DMT = disease-modifying therapy; IST = immunosuppressant therapy; freq. = frequency.

† 25% increments.

Supplementary table 1.6.
Andersen-Gill model for hazard of confirmed disability accrual, stratified by phenotype, with activity–DMT interaction

Variable	PPMS		SPMS	
	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
Relapse activity	0.96 (0.86–1.09)	.56	0.93 (0.79–1.10)	.41
Sex, male	1.21 (1.10–1.32)	< .001	1.11 (1.00–1.23)	.05
Age, at start of epoch	1.00 (1.00–1.00)	.88	0.99 (0.99–1.00)	.02
EDSS baseline, at start of epoch	0.92 (0.89–0.94)	< .001	0.94 (0.89–0.98)	.006
DMT, % of epoch on treatment†	0.98 (0.93–1.04)	.60	1.00 (0.96–1.04)	.98
IST, % of epoch on treatment†	0.92 (0.88–0.96)	< .001	1.00 (0.95–1.06)	1.00
EDSS score freq., during epoch	1.15 (1.13–1.17)	< .001	1.16 (1.12–1.19)	< .001
Interaction, relapse activity × DMT	0.98 (0.92–1.05)	.60	0.96 (0.90–1.01)	.13

Treating center and patient identity were modelled as random effects, with identity nested within center.
The proportional hazards assumption was violated for EDSS score frequency.

Abbreviations: CI = confidence interval; EDSS = Expanded Disability Status Scale;
DMT = disease-modifying therapy; IST = immunosuppressant therapy; freq. = frequency..

† 25% increments.

Supplementary table 1.7.
Sensitivity analyses—comparison of PPMS and SPMS

Sensitivity analysis (number of patients included)	Confirmed disability accrual		Age, years (95% CI)		
	Hazard ratio (95% CI) SPMS vs. PPMS (reference)	*P*		Onset (median)	Confirmed EDSS ≥ 7 (25th percentile)
Onset since July 1, 2004 (955 PPMS, 2297 SPMS)	0.78 (0.69–0.88)	< .001	**PPMS**	45.3 (44.5–46.2)	66.8 (64.4–70.8)
			SPMS	47.1 (46.6–47.6)	65.8 (63.1–68.4)
EDSS score every ≤ 15 months (1602 PPMS, 2315 SPMS)	0.79 (0.70–0.88)	< .001	**PPMS**	43.9 (43.3–44.5)	59.8 (58.1–61.7)
			SPMS	46.6 (45.9–47.1)	60.7 (58.3–62.8)
365-day EDSS score confirmation (1734 PPMS, 2320 SPMS)	0.86 (0.78–0.94)	.002	**PPMS**	43.9 (43.3–44.4)	60.6 (59.4–62.8)
			SPMS	46.6 (46.0–47.2)	62.6 (60.3–64.2)
Period-specific hazard ratios					
0–5 years from onset (1096 PPMS, 2575 SPMS)	0.88 (0.77–1.01)	.08		--	--
5–10 years from onset (1285 PPMS, 967 SPMS)	0.81 (0.71–0.93)	.002		--	--
10–15 years from onset (938 PPMS, 282 SPMS)	0.78 (0.62–0.97)	.03		--	--
Disability accrual from EDSS 4–5 (876 PPMS, 1585 SPMS)	0.77 (0.69–0.85)	< .001	**PPMS**	44.2 (43.5–45.0)	--
			SPMS	46.6 (45.7–47.2)	--

'Onset' refers to onset of the progressive phase. Disability accrual is assessed from onset of the progressive phase, except in the fifth sensitivity analysis, in which it is assessed from EDSS 4–5. Hazard ratios for confirmed disability accrual are adjusted for sex and (as time-dependent covariates) age at the start of each epoch; EDSS score at the start of each epoch; the proportion of each epoch receiving any disease-modifying therapy; the proportion of each epoch receiving any immunosuppressant therapy; and the annualized frequency of EDSS scores during each epoch. Treating center and patient identity were modelled as random effects, with identity nested within center. The proportional hazards assumption was violated for EDSS score frequency. Ages at onset were estimated using the Kaplan-Meier estimator, and ages at EDSS ≥ 7 using the Turnbull estimator, as for the main analyses.

Abbreviations: CI = confidence interval; EDSS = Expanded Disability Status Scale.

Supplementary table 1.8.
Sensitivity analyses—comparison of PPMS-N, PPMS-A, SPMS-N, and SPMS-A

Sensitivity analysis (number of patients included)	Confirmed disability accrual		
	Hazard ratio (95% CI) vs. PPMS-N (reference)		*P*
Onset since July 1, 2004 (478 PPMS-N, 477 PPMS-A, 1426 SPMS-N, 871 SPMS-A)	PPMS-A	1.04 (0.89–1.21)	.64
	SPMS-N	0.85 (0.73–1.00)	.04
	SPMS-A	0.74 (0.63–0.86)	< .001
EDSS score every ≤ 15 months (773 PPMS-N, 829 PPMS-A, 1345 SPMS-N, 970 SPMS-A)	PPMS-A	1.08 (0.95–1.23)	.23
	SPMS-N	0.88 (0.75–1.02)	.08
	SPMS-A	0.79 (0.68–0.91)	.001
365-day EDSS score confirmation (855 PPMS-N, 879 PPMS-A, 1326 SPMS-N, 994 SPMS-A)	PPMS-A	0.98 (0.88–1.09)	.64
	SPMS-N	0.95 (0.84–1.08)	.46
	SPMS-A	0.77 (0.67–0.87)	< .001
Period-specific hazard ratios			
0–5 years from onset (548 PPMS-N, 548 PPMS-A, 1541 SPMS-N, 1034 SPMS-A)	PPMS-A	0.90 (0.75–1.08)	.26
	SPMS-N	0.92 (0.78–1.10)	.37
	SPMS-A	0.76 (0.63–0.91)	.002
5–10 years from onset (637 PPMS-N, 648 PPMS-A, 420 SPMS-N, 547 SPMS-A)	PPMS-A	1.04 (0.90–1.21)	.59
	SPMS-N	0.85 (0.70–1.03)	.10
	SPMS-A	0.82 (0.68–0.98)	.03
10–15 years from onset (449 PPMS-N, 489 PPMS-A, 92 SPMS-N, 190 SPMS-A)	PPMS-A	0.92 (0.77–1.08)	.30
	SPMS-N	1.03 (0.74–1.43)	.85
	SPMS-A	0.61 (0.45–0.82)	< .001
Disability accrual from EDSS 4–5 (426 PPMS-N, 450 PPMS-A, 932 SPMS-N, 653 SPMS-A)	PPMS-A	1.01 (0.87–1.17)	.91
	SPMS-N	0.81 (0.70–0.94)	0.007
	SPMS-A	0.73 (0.63–0.85)	< .001

'Onset' refers to onset of the progressive phase. Disability accrual is assessed from onset of the progressive phase, except in the fifth sensitivity analysis, in which it is assessed from EDSS 4–5. Hazard ratios for confirmed disability accrual are adjusted for sex and (as time-dependent covariates) age at the start of each epoch; EDSS score at the start of each epoch; the proportion of each epoch receiving any disease-modifying therapy; the proportion of each epoch receiving any immunosuppressant therapy; and the annualized frequency of EDSS scores during each epoch. Treating center and patient identity were modelled as random effects, with identity nested within center. The proportional hazards assumption was violated for EDSS score frequency.

Abbreviations: CI = confidence interval; EDSS = Expanded Disability Status Scale.

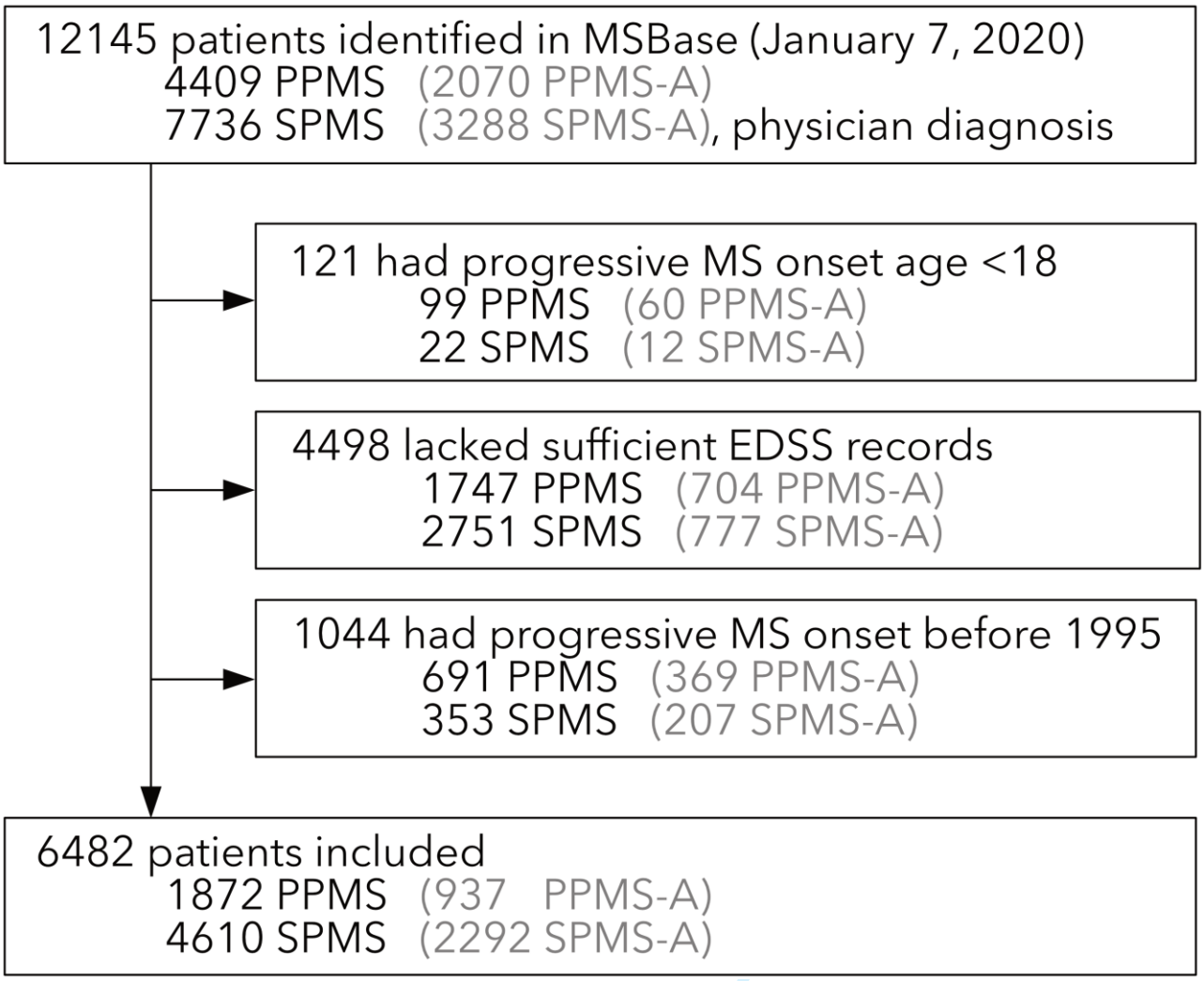
Supplement 2. Alternative analyses: SPMS identified by physician diagnosis (since Jan 1, 1995)

Harding-Forrester S, Roos I, Nguyen A-L, et al. Disability accrual in primary and secondary progressive multiple sclerosis.

Abbreviations

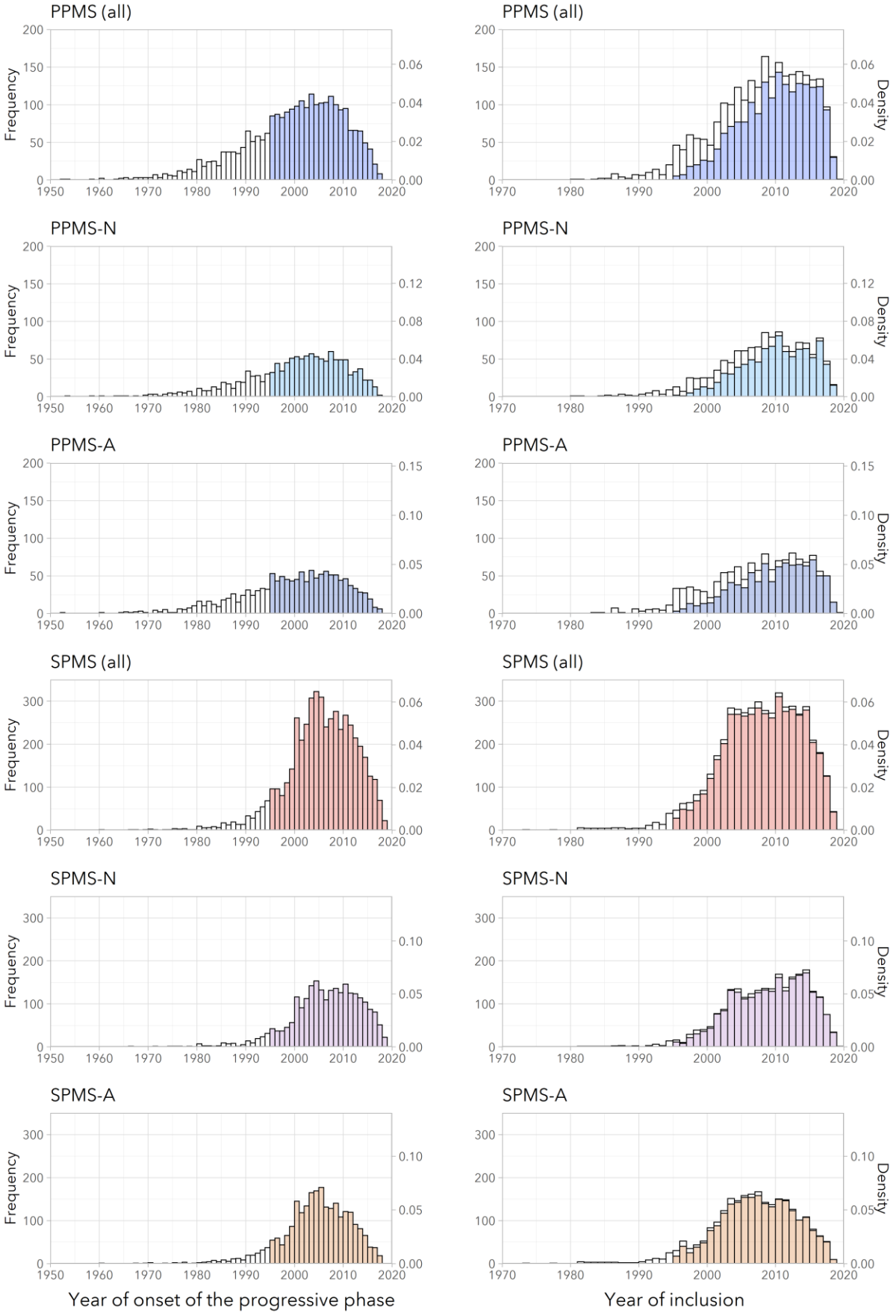
MS = multiple sclerosis
PPMS = primary progressive MS; PPMS-N = PPMS with no superimposed relapse activity; PPMS-A = PPMS with superimposed relapse activity
RRMS = relapsing-remitting MS
SPMS = secondary progressive MS; SPMS-N = SPMS with no superimposed relapse activity; SPMS-A = SPMS with superimposed relapse activity

Supplementary figure 2.1. SPMS identified by physician diagnosis.
Flow diagram of patient inclusion



49730 patients with RRMS, and without a physician diagnosis of SPMS, were excluded.

Supplementary figure 2.2. SPMS identified by physician diagnosis. Dates of onset of the progressive phase and of inclusion



White regions in histogram bars indicate patients excluded by the requirement for onset of the progressive phase since January 1, 1995, who would otherwise have been included.

Supplementary table 2.1. SPMS identified by physician diagnosis. Included patients and treating centers, by country

Country	Centers	Patients (n)				
		Total	PPMS-N	PPMS-A	SPMS-N	SPMS-A
IT	11	**1384**	146	235	407	596
CA	7	**969**	178	44	448	299
AU	21	**793**	127	100	305	261
ES	10	**780**	216	60	254	250
TR	7	**534**	36	113	106	279
NL	6	**370**	83	51	103	133
CZ	2	**335**	5	89	111	130
US	2	**295**	13	9	194	79
BE	3	**227**	51	32	72	72
KW	1	**127**	7	32	70	18
PT	2	**111**	11	18	46	36
LB	1	**99**	3	23	45	28
CH	3	**99**	0	42	37	20
TN	1	**60**	1	17	19	23
GB	3	**53**	14	1	29	9
AR	5	**49**	8	8	21	12
EG	3	**39**	0	10	8	21
IR	2	**38**	11	27	0	0
CU	1	**27**	6	4	12	5
BR	2	**18**	8	3	6	1
IE	1	**16**	3	0	10	3
SA	1	**15**	2	8	2	3
OM	2	**9**	0	3	4	2
IN	2	**8**	1	2	3	2
IL	1	**7**	0	0	2	5
DK	1	**5**	1	1	0	3
RO	1	**4**	0	1	2	1
MT	1	**3**	1	1	0	1
HU	1	**3**	0	2	1	0
MY	1	**2**	2	0	0	0
NZ	2	**2**	0	1	1	0
GR	1	**1**	1	0	0	0
Total	**108**	**6482**	**935**	**937**	**2318**	**2292**

Each country is indicated by its ISO 3166-1 alpha-2 code.

Supplementary table 2.2. SPMS identified by physician diagnosis. Clinical characteristics of included patients

Characteristics	PPMS (all)	PPMS-N	PPMS-A	SPMS (all)	SPMS-N	SPMS-A
Patients	**1872**	935	937	**4610**	2318	2292
Sex, male (%)	**878 (47)**	442 (47)	436 (47)	**1485 (32)**	770 (33)	715 (31)
Age, MS onset	**43.5 ± 10.5**	45.6 ± 9.8	41.5 ± 10.7	**31.9 ± 10.2**	32.9 ± 10.6	30.9 ± 9.8
Age, progressive phase	**43.5 ± 10.5**	45.6 ± 9.8	41.5 ± 10.7	**46.4 ± 10.4**	48.5 ± 10.5	44.3 ± 9.7
Age, inclusion	**48.7 ± 10.8**	50.7 ± 10.1	46.7 ± 11.2	**48.3 ± 10.5**	50.4 ± 10.6	46.2 ± 9.9
Time, MS onset to inclusion; years	**4.1 [2.0–7.3]**	4.1 [2.1–7.3]	4.1 [1.9–7.3]	**15.0 [9.2–22.1]**	16.0 [9.9–23.7]	14.0 [8.6–20.3]
Time, follow-up; years	**4.2 [1.9–7.9]**	3.8 [1.7–7.5]	4.4 [2.1–8.2]	**5.1 [2.3–8.9]**	4.1 [1.9–7.3]	6.5 [3.0–10.3]
EDSS score frequency, annualized	**1.53 [1.00–2.28]**	1.37 [0.92–2.10]	1.68 [1.12–2.44]	**1.44 [0.95–2.10]**	1.30 [0.86–1.95]	1.59 [1.06–2.27]
Disability at inclusion; EDSS	**4.0 [3.0–6.0]**	4.0 [3.0–6.0]	4.0 [3.0–6.0]	**5.5 [4.0–6.5]**	6.0 [4.0–6.5]	5.5 [4.0–6.0]
Disability at censoring; EDSS	**6.0 [4.5–6.5]**	6.0 [4.5–6.5]	6.0 [4.0–6.5]	**6.5 [5.5–7.0]**	6.5 [5.5–7.0]	6.5 [5.5–7.0]
Disability increase, annualized; EDSS	**0.15 [0.00–0.38]**	0.15 [0.00–0.37]	0.15 [0.00–0.39]	**0.08 [0.00–0.24]**	0.02 [0.00–0.24]	0.10 [0.00–0.24]
Deaths recorded, from any cause (%)	**59 (3)**	33 (4)	26 (3)	**212 (5)**	127 (5)	85 (4)
Relapses during follow-up						
Patients (%)	**336 (18)**	0 (0)	336 (36)	**1744 (38)**	0 (0)	1744 (76)
Annualized relapse rate	**0.26 [0.14–0.48]**	NA	0.26 [0.14–0.48]	**0.27 [0.14–0.52]**	NA	0.27 [0.14–0.52]
Cerebrospinal fluid oligoclonal bands; patients (%)						
Present	**1149 (61)**	546 (58)	603 (64)	**2124 (46)**	986 (43)	1138 (50)
Absent	**89 (5)**	46 (5)	43 (5)	**102 (2)**	42 (2)	60 (3)
Not assessed	**634 (34)**	343 (37)	291 (31)	**2384 (52)**	1290 (56)	1094 (48)
Disease-modifying therapy, proportion of follow-up receiving treatment; patients (%)						
0%	**1104 (59)**	652 (70)	452 (48)	**1623 (35)**	1001 (43)	622 (27)
> 0–25%	**221 (12)**	105 (11)	116 (12)	**549 (12)**	235 (10)	314 (14)
> 25–50%	**144 (8)**	46 (5)	98 (10)	**401 (9)**	161 (7)	240 (10)
> 50–75%	**106 (6)**	36 (4)	70 (7)	**384 (8)**	137 (6)	247 (11)
> 75%	**297 (16)**	96 (10)	201 (21)	**1653 (36)**	784 (34)	869 (38)
Disease-modifying therapy, exposure to specific agents during follow-up; patients (%)						
Interferon beta	**318 (17)**	85 (9)	233 (25)	**1787 (39)**	728 (31)	1059 (46)
Glatiramer acetate	**154 (8)**	46 (5)	108 (12)	**687 (15)**	260 (11)	427 (19)
Fingolimod	**118 (6)**	39 (4)	79 (8)	**483 (10)**	169 (7)	314 (14)
Teriflunomide	**28 (1)**	7 (1)	21 (2)	**146 (3)**	56 (2)	90 (4)
Dimethyl fumarate	**24 (1)**	8 (1)	16 (2)	**162 (4)**	62 (3)	100 (4)
Cladribine	**2 (0)**	0 (0)	2 (0)	**36 (1)**	10 (0)	26 (1)
Mitoxantrone	**91 (5)**	29 (3)	62 (7)	**507 (11)**	168 (7)	339 (15)
Natalizumab	**83 (4)**	27 (3)	56 (6)	**457 (10)**	182 (8)	275 (12)
Alemtuzumab	**12 (1)**	3 (0)	9 (1)	**44 (1)**	10 (0)	34 (1)
Daclizumab	**1 (0)**	0 (0)	1 (0)	**1 (0)**	1 (0)	0 (0)
Rituximab	**62 (3)**	16 (2)	46 (5)	**108 (2)**	57 (2)	51 (2)
Ocrelizumab	**169 (9)**	90 (10)	79 (8)	**83 (2)**	39 (2)	44 (2)
Siponimod	**0 (0)**	0 (0)	0 (0)	**10 (0)**	8 (0)	2 (0)
ASCT	**4 (0)**	0 (0)	4 (0)	**22 (0)**	12 (1)	10 (0)
Immunosuppressant therapy, exposure to specific agents during follow-up; patients (%)						
Azathioprine	**233 (12)**	61 (7)	172 (18)	**493 (11)**	157 (7)	336 (15)
Methotrexate	**121 (6)**	41 (4)	80 (9)	**275 (6)**	86 (4)	189 (8)
Cyclophosphamide	**94 (5)**	26 (3)	68 (7)	**244 (5)**	79 (3)	165 (7)
Mycophenolate mofetil	**5 (0)**	2 (0)	3 (0)	**22 (0)**	11 (0)	11 (0)
Pregnancy during follow-up						
Patients (%)	**15 (1)**	2 (0)	13 (1)	**36 (1)**	8 (0)	28 (1)

Values are number (%), mean ± standard deviation, or median [interquartile range]. Patients classified as having PPMS-A include all eligible patients with a recorded diagnosis of progressive-relapsing MS (n = 540 patients; 58%). Patients classified as having SPMS under physician diagnosis include 2458 patients (53%) with SPMS under the operationalized diagnostic criteria. Annualized relapse rate is calculated for the subset of patients with one or more relapses during follow-up. Abbreviations: EDSS = Expanded Disability Status Scale; ASCT = autologous stem-cell transplant, assumed effective for 5 years.

Supplementary table 2.3. SPMS identified by physician diagnosis. Relapse characteristics of included patients

	PPMS-A (n = 937 patients)	**SPMS-A** (n = 2292 patients)
Patient characteristics		
Patients with relapse during follow-up; No. (%)	336 (36)	1744 (76)
Annualized relapse rate; median [IQR]	0.26 [0.14–0.48]	0.27 [0.14–0.52]
Relapse characteristics (across patients)		
Relapses recorded	743	4096
Relapses with phenotype(s) recorded; No. (% of all relapses)	610 (82)	3206 (78)
Relapse phenotypes; number of relapses (% of relapses with phenotype(s) recorded)		
Pyramidal	450 (74)	2200 (69)
Sensory	206 (34)	1026 (32)
Cerebellar	95 (16)	430 (13)
Brainstem	76 (12)	461 (14)
Bowel/Bladder	46 (8)	224 (7)
Visual	56 (9)	242 (8)
Neuropsychology	16 (3)	64 (2)

Annualized relapse rate is calculated for the subset of patients with one or more relapses during follow-up.

Abbreviations: No. = number; IQR = interquartile range.

Supplementary table 2.4. SPMS identified by physician diagnosis. Ages at onset of the progressive phase and at confirmed EDSS ≥ 7

Phenotype	All patients	Female	Male
Age at onset of the progressive phase (median), years (95% CI)			
PPMS	**43.9 (43.3–44.4)**	**44.4 (43.8–45.2)**	**43.0 (42.3–44.0)**
PPMS-N	46.0 (45.2–46.8)	46.5 (45.3–47.7)	45.5 (44.5–46.7)
PPMS-A	41.9 (40.7–42.6)	42.8 (42.0–43.7)	40.0 (38.6–41.8)
SPMS	**46.3 (45.8–46.7)**	**46.8 (46.3–47.4)**	**45.0 (44.3–45.8)**
SPMS-N	48.4 (47.8–49.1)	48.9 (48.3–49.8)	47.3 (46.2–48.4)
SPMS-A	44.2 (43.7–44.8)	44.8 (44.3–45.5)	43.0 (42.1–43.8)
Age at confirmed EDSS ≥ 7 (25th percentile), years (95% CI)			
PPMS	**60.3 (58.8–62.5)**	**63.4 (60.5–66.2)**	**58.1 (56.6–60.1)**
PPMS-N	62.5 (60.1–65.8)	66.0 (62.5–68.7)	60.1 (57.3–62.7)
PPMS-A	57.6 (55.4–60.9)	60.9 (56.3–65.3)	55.8 (52.8–58.6)
SPMS	**54.4 (53.7–55.2)**	**55.1 (54.1–56.1)**	**53.1 (50.8–54.5)**
SPMS-N	55.4 (54.1–56.8)	55.7 (54.1–57.1)	54.8 (52.2–57.5)
SPMS-A	53.7 (52.4–54.8)	54.7 (53.5–55.8)	51.2 (49.2–53.4)

Ages at onset of the progressive phase (Kaplan-Meier estimator; log-rank test) were younger in PPMS versus SPMS ($P < .001$), in subgroups with activity (-A) versus those without (-N) ($P < .001$ in both PPMS and SPMS), and in males versus females ($P = .22$ in PPMS, $P = .02$ in SPMS). Ages at confirmed EDSS ≥ 7 (Turnbull estimator; generalized log-rank test) were younger in SPMS versus PPMS ($P < .001$; among females, $P < .001$; among males, $P = .002$; among patients with activity, $P < .001$; without activity, $P < .001$), and younger in patients with activity than in those without (PPMS-A vs. PPMS-N, $P = .002$; SPMS-A vs. SPMS-N, $P = .004$).

Abbreviations: CI = confidence interval; EDSS = Expanded Disability Status Scale.

Supplementary table 2.5. SPMS identified by physician diagnosis. Andersen-Gill model for hazard of confirmed disability accrual, adjusted for sex and age

Variable	Hazard ratio (95% CI)	*P*
Phenotype, SPMS	0.77 (0.73–0.82)	< .001
Sex, male	1.12 (1.07–1.18)	< .001
Age, at start of epoch	0.99 (0.99–1.00)	< .001

Treating center and patient identity were modelled as random effects, with identity nested within center.

Abbreviations: CI = confidence interval.

Supplementary table 2.6. SPMS identified by physician diagnosis. Andersen-Gill models for hazard of confirmed disability accrual, fully adjusted

Variable	Hazard ratio (95% CI)	*P*
Model comparing SPMS to PPMS (reference)		
Phenotype, SPMS	0.89 (0.83–0.95)	< .001
Sex, male	1.12 (1.06–1.18)	< .001
Age, at start of epoch	1.00 (0.99–1.00)	.002
EDSS baseline, at start of epoch	0.89 (0.87–0.90)	< .001
DMT, % of epoch on treatment†	1.01 (0.99–1.02)	.56
IST, % of epoch on treatment†	0.98 (0.95–1.01)	.14
EDSS score freq., during epoch	1.07 (1.06–1.08)	< .001
Model comparing PPMS-A, SPMS-N, and SPMS-A to PPMS-N (reference)		
Phenotype		
PPMS-A	0.92 (0.83–1.02)	.11
SPMS-N	0.86 (0.79–0.94)	.001
SPMS-A	0.85 (0.78–0.93)	< .001
Sex, male	1.11 (1.05–1.18)	< .001
Age, at start of epoch	1.00 (0.99–1.00)	.001
EDSS baseline, at start of epoch	0.89 (0.87–0.90)	< .001
DMT, % of epoch on treatment†	1.01 (0.99–1.02)	.45
IST, % of epoch on treatment†	0.98 (0.95–1.01)	.17
EDSS score freq., during epoch	1.07 (1.06–1.08)	< .001

Treating center and patient identity were modelled as random effects, with identity nested within center.
The proportional hazards assumption was violated for EDSS score frequency.

Abbreviations: CI = confidence interval; EDSS = Expanded Disability Status Scale;
DMT = disease-modifying therapy; IST = immunosuppressant therapy; freq. = frequency.

† 25% increments.

Supplementary table 2.7. SPMS identified by physician diagnosis. Andersen-Gill model for hazard of confirmed disability accrual, stratified by phenotype

Variable	PPMS		SPMS	
	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
Sex, male	1.21 (1.10–1.33)	< .001	1.07 (0.99–1.14)	.07
Age, at start of epoch	1.00 (1.00–1.00)	.97	0.99 (0.99–1.00)	< .001
EDSS baseline, at start of epoch	0.92 (0.89–0.94)	< .001	0.87 (0.85–0.89)	< .001
DMT, % of epoch on treatment†	0.97 (0.94–1.01)	.10	1.02 (1.00–1.04)	.11
IST, % of epoch on treatment†	0.91 (0.87–0.96)	< .001	1.01 (0.98–1.04)	.58
EDSS score freq., during epoch	1.15 (1.13–1.17)	< .001	1.05 (1.03–1.07)	< .001

Treating center and patient identity were modelled as random effects, with identity nested within center.
The proportional hazards assumption was violated for EDSS score frequency.

Abbreviations: CI = confidence interval; EDSS = Expanded Disability Status Scale;
DMT = disease-modifying therapy; IST = immunosuppressant therapy; freq. = frequency.

† 25% increments.

Supplementary table 2.8. SPMS identified by physician diagnosis. Andersen-Gill model for hazard of confirmed disability accrual, stratified by phenotype, with activity–DMT interaction

Variable	PPMS		SPMS	
	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
Relapse activity	0.96 (0.86–1.09)	.56	1.10 (1.00–1.21)	.05
Sex, male	1.21 (1.10–1.32)	< .001	1.06 (0.99–1.14)	.10
Age, at start of epoch	1.00 (1.00–1.00)	.88	0.99 (0.99–1.00)	< .001
EDSS baseline, at start of epoch	0.92 (0.89–0.94)	< .001	0.86 (0.84–0.88)	< .001
DMT, % of epoch on treatment†	0.98 (0.93–1.04)	.60	1.06 (1.03–1.09)	< .001
IST, % of epoch on treatment†	0.92 (0.88–0.96)	< .001	1.01 (0.97–1.04)	.66
EDSS score freq., during epoch	1.15 (1.13–1.17)	< .001	1.05 (1.03–1.07)	< .001
Interaction, relapse activity × DMT	0.98 (0.92–1.05)	.60	0.93 (0.90–0.97)	< .001

Treating center and patient identity were modelled as random effects, with identity nested within center.
The proportional hazards assumption was violated for EDSS score frequency.

Abbreviations: CI = confidence interval; EDSS = Expanded Disability Status Scale;
DMT = disease-modifying therapy; IST = immunosuppressant therapy; freq. = frequency.

† 25% increments.

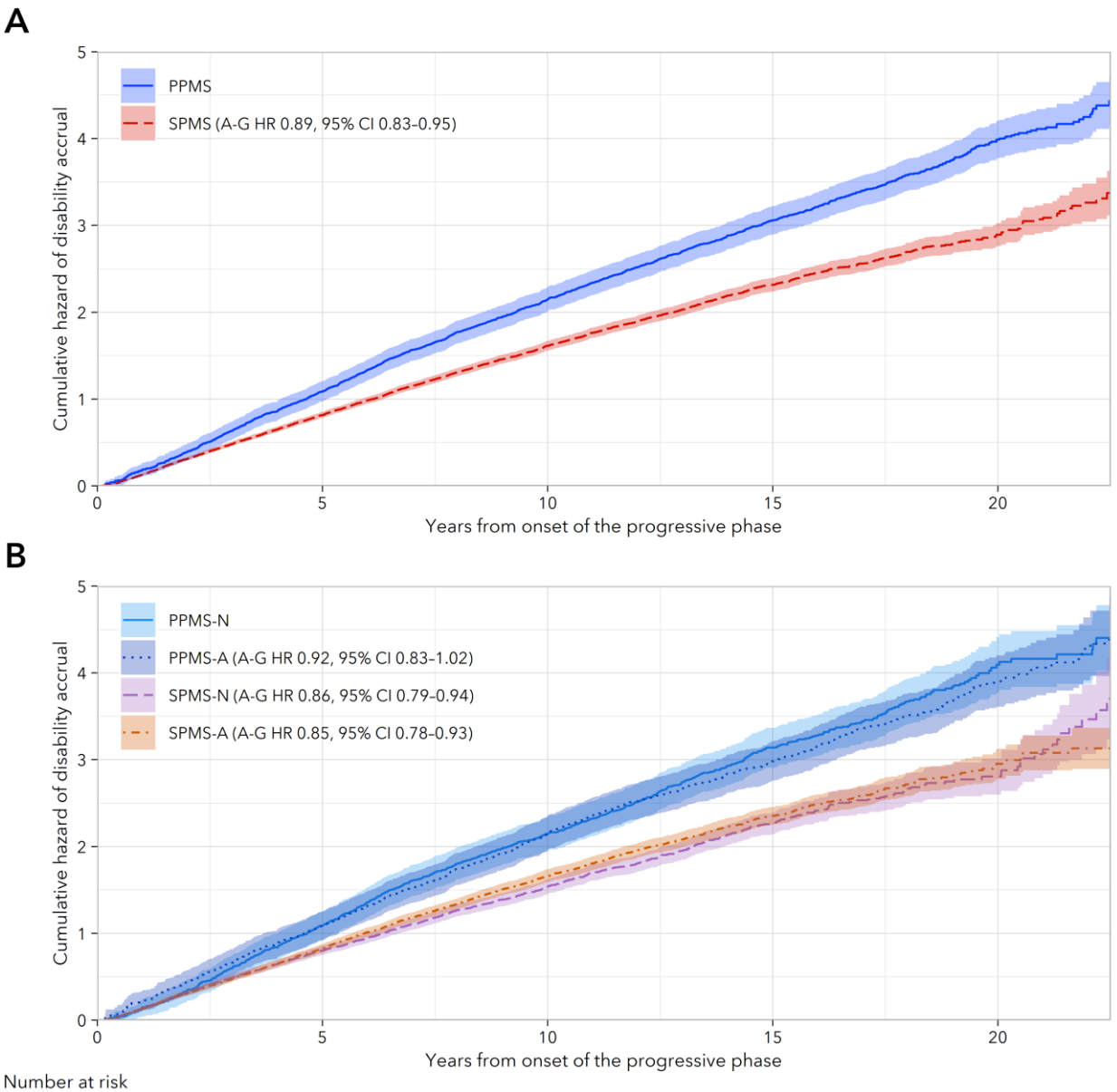
Supplementary table 2.9. SPMS identified by physician diagnosis. Ages at onset of the progressive phase and at confirmed EDSS scores, by time period

	Median age at progressive multiple sclerosis milestones, years (95% CI)			
	Onset	**EDSS ≥ 4**	**EDSS ≥ 6**	**EDSS ≥ 7**
Complete dataset (1995–2020)				
PPMS (*n* = 1872)	**43.9 (43.3–44.4)**	**50.4 (49.6–51.1)**	**56.9 (55.8–57.4)**	**72.8 (70.8–76.4)**
PPMS-N (*n* = 935)	46.0 (45.2–46.8)	51.9 (50.8–53.2)	57.5 (56.9–59.0)	75.4 (71.0–NA)
PPMS-A (*n* = 937)	41.9 (40.7–42.6)	47.7 (46.2–49.6)	54.8 (53.6–56.6)	70.8 (68.9–NA)
SPMS (*n* = 4610)	**46.3 (45.8–46.7)**	**43.6 (43.0–44.2)**	**50.4 (50.0–50.8)**	**69.3 (67.5–70.6)**
SPMS-N (*n* = 2318)	48.4 (47.8–49.1)	45.8 (44.9–46.5)	51.9 (51.3–52.5)	71.3 (70.0–73.3)
SPMS-A (*n* = 2292)	44.2 (43.7–44.8)	41.8 (41.2–42.5)	48.8 (47.9–49.8)	66.9 (65.4–69.3)
1995–2003				
PPMS (*n* = 125)	**41.9 (39.3–44.9)**	**47.0 (45.8–50.9)**	**51.9 (50.0–55.2)**	**60.6 (56.0–65.0)**
PPMS-N (*n* = 56)	44.5 (41.5–48.7)	50.7 (47.9–53.5)	54.3 (51.0–57.5)	62.2 (56.0–68.5)
PPMS-A (*n* = 69)	41.0 (37.5–43.7)	44.4 (43.3–50.8)	47.6 (46.2–54.5)	58.8 (55.0–65.4)
SPMS (*n* = 511)	**44.9 (44.1–46.3)**	**42.0 (40.9–43.6)**	**47.1 (46.2–48.1)**	**56.4 (55.2–57.5)**
SPMS-N (*n* = 183)	48.8 (47.1–50.6)	45.1 (42.0–47.4)	48.2 (46.1–51.5)	57.5 (57.1–60.9)
SPMS-A (*n* = 328)	43.8 (42.7–44.7)	41.2 (39.6–42.5)	46.5 (45.8–47.9)	55.4 (54.2–56.6)
2004–2011				
PPMS (*n* = 266)	**44.4 (43.3–45.9)**	**49.3 (46.6–50.8)**	**53.4 (52.2–56.9)**	**65.1 (62.4–NA)**
PPMS-N (*n* = 132)	46.5 (44.5–48.3)	50.5 (48.3–52.5)	54.8 (52.4–57.3)	67.5 (60.0–NA)
PPMS-A (*n* = 134)	42.8 (40.6–44.5)	46.4 (45.1–49.7)	53.0 (50.2–59.0)	65.1 (62.4–NA)
SPMS (*n* = 1269)	**47.3 (46.6–48.1)**	**44.6 (43.6–45.5)**	**50.8 (50.2–51.7)**	**64.2 (62.3–66.2)**
SPMS-N (*n* = 575)	49.7 (48.7–50.9)	46.6 (45.9–48.2)	52.0 (51.3–53.5)	65.9 (62.9–70.8)
SPMS-A (*n* = 694)	45.0 (44.2–46.0)	43.0 (42.1–44.1)	50.0 (48.4–50.7)	62.1 (60.8–64.6)
2012–2020 (ending January 7, 2020)				
PPMS (*n* = 250)	**47.6 (45.9–49.8)**	**54.2 (52.6–59.1)**	**63.3 (61.1–70.6)**	**80.8 (NA–NA)**
PPMS-N (*n* = 129)	48.3 (47.2–51.5)	57.8 (52.6–60.8)	64.8 (60.8–NA)	NA (71.9–NA)
PPMS-A (*n* = 121)	45.5 (42.8–50.2)	54.2 (50.3–58.7)	62.3 (58.8–NA)	80.8 (NA–NA)
SPMS (*n* = 912)	**47.5 (46.6–48.4)**	**44.6 (43.5–45.9)**	**52.7 (51.5–54.1)**	**87.8 (NA–NA)**
SPMS-N (*n* = 582)	48.8 (47.7–49.8)	46.4 (44.6–47.9)	53.9 (52.6–56.0)	87.8 (NA–NA)
SPMS-A (*n* = 330)	45.5 (43.7–46.6)	42.2 (41.0–44.3)	50.1 (48.8–52.7)	75.7 (NA–NA)

Median ages at onset of the progressive phase (Kaplan-Meier estimator) and at confirmed EDSS scores **≥** 4, 6, and 7 (Turnbull estimator), for the complete dataset and for three constituent time periods. Analyses for each time period include only those patients with onset of PPMS or (physician-diagnosed) SPMS during that period, and only EDSS scores recorded by the end of that period (such that the combined number of patients across the three periods is less than the total number of patients in the complete dataset). Note that in some cases data were insufficient for complete Turnbull estimates of the median ages at EDSS **≥** 6 or 7.

Abbreviations: CI = confidence interval; EDSS = Expanded Disability Status Scale.

Supplementary figure 2.3. SPMS identified by physician diagnosis. Nelson-Aalen cumulative hazard curves for confirmed disability accrual



Number at risk

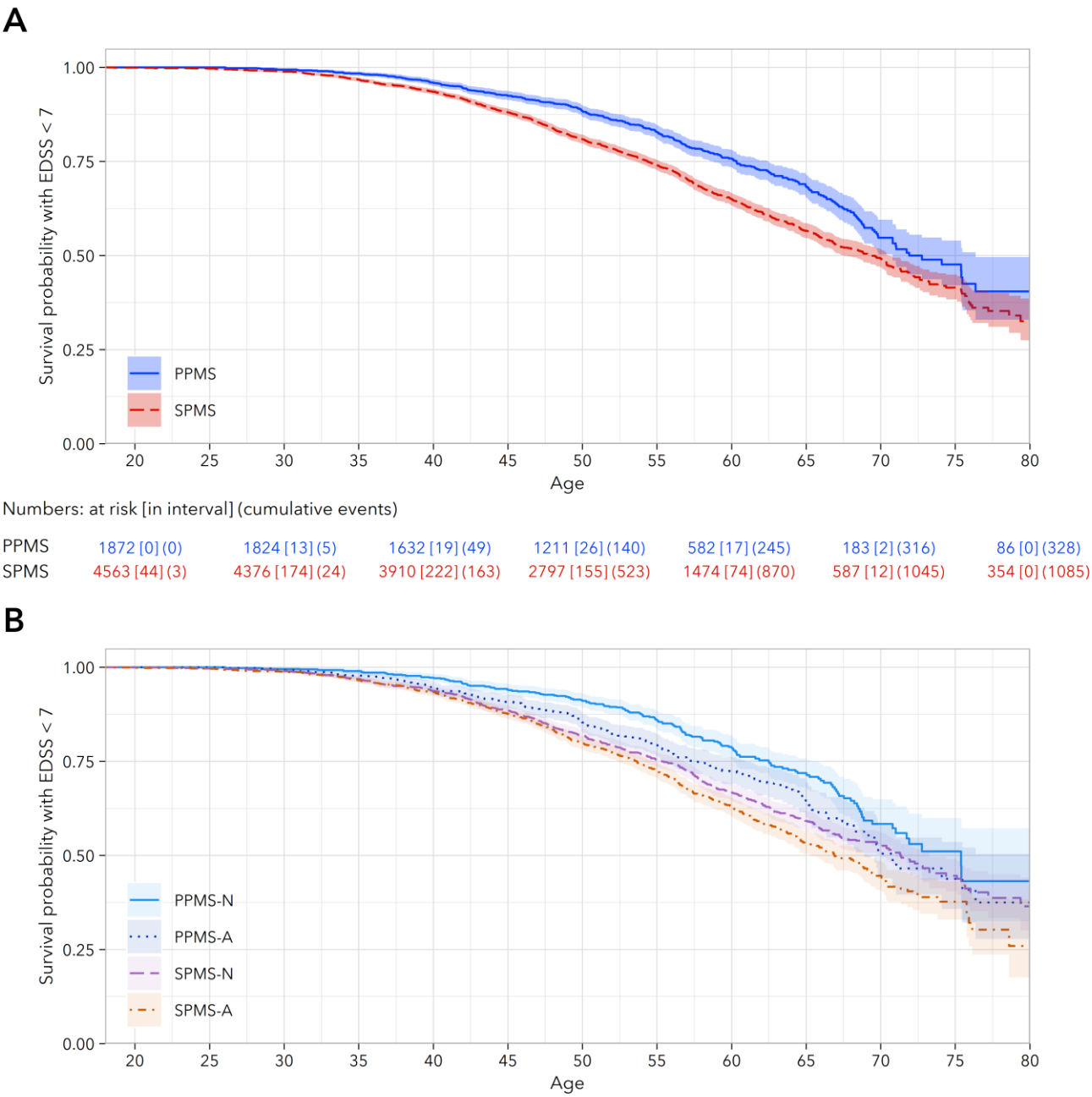
PPMS-N	24	260	384	375	315	262	163	91	31	10
PPMS-A	14	278	409	411	339	269	184	115	55	8
SPMS-N	934	1294	1017	720	478	311	165	84	30	7
SPMS-A	805	1494	1410	1133	813	508	282	145	52	8

Cumulative exits (events)

PPMS-N	0 (0)	38 (67)	164 (274)	336 (505)	486 (657)	607 (800)	740 (904)	834 (956)	902 (988)	925 (994)
PPMS-A	0 (0)	30 (88)	139 (274)	299 (494)	448 (697)	598 (834)	719 (919)	808 (984)	880 (1025)	929 (1039)
SPMS-N	0 (0)	487 (552)	990 (1011)	1417 (1343)	1738 (1555)	1956 (1690)	2117 (1780)	2224 (1818)	2284 (1832)	2311 (1846)
SPMS-A	0 (0)	231 (553)	584 (1190)	996 (1746)	1381 (2141)	1730 (2373)	1989 (2508)	2143 (2573)	2240 (2598)	2284 (2604)

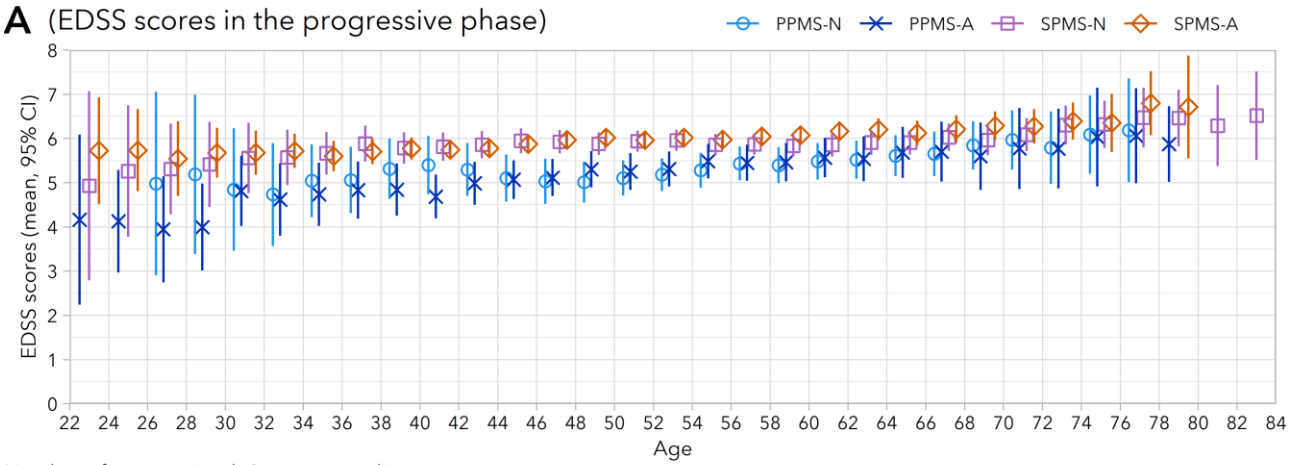
(**A**) PPMS and SPMS. (**B**) PPMS-N, PPMS-A, SPMS-N, and SPMS-A. The cumulative hazard indicates the expected number of confirmed disability accrual events for a patient observed for a given duration of time. Shaded regions indicate 95% confidence intervals. A-G HR = adjusted hazard ratio obtained with the Andersen-Gill model (see **supplementary table 2.6**); CI = confidence interval.

Supplementary figure 2.4. SPMS identified by physician diagnosis. Turnbull survival curves for confirmed EDSS ≥ 7 (wheelchair dependence)



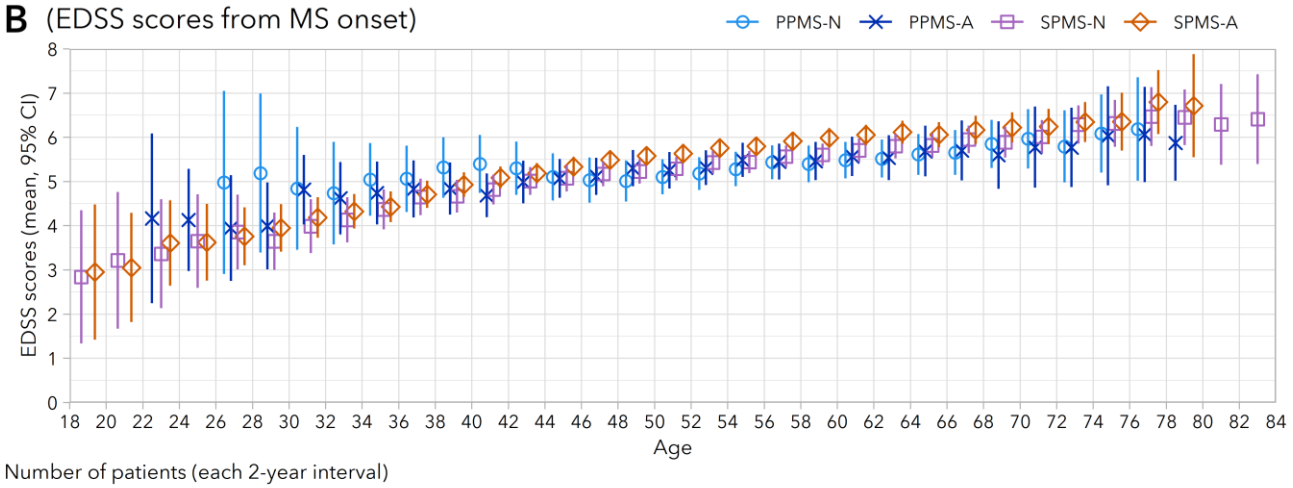
(**A**) PPMS and SPMS. (**B**) PPMS-N, PPMS-A, SPMS-N, and SPMS-A. Patients who entered observation having already reached confirmed EDSS ≥ 7 are analyzed as interval-censored observations, with EDSS ≥ 7 reached in the interval (date of MS onset, date of first observation] (*n* = 37 PPMS-N, 43 PPMS-A, 227 SPMS-N, 107 SPMS-A). Among patients with SPMS, 120 reached EDSS ≥ 7 at the date of onset of the progressive phase (93 SPMS-N, 27 SPMS-A); 75 reached EDSS ≥ 7 prior to the progressive phase (50 SPMS-N, 25 SPMS-A). *P* values (generalized log-rank tests): SPMS vs. PPMS, $P < .001$; SPMS-N vs. PPMS-N, $P < .001$; SPMS-A vs. PPMS-A, $P < .001$; PPMS-A vs. PPMS-N, $P = .002$; SPMS-A vs. SPMS-N, $P = .004$. Values in the risk table indicate the number of patients at risk at each age; the number of interval-censored patients with an interval including that age (square brackets); and the cumulative number of patients having reached confirmed EDSS ≥ 7 at that age (curved brackets). Shaded regions indicate 95% confidence intervals. EDSS = Expanded Disability Status Scale.

Supplementary figure 2.5. SPMS identified by physician diagnosis. Mean EDSS trajectories in PPMS-N, PPMS-A, SPMS-N, and SPMS-A



Number of patients (each 2-year interval)

PPMS-N	1	6	13	17	29	39	65	81	100	111	130	169	185	216	258	282	279	276	253	231	212	185	147	115	78	51	32	20	10	5	2
PPMS-A	12	27	43	61	77	91	111	135	151	194	216	228	237	245	253	258	241	233	221	189	145	121	100	69	49	44	23	16	12	6	1
SPMS-N	11	21	33	44	68	108	154	194	253	309	399	457	522	576	608	647	624	647	599	556	482	428	354	275	203	154	100	69	42	18	13
SPMS-A	21	34	56	86	137	205	285	370	475	581	651	720	750	768	800	805	751	697	646	555	450	364	287	212	148	89	55	31	21	10	5



Number of patients (each 2-year interval)

PPMS-N	0	1	1	6	13	17	29	39	65	81	100	111	130	169	185	216	258	282	279	276	253	231	212	185	147	115	78	51	32	20	10	5	2
PPMS-A	2	6	12	27	43	61	77	91	111	135	151	194	216	228	237	245	253	258	241	233	221	189	145	121	100	69	49	44	23	16	12	6	1
SPMS-N	11	23	41	62	96	145	177	248	314	362	443	512	600	675	737	764	795	803	760	755	679	612	519	462	375	287	213	157	101	70	43	18	14
SPMS-A	26	36	67	99	150	217	297	395	496	595	693	779	855	899	920	931	907	896	812	744	675	584	468	377	293	217	151	91	55	31	21	10	5

Mean EDSS scores by age in PPMS-N, PPMS-A, SPMS-N, and SPMS-A, (**A**) for study-eligible EDSS scores, starting from onset of the progressive phase. (**B**) for all available EDSS scores, starting from MS onset (including RRMS). Mean scores are plotted for each 2-year age interval, for groups with 10 or more patients contributing data in that interval. Error bars indicate 95% confidence intervals. EDSS = Expanded Disability Status Scale.

Supplementary table 2.10. SPMS identified by physician diagnosis. Sensitivity analyses—comparison of PPMS and SPMS

Sensitivity analysis (number of patients included)	Confirmed disability accrual		Age, years (95% CI)		
	Hazard ratio (95% CI) SPMS vs. PPMS (reference)	*P*		Onset (median)	Confirmed EDSS ≥ 7 (25th percentile)
Onset since July 1, 2004 (955 PPMS, 2864 SPMS)	0.85 (0.77–0.93)	< .001	**PPMS**	45.3 (44.5–46.2)	66.8 (64.4–70.8)
			SPMS	47.2 (46.6–47.6)	58.3 (57.0–60.2)
EDSS score every ≤ 15 months (1602 PPMS, 3881 SPMS)	0.84 (0.77–0.91)	< .001	**PPMS**	43.9 (43.3–44.5)	59.8 (58.1–61.7)
			SPMS	46.1 (45.7–46.6)	54.1 (53.2–55.0)
365-day EDSS score confirmation (1734 PPMS, 4328 SPMS)	0.90 (0.84–0.97)	.005	**PPMS**	43.9 (43.3–44.4)	60.6 (59.4–62.8)
			SPMS	46.3 (45.8–46.8)	54.9 (54.0–55.8)
Period-specific hazard ratios					
0–5 years from onset (1096 PPMS, 4001 SPMS)	0.91 (0.85–1.08)	.51		--	--
5–10 years from onset (1285 PPMS, 2836 SPMS)	0.83 (0.73–0.92)	< .001		--	--
10–15 years from onset (938 PPMS, 1491 SPMS)	0.84 (0.73–0.96)	.003		--	--
Disability accrual from EDSS 4–5 (876 PPMS, 1639 SPMS)	0.84 (0.77–0.92)	< .001	**PPMS**	44.2 (43.5–45.0)	65.8 (63.7–68.2)
			SPMS	46.1 (45.4–46.8)	65.9 (64.1–70.4)

'Onset' refers to onset of the progressive phase. Disability accrual is assessed from onset of the progressive phase, except in the fifth sensitivity analysis, in which it is assessed from EDSS 4–5. Hazard ratios for confirmed disability accrual are adjusted for sex and (as time-dependent covariates) age at the start of each epoch; EDSS score at the start of each epoch; the proportion of each epoch receiving any disease-modifying therapy; the proportion of each epoch receiving any immunosuppressant therapy; and the annualized frequency of EDSS scores during each epoch. Treating center and patient identity were modelled as random effects, with identity nested within center. The proportional hazards assumption was violated for EDSS score frequency. Ages at onset were estimated using the Kaplan-Meier estimator, and ages at EDSS ≥ 7 using the Turnbull estimator, as for the main analyses.

Abbreviations: CI = confidence interval; EDSS = Expanded Disability Status Scale.

Supplementary table 2.11. SPMS identified by physician diagnosis. Sensitivity analyses—comparison of PPMS-N, PPMS-A, SPMS-N, and SPMS-A

Sensitivity analysis (number of patients included)	Confirmed disability accrual		
	Hazard ratio (95% CI) vs. PPMS-N (reference)		*P*
Onset since July 1, 2004 (478 PPMS-N, 477 PPMS-A, 1534 SPMS-N, 1330 SPMS-A)	PPMS-A	0.98 (0.84–1.13)	.75
	SPMS-N	0.86 (0.75–0.98)	.02
	SPMS-A	0.82 (0.72–0.94)	.004
EDSS score every ≤ 15 months (773 PPMS-N, 829 PPMS-A, 1869 SPMS-N, 2012 SPMS-A)	PPMS-A	0.98 (0.87–1.11)	.80
	SPMS-N	0.85 (0.75–0.95)	.006
	SPMS-A	0.82 (0.73–0.92)	< .001
365-day EDSS score confirmation (855 PPMS-N, 879 PPMS-A, 2135 SPMS-N, 2193 SPMS-A)	PPMS-A	0.91 (0.82–1.01)	.09
	SPMS-N	0.88 (0.79–0.97)	.008
	SPMS-A	0.85 (0.77–0.94)	< .001
Period-specific hazard ratios			
0–5 years from onset (548 PPMS-N, 548 PPMS-A, 2007 SPMS-N, 1994 SPMS-A)	PPMS-A	0.84 (0.66–1.02)	.06
	SPMS-N	0.91 (0.76–1.07)	.25
	SPMS-A	0.85 (0.70–1.01)	.04
5–10 years from onset (637 PPMS-N, 648 PPMS-A, 1226 SPMS-N, 1610 SPMS-A)	PPMS-A	1.02 (0.87–1.17)	.80
	SPMS-N	0.78 (0.64–0.92)	< .001
	SPMS-A	0.87 (0.74–1.00)	.04
10–15 years from onset (449 PPMS-N, 489 PPMS-A, 580 SPMS-N, 911 SPMS-A)	PPMS-A	0.88 (0.72–1.04)	.11
	SPMS-N	0.82 (0.66–0.99)	.02
	SPMS-A	0.76 (0.61–0.92)	< .001
Disability accrual from EDSS 4–5 (426 PPMS-N, 450 PPMS-A, 750 SPMS-N, 889 SPMS-A)	PPMS-A	0.94 (0.82–1.09)	.42
	SPMS-N	0.81 (0.71–0.92)	.002
	SPMS-A	0.82 (0.72–0.93)	.002

'Onset' refers to onset of the progressive phase. Disability accrual is assessed from onset of the progressive phase, except in the fifth sensitivity analysis, in which it is assessed from EDSS 4–5. Hazard ratios for confirmed disability accrual are adjusted for sex and (as time-dependent covariates) age at the start of each epoch; EDSS score at the start of each epoch; the proportion of each epoch receiving any disease-modifying therapy; the proportion of each epoch receiving any immunosuppressant therapy; and the annualized frequency of EDSS scores during each epoch. Treating center and patient identity were modelled as random effects, with identity nested within center. The proportional hazards assumption was violated for EDSS score frequency.

Abbreviations: CI = confidence interval; EDSS = Expanded Disability Status Scale.