Original research

Disability accrual in primary and secondary progressive multiple sclerosis

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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 centre 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% men; 50% with activity) and 2575 with SPMS (32% men; 40% with activity). Relative to PPMS, SPMS had older age at onset of the progressive phase (median 46.7 years (95% CI 46.2–47.3) vs 43.9 (43.3–44.4); p<0.001), greater baseline disability, slower disability accrual (HR 0.86 (0.78–0.94); p<0.001) 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.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Some studies comparing primary and secondary progressive multiple sclerosis (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.

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

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.

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 non-parametric 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] On this basis, many authors (not all)[13] have 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 standardised 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 operationalised 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 7 January 2020. MSBase is an international, clinic-based MS registry,[23] and includes records entered prospectively since 1 July 2004, in addition to retrospectively added records. Participants gave written informed consent as per MSBase and local regulations. Data quality and generalisability procedures were applied before inclusion screening (online supplemental 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 1 January 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 the 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 2-year intervals, were calculated for each phenotype ('mean EDSS trajectories'). For these calculations, if a patient had multiple scores within a 2-year interval, the median was taken as the patient's score for that interval.

Statistical analysis

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

All Andersen-Gill models included random-effects terms for treating centre and for patient identity (nested within treating centre). The initial model, estimating the total effect of phenotype (PPMS or SPMS), included terms for sex and for age at the

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, annualised	**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, annualised; 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)
Annualised 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)

Values are number (%), mean±SD, or median (IQR). 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 operationalised diagnostic criteria include 1134 patients (44%) with SPMS under physician diagnosis. Annualised relapse rate is calculated for the subset of patients with one or more relapses during follow-up.
ASCT, autologous stem-cell transplant, assumed effective for 5 years; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; PPMS, primary progressive MS; PPMS-A, PPMS with superimposed relapse activity; PPMS-N, PPMS with no superimposed relapse activity; SPMS, secondary progressive MS; SPMS-A, SPMS with superimposed relapse activity; SPMS-N, SPMS with no superimposed relapse activity.

start of each epoch. The 'complete' model (online supplemental 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 annualised 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 reassessed with phenotype comprising PPMS-N, PPMS-A,

SPMS-N and SPMS-A. Finally, to assess whether HRs 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 generalised log-rank test.[25] Median ages at onset of the progressive phase and at confirmed EDSS ≥4, ≥6 and ≥7 were likewise estimated for the full data set (1995–2020; all patients) and for three constituent time periods (1995–2003, 2004–2011 and 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 1 July 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 HRs 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 1 January 1995), rather than operationalised 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 (online supplemental 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 V.4.1.3 (packages 'survival' 3.3–1, 'coxme' 2.2–16, 'lme4' 1.1–28, 'glrt' 2.0, 'survminer' 0.4.9).

RESULTS

Main analyses

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

The Kaplan-Meier median age at onset of the progressive phase was younger in PPMS (43.9; 95% CI 43.3–44.4) versus SPMS (46.7; 95% CI 46.2–47.3) (p<0.001), and in the subgroup of each phenotype with activity (PPMS-A, SPMS-A) versus those without (p<0.001 in both PPMS and SPMS) (table 2).

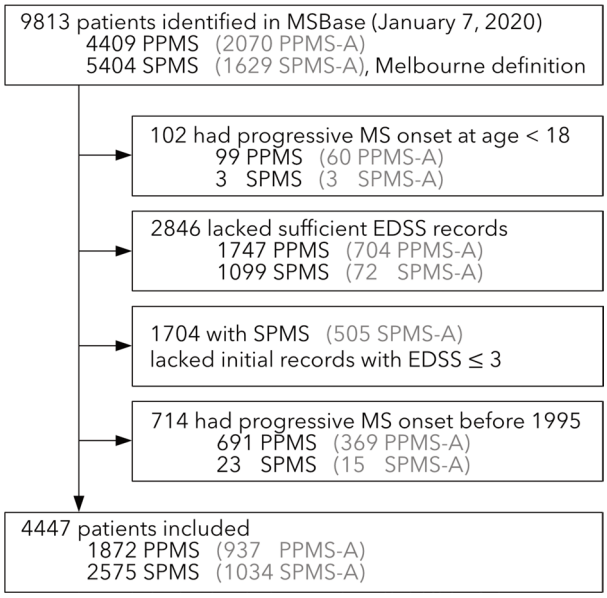

Figure 1 Flow diagram of patient inclusion. 52 062 patients with RRMS, and not meeting the operationalised diagnostic criteria for SPMS, were excluded. MS, multiple sclerosis; PPMS, primary progressive MS; PPMS-A, PPMS with superimposed relapse activity; PPMS-N, PPMS with no superimposed relapse activity; RRMS, relapsing-remitting MS; SPMS, secondary progressive MS; SPMS-A, SPMS with superimposed relapse activity; SPMS-N, SPMS with no superimposed relapse activity.

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<0.001; online supplemental 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<0.001; table 3). The proportional hazards assumption was violated for EDSS score frequency; correction did not alter findings (online supplemental table 1.4).

In the Andersen-Gill model adding a phenotype–activity interaction, disability accrual was not associated with phenotype (SPMS vs PPMS; HR=0.94; 95% CI 0.84–1.06; p=0.34) or activity (present vs absent; HR=0.98; 95% CI 0.89–1.09; p=0.75), but an interaction was observed between SPMS and activity (HR=0.84; 95% CI 0.73–0.96; p=0.01). 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<0.001; table 3; cf. unadjusted comparison, figure 2B). Analyses stratified by phenotype yielded no evidence of interactions between DMT and activity (PPMS, p=0.60; SPMS, p=0.13; online supplemental 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=0.06; among women, p=0.45; men, p=0.44). However, ages at EDSS ≥7 were younger in patients with relapse activity versus those without (PPMS-A vs PPMS-N, p=0.002; SPMS-A vs SPMS-N, p=0.007; 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

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

Phenotype	All patients	Women	Men
Age at onset of the progressive phase (median), years (95% CI)			
PPMS	**43.9 (43.3 to 44.4)**	**44.4 (43.8 to 45.2)**	**43.0 (42.3 to 44.0)**
PPMS-N	46.0 (45.2 to 46.8)	46.5 (45.3 to 47.7)	45.5 (44.5 to 46.7)
PPMS-A	41.9 (40.7 to 42.6)	42.8 (42.0 to 43.7)	40.0 (38.6 to 41.8)
SPMS	**46.7 (46.2 to 47.3)**	**47.3 (46.6 to 47.8)**	**45.6 (44.9 to 46.7)**
SPMS-N	48.3 (47.7 to 49.0)	49.3 (48.3 to 50.2)	46.7 (45.6 to 48.0)
SPMS-A	44.1 (43.1 to 44.8)	44.2 (43.2 to 45.0)	43.0 (42.1 to 45.5)
Age at confirmed EDSS ≥7 (25th percentile), years (95% CI)			
PPMS	**60.3 (58.8 to 62.5)**	**63.4 (60.5 to 66.2)**	**58.1 (56.6 to 60.1)**
PPMS-N	62.5 (60.1 to 65.8)	66.0 (62.5 to 68.7)	60.1 (57.3 to 62.7)
PPMS-A	57.6 (55.4 to 60.9)	60.9 (56.3 to 65.3)	55.8 (52.8 to 58.6)
SPMS	**62.2 (60.2 to 64.0)**	**63.2 (62.1 to 66.0)**	**58.3 (56.5 to 62.3)**
SPMS-N	63.6 (62.1 to 66.9)	63.6 (62.1 to 67.1)	64.7 (60.4 to 70.8)
SPMS-A	58.2 (57.0 to 62.1)	63.2 (60.7 to 70.0)	55.4 (50.8 to 57.8)

Ages at onset of the progressive phase (Kaplan-Meier estimator; log-rank test) were younger in PPMS vs SPMS (p<0.001), in subgroups with activity (-A) vs those without (-N) (p<0.001 in both PPMS and SPMS), and in men vs women (p=0.22 in PPMS, p=0.01 in SPMS). Ages at confirmed EDSS ≥7 (Turnbull estimator; generalised log-rank test) were similar in SPMS and PPMS (p=0.06; among women, p=0.45; among men, p=0.44; among patients with activity, p=0.22; without activity, p=0.38), but younger in patients with activity than in those without (PPMS-A vs PPMS-N, p=0.002; SPMS-A vs SPMS-N, p=0.007). Bold font is only used here to visually differentiate the estimates for the main groups (PPMS, SPMS) from the subgroups (PPMS-N, PPMS-A, SPMS-N, SPMS-A).
EDSS, Expanded Disability Status Scale; PPMS, primary progressive multiple sclerosis; PPMS-A, PPMS with superimposed relapse activity; PPMS-N, PPMS with no superimposed relapse activity; SPMS, secondary progressive multiple sclerosis; SPMS-A, SPMS with superimposed relapse activity; SPMS-N, SPMS with no superimposed relapse activity.

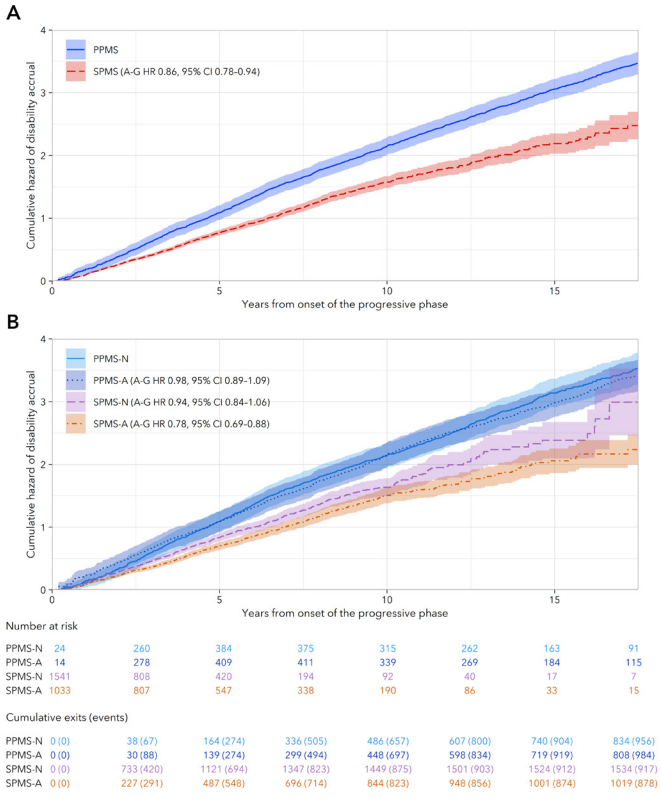

Figure 2 Nelson-Aalen cumulative hazard curves for confirmed disability accrual. (A) PPMS and SPMS. (B) PPMS-N, PPMS-A, SPMS-N and SPMS-A. The cumulative hazard indicates the expected number of confirmed disability accrual events for a patient observed for a given duration of time. Shaded regions indicate 95% CIs. A-G HR, adjusted HR obtained with Andersen-Gill models (see table 3). PPMS,primary progressive multiple sclerosis; PPMS-A, PPMS with superimposed relapse activity; PPMS-N, PPMS with no superimposed relapse activity; SPMS, secondary progressive multiple sclerosis; SPMS-A, SPMS with superimposed relapse activity; SPMS-N, SPMS with no superimposed relapse activity.

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.

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 summarised in online supplemental tables 1.7–1.8.

The analyses with SPMS defined by physician diagnosis (n=4610 SPMS; 32% men; 50% SPMS-A) are presented in online supplemental 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<0.001; 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<0.001) and SPMS-N (HR=0.86; 95% CI 0.79–0.94; p=0.001) 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<0.001), although still to a lesser extent than EDSS ≥4. Among patients with physician-diagnosed SPMS, 2458 (53%) met the operationalised diagnostic criteria.

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 to 0.94)	<0.001
Sex, male	1.17 (1.09 to 1.25)	<0.001
Age, at start of epoch	1.00 (0.99 to 1.00)	0.28
EDSS baseline, at start of epoch	0.92 (0.90 to 0.95)	<0.001
DMT, % of epoch on treatment (25% increments)	0.97 (0.94 to 0.99)	0.004
IST, % of epoch on treatment (25% increments)	0.96 (0.92 to 0.99)	0.01
EDSS score frequency, annualised, during epoch	1.14 (1.13 to 1.16)	<0.001
Model comparing PPMS-A, SPMS-N and SPMS-A to PPMS-N (reference)		
Phenotype		
PPMS-A	0.98 (0.89 to 1.09)	0.75
SPMS-N	0.94 (0.84 to 1.06)	0.34
SPMS-A	0.78 (0.69 to 0.88)	<0.001
Sex, male	1.17 (1.09 to 1.25)	<0.001
Age, at start of epoch	1.00 (0.99 to 1.00)	0.13
EDSS baseline, at start of epoch	0.92 (0.90 to 0.94)	<0.001
DMT, % of epoch on treatment (25% increments)	0.97 (0.95 to 0.99)	0.006
IST, % of epoch on treatment (25% increments)	0.96 (0.92 to 0.99)	0.01
EDSS score frequency, annualised, during epoch	1.15 (1.13 to 1.16)	<0.001

Treating centre and patient identity were modelled as random effects, with identity nested within centre. The proportional hazards assumption was violated for EDSS score frequency. Bold font is only used here to visually differentiate the estimates for the main groups (PPMS, SPMS) from the subgroups (PPMS-N, PPMS-A, SPMS-N, SPMS-A).
DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; IST, immunosuppressant therapy; PPMS, primary progressive multiple sclerosis; PPMS-A, PPMS with superimposed relapse activity; PPMS-N, PPMS with no superimposed relapse activity; SPMS, secondary progressive multiple sclerosis; SPMS-A, SPMS with superimposed relapse activity; SPMS-N, SPMS with no superimposed relapse activity.

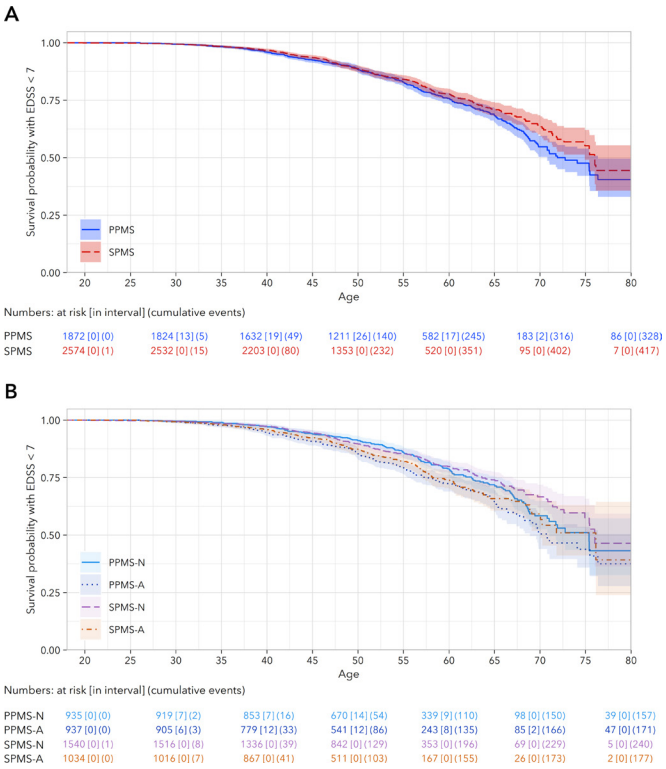

Figure 3 Turnbull survival curves for confirmed EDSS ≥7 (wheelchair dependence). (A) PPMS and SPMS. (B) PPMS-N, PPMS-A, SPMS-N and SPMS-A. Patients who entered observation having already reached confirmed EDSS≥7 are analysed as interval-censored observations, with EDSS ≥7 reached in the interval (date 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 (generalised log-rank tests): SPMS vs PPMS, p=0.06; SPMS-N vs PPMS-N, p=0.38; SPMS-A vs PPMS-A, p=0.22; PPMS-A vs PPMS-N, p=0.002; SPMS-A vs SPMS-N, p=0.007. 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% CIs. EDSS, Expanded Disability Status Scale; PPMS, primary progressive multiple sclerosis; PPMS-A, PPMS with superimposed relapse activity; PPMS-N, PPMS with no superimposed relapse activity; SPMS, secondary progressive multiple sclerosis; SPMS-A, SPMS with superimposed relapse activity; SPMS-N, SPMS with no superimposed relapse activity.

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 (annualised; HR=1.01; 95% CI 1.00–1.02), and a substantial 'direct' effect via other pathways (SPMS vs 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 vs 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 1 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 operationalised 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 operationalised 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

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 to 44.4)**	**50.4 (49.6 to 51.1)**	**56.9 (55.8 to 57.4)**	**72.8 (70.8 to 76.4)**
PPMS-N (n=935)	46.0 (45.2 to 46.8)	51.9 (50.8 to 53.2)	57.5 (56.9 to 59.0)	75.4 (71.0 to NA)
PPMS-A (n=937)	41.9 (40.7 to 42.6)	47.7 (46.2 to 49.6)	54.8 (53.6 to 56.6)	70.8 (68.9 to NA)
SPMS (n=2575)	**46.7 (46.2 to 47.3)**	**46.1 (45.5 to 46.6)**	**55.4 (54.6 to 56.5)**	**76.0 (74.9 to NA)**
SPMS-N (n=1541)	48.3 (47.7 to 49.0)	47.6 (47.1 to 48.3)	57.8 (56.3 to 58.9)	76.0 (75.4 to NA)
SPMS-A (n=1034)	44.1 (43.1 to 44.8)	43.5 (42.9 to 44.3)	53.0 (52.0 to 54.1)	76.1 (70.0 to NA)
1995–2003				
PPMS (n=125)	**41.9 (39.3 to 44.9)**	**47.0 (45.8 to 50.9)**	**51.9 (50.0 to 55.2)**	**60.6 (56.0 to 65.0)**
PPMS-N (n=56)	44.5 (41.5 to 48.7)	50.7 (47.9 to 53.5)	54.3 (51.0 to 57.5)	62.2 (56.0 to 68.5)
PPMS-A (n=69)	41.0 (37.5 to 43.7)	44.4 (43.3 to 50.8)	47.6 (46.2 to 54.5)	58.8 (55.0 to 65.4)
SPMS (n=121)	**43.0 (41.4 to 46.3)**	**42.9 (40.5 to 44.9)**	**47.4 (45.6 to 50.4)**	**57.4 (55.7 to 63.8)**
SPMS-N (n=48)	45.5 (42.6 to 51.5)	44.5 (42.0 to 51.5)	48.8 (44.5 to 52.8)	57.4 (53.1 to 72.6)
SPMS-A (n=73)	42.1 (39.8 to 44.9)	41.8 (39.8 to 44.5)	47.1 (45.1 to 51.5)	58.0 (56.3 to NA)
2004–2011				
PPMS (n=266)	**44.4 (43.3 to 45.9)**	**49.3 (46.6 to 50.8)**	**53.4 (52.2 to 56.9)**	**65.1 (62.4 to NA)**
PPMS-N (n=132)	46.5 (44.5 to 48.3)	50.5 (48.3 to 52.5)	54.8 (52.4 to 57.3)	67.5 (60.0 to NA)
PPMS-A (n=134)	42.8 (40.6 to 44.5)	46.4 (45.1 to 49.7)	53.0 (50.2 to 59.0)	65.1 (62.4 to NA)
SPMS (n=687)	**45.2 (44.2 to 46.0)**	**44.7 (43.8 to 45.6)**	**51.6 (49.7 to 52.5)**	**65.0 (62.1 to 68.4)**
SPMS-N (n=329)	46.6 (45.7 to 48.2)	46.3 (45.3 to 47.6)	52.3 (50.6 to 54.6)	67.4 (63.6 to 71.4)
SPMS-A (n=358)	43.3 (42.3 to 44.8)	43.0 (42.0 to 44.4)	49.8 (48.3 to 52.2)	61.3 (58.5 to 68.9)
2012–2020 (ending 7 January 2020)				
PPMS (n=250)	**47.6 (45.9 to 49.8)**	**54.2 (52.6 to 59.1)**	**63.3 (61.1 to 70.6)**	**80.8 (NA to NA)**
PPMS-N (n=129)	48.3 (47.2 to 51.5)	57.8 (52.6 to 60.8)	64.8 (60.8–NA)	NA (71.9 to NA)
PPMS-A (n=121)	45.5 (42.8 to 50.2)	54.2 (50.3 to 58.7)	62.3 (58.8–NA)	80.8 (NA to NA)
SPMS (n=1353)	**47.9 (47.3 to 48.5)**	**47.2 (46.3 to 47.7)**	**59.5 (58.2 to 60.6)**	**NA (76.0 to NA)**
SPMS-N (n=950)	49.0 (48.2 to 49.9)	48.4 (47.5 to 49.1)	60.5 (59.5 to 63.6)	NA (76.0 to NA)
SPMS-A (n=403)	44.7 (43.2 to 46.7)	44.1 (42.9 to 45.6)	55.5 (54.4 to 58.0)	71.8 (71.8 to 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 (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. P values comparing PPMS and SPMS in the complete dataset (1995–2020): onset, p<0.001; EDSS ≥4, p<0.001; EDSS ≥6, p=0.41; EDSS ≥7, p=0.06 (for onset, the log-rank test was used; for EDSS scores, a generalised log-rank test was used).Bold font is only used here to visually differentiate the estimates for the main groups (PPMS, SPMS) from the subgroups (PPMS-N, PPMS-A, SPMS-N, SPMS-A).
EDSS, Expanded Disability Status Scale; PPMS, primary progressive multiple sclerosis; PPMS-A, PPMS with superimposed relapse activity; PPMS-N, PPMS with no superimposed relapse activity; SPMS, secondary progressive multiple sclerosis; SPMS-A, SPMS with superimposed relapse activity; SPMS-N, SPMS with no superimposed relapse activity.

trends towards 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] Disability accrual in RRMS-SPMS begins at RRMS onset (mean age 32.3 years in our SPMS cohort), whereas 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]

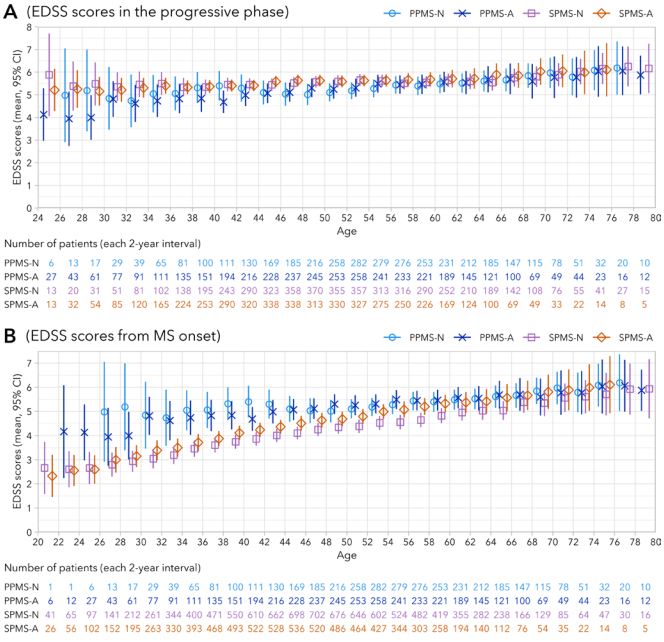

Figure 4 Mean EDSS trajectories in PPMS-N, PPMS-A, SPMS-N and SPMS-A. (A) Including only study-eligible EDSS scores, starting from onset of the progressive phase. (B) Including all available EDSS scores, starting from MS onset (including RRMS). Mean scores are plotted for each 2-year age interval, for groups with 10 or more patients contributing data in that interval. Error bars indicate 95% CIs. EDSS, Expanded Disability Status Scale; PPMS, primary progressive multiple sclerosis; PPMS-A, PPMS with superimposed relapse activity; PPMS-N, PPMS with no superimposed relapse activity; SPMS, secondary progressive multiple sclerosis; SPMS-A, SPMS with superimposed relapse activity; SPMS-N, SPMS with no superimposed relapse activity.

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 operationalised diagnosis, SPMS-A had slower disability accrual versus PPMS-N, whereas SPMS-N did not. This may reflect a genuine phenotypic difference (eg, 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 operationalised 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 that modeled 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 operationalised 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 operationalised 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, operationalised criteria for SPMS are not yet widely applied in clinical trials, which may limit generalisability 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 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 operationalised and physician diagnosis of SPMS, the median annualised frequency of EDSS scores was greater in SPMS versus PPMS (table 1; online supplemental table 2.2). Moreover, epochs with an EDSS increase at least two times 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 recognised 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 vulnerable 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-rater and inter-rater reliability at low scores, poor responsiveness to upper-limb and cognitive impairments and non-linearity.[24] In future studies, MRI 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 ageing to drive similar long-term outcomes across phenotypes.

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