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Title:
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Date:
2023-04-17

Citation:
Harding-Forrester, S., Roos, I., Nguyen, A. -L., Malpas, C. B., Diouf, I., Moradi, N., Sharmin, S., Izquierdo, G., Eichau, S., Patti, F., Horakova, D., Kubala Havrdova, E., Prat, A., Girard, M., Duquette, P., Maison, F. G., Onofrj, M., Lugaresi, A., Grammond, P. ,... Kalincik, T. (2023). Disability accrual in primary and secondary progressive multiple sclerosis. Journal of Neurology, Neurosurgery and Psychiatry, 94 (9), pp.707-717. https://doi.org/10.1136/jnnp-2022-330726.

Disability accrual in primary and secondary progressive multiple sclerosis

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Word count: Abstract, 256; Main text, 3544
Display items: Tables, 4; Figures, 4

Keywords: multiple sclerosis, chronic progressive; disease progression; prognosis; observational study; MSBase

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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Acknowledgements

We thank all patients and caregivers who contributed data to the MSBase registry and participated in this study. MSBase Study Group co-investigators: Magd Zakaria, MD (Faculty of Medicine, Ain Shams University, Cairo, Egypt).

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Administrative, technical, or material support: Kalincik.
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Funding

This study was financially supported by the National Health and Medical Research Council of Australia (1129189, 1140766). The MSBase Foundation is a not-for-profit organization that has received support from Biogen, CSL, Merck, Novartis, Roche, Sanofi, and Teva; this study was conducted independently of the sponsors.

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-

Aventis, Teva, and Merck. Dr Granella received an institutional research grant from Biogen and Sanofi Genzyme; served on scientific advisory boards for Biogen, Novartis, Merck, Sanofi Genzyme, and Roche; and received funding for travel and speaker honoraria from Biogen, Merck, and Sanofi-Aventis. Dr Slee participated in, but did not receive honoraria for, advisory board activity for Biogen, Merck, Bayer Schering, Sanofi-Aventis, and Novartis. Dr Bergamaschi received speaker honoraria from Bayer Schering, Biogen, Genzyme, Merck, Novartis, Sanofi-Aventis, and Teva; research grants from Bayer Schering, Biogen, Merck, Novartis, Sanofi-Aventis, and Teva; and congress, travel, and accommodation expense compensations from Almirall, Bayer Schering, Biogen, Genzyme, Merck, Novartis, Sanofi-Aventis, and Teva. Dr Ampapa received conference travel support from Novartis, Teva, Biogen, Bayer, and Merck, and participated in clinical trials by Biogen, Novartis, Teva, and Actelion. Dr Sánchez-Menoyo received travel compensation from Novartis and Biogen; received speaking honoraria from Biogen, Novartis, Sanofi, Merck, Almirall, Bayer, and Teva; and participated in a clinical trial by Biogen. Dr Prévost received travel compensation from Novartis, Biogen, Genzyme, and Teva, and speaking honoraria from Biogen, Novartis, Genzyme and Teva. Dr Castillo-Triviño received speaking or consulting fees and/or travel funding from Bayer, Biogen, Merck, Novartis, Roche, Sanofi Genzyme, and Teva. Dr Laureys received travel and/or consultancy compensation from Sanofi Genzyme, Roche, Teva, Merck, Novartis, Celgene, and Biogen. Dr Oh received research funding from the MS Society of Canada, the National MS Society, Brain Canada, Biogen Idec, Roche, and EMD Serono, and personal compensation for consulting or speaking from EMD Serono, Sanofi Genzyme, Biogen Idec, Roche, Celgene, and Novartis. Dr Altintas received personal fees and speaker honoraria from Teva, Merck, Biogen Gen Pharma, Roche, Novartis, Bayer, and Sanofi Genzyme, and received travel and registration grants from Merck, Biogen Gen Pharma, Roche, Sanofi Genzyme, and Bayer. Dr Butzkueven received compensation for consulting, talks, and advisory or steering board activities from Biogen, Merck, Novartis, Genzyme, Alfred Health, and Oxford Health Policy Forum, and research support from Novartis, Biogen, Roche, Merck, the National Health and Medical Research Council of Australia, Pennycook Foundation, and MS Research Australia. Dr Barnett served on scientific advisory boards for Biogen, Novartis, and Genzyme, received conference travel support from Biogen and Novartis, and serves on steering committees for trials conducted by Novartis; his institution received research support from Biogen, Merck, and Novartis. Dr Cristiano received honoraria as a consultant on scientific advisory boards for Biogen, Bayer Schering, Merck, Genzyme, and Novartis, and participated in clinical trials or other research projects by Merck, Roche, and Novartis. Dr Hodgkinson received honoraria and consulting fees from Novartis, Bayer Schering, and Sanofi, and travel grants from Novartis, Biogen Idec, and Bayer Schering. Dr Iuliano received compensation for travel, accommodations, and meeting expenses from Bayer Schering, Biogen, Merck, Novartis, Sanofi-Aventis, and Teva. Dr Kappos received research support from Acorda, Actelion, Allozyne, BaroFold, Bayer HealthCare, Bayer Schering, Bayhill Therapeutics, Biogen, Elan, European Union, Genmab, Gianni Rubatto Foundation, GlaxoSmithKline, Glenmark, MediciNova, Merck, Novartis, Novartis Research Foundation, Roche, Roche Research Foundation, Sanofi-Aventis, Santhera, the Swiss MS Society, the Swiss National Research Foundation, Teva Neuroscience, UCB, and Wyeth. Dr Weinstock-Guttman participated in speakers' bureaus and/or served as a consultant for Biogen, EMD Serono, Novartis, Genentech, Celgene/Bristol Meyers Squibb, Sanofi Genzyme, Bayer, Janssen, and Horizon; received grant/research support from these same agencies; and serves on editorial boards for BMJ Neurology, Children, CNS Drugs, MS International, and Frontiers Epidemiology. Dr Van Wijmeersch received research and travel grants and honoraria for advisory and speaking fees from Bayer Schering, Biogen, Sanofi Genzyme, Merck, Novartis, Roche, and Teva. Dr Kalincik served on scientific advisory boards for BMS, Roche, Sanofi Genzyme, Novartis, Merck, and Biogen, and the steering committee for the Brain Atrophy Initiative by Sanofi Genzyme; received conference travel support and/or speaker honoraria from WebMD Global, Novartis, Biogen, Sanofi Genzyme, Teva, BioCSL, and Merck; and received support for research or educational events from Biogen, Novartis, Genzyme, Roche, Celgene, and Merck. No other disclosures relevant to the manuscript were reported.

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.