

# Risk of secondary progressive multiple sclerosis: A longitudinal study

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## Abstract

**Background:** The risk factors for conversion from relapsing-remitting to secondary progressive multiple sclerosis remain highly contested.

**Objective:** The aim of this study was to determine the demographic, clinical and paraclinical features that influence the risk of conversion to secondary progressive multiple sclerosis.

**Methods:** Patients with adult-onset relapsing-remitting multiple sclerosis and at least four recorded disability scores were selected from MSBase, a global observational cohort. The risk of conversion to objectively defined secondary progressive multiple sclerosis was evaluated at multiple time points per patient using multivariable marginal Cox regression models. Sensitivity analyses were performed.

**Results:** A total of 15,717 patients were included in the primary analysis. Older age (hazard ratio (HR) = 1.02,  $p < 0.001$ ), longer disease duration (HR = 1.01,  $p = 0.038$ ), a higher Expanded Disability Status Scale score (HR = 1.30,  $p < 0.001$ ), more rapid disability trajectory (HR = 2.82,  $p < 0.001$ ) and greater number of relapses in the previous year (HR = 1.07,  $p = 0.010$ ) were independently associated with an increased risk of secondary progressive multiple sclerosis. Improving disability (HR = 0.62,  $p = 0.039$ ) and disease-modifying therapy exposure (HR = 0.71,  $p = 0.007$ ) were associated with a lower risk. Recent cerebral magnetic resonance imaging activity, evidence of spinal cord lesions and oligoclonal bands in the cerebrospinal fluid were not associated with the risk of conversion.

**Conclusion:** Risk of secondary progressive multiple sclerosis increases with age, duration of illness and worsening disability and decreases with improving disability. Therapy may delay the onset of secondary progression.

**Keywords:** SPMS, multiple sclerosis, disease modifying therapies, prediction, prognostics

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## Introduction

Previous efforts to identify prognostic markers of secondary progressive multiple sclerosis (SPMS) have used large natural history cohorts, limited to certain geographic location and composed of mostly untreated

patients. As a result, they do not take into consideration the impact that disease-modifying therapy (DMT) has on delaying SPMS.<sup>1</sup> Furthermore, the comparability of these studies is hampered by the use of varying methodologies and outcomes, including different

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definitions of SPMS.<sup>2</sup> Most examined risk factors of SPMS within the initial 5 years of the onset of multiple sclerosis (MS), but did not assess how the risk of SPMS might change over time.

Recently, an objective definition of SPMS was developed using the MSBase cohort.<sup>3</sup> Using this definition, we have investigated various demographic, clinical and paraclinical factors that influence the risk of developing SPMS in a large, multinational cohort with relapsing–remitting multiple sclerosis (RRMS) treated with contemporary therapies.

## Methods

### Ethics

The MSBase registry<sup>4</sup> (registered with World Health Organization (WHO) ICTRP, ID ACTRN1260500 0455662) was approved by the Melbourne Health Human Research Ethics Committee and by the local ethics committees in all participating centres (or exemptions granted, according to local protocols). Written informed consent was provided by enrolled patients as required.

### Patient population and inclusion criteria

Longitudinal data from 44,449 patients treated in 36 countries were extracted from MSBase in February 2017. A rigorous, automated quality assurance procedure was applied (Online Supplement Table S2).<sup>5</sup>

Inclusion criteria consisted of a diagnosis of RRMS according to the 2005 or 2010 McDonald criteria,<sup>6,7</sup>  $\geq 4$  Expanded Disability Status Scale (EDSS) scores recorded (with  $\geq 6$  months between the first and second recorded scores and  $\geq 3$  months between the first EDSS score after the initial prediction time point and final score), age at symptom onset  $\geq 18$  years and availability of the minimum dataset (date of birth, sex, date of symptom onset, onset phenotype and MS course entries to confirm RRMS). Patients diagnosed with RRMS who reached SPMS before the first prediction time point were excluded. The secondary and sensitivity analyses also required magnetic resonance imaging (MRI) data or cerebrospinal fluid (CSF) data, a follow-up time of  $\geq 9$  years or more stringent data quality thresholds.

### Study design

This observational cohort study examined risk factors of conversion to SPMS. Previous studies evaluating the risk of SPMS have used data at entry into the

study and once the endpoint is reached (or data are censored) to evaluate hazard ratios (HRs), and some have employed time-dependent variables. With the exception of a study that used a Poisson process,<sup>8</sup> these studies did not consider that, in an individual patient, the importance of each risk factor may change with patient age, disease progression or level of disability. To model the changing risk of SPMS, we predicted the hazard of each patient reaching SPMS at every clinic visit using their updated results as entered by the clinician. The resultant HRs, therefore, more appropriately reflect an ‘average’ hazard of conversion to SPMS over the entire disease course and allows for the evaluation of risk of SPMS in individual patients.

Specifically, the data from each visit entry per patient were assessed for their suitability as a ‘prediction time point’ to evaluate the subsequent hazard of SPMS. ‘Prediction time points’ were defined as any visit entries recorded during RRMS with  $\geq 1$  visit recorded  $\geq 6$  months prior and  $\geq 2$  subsequent visits. Thus, the study included multiple prediction time points per patient, and each prediction time point could also count as a visit entry for others. The period between the first visit entry and each prediction time point was called the pre-baseline period. The post-baseline period was the time between each prediction time point and the final eligible visit (i.e. the last visit that was followed by an additional visit  $\geq 3$  months later). The follow-up period was the time between the first prediction time point and the final eligible visit (Online Supplement Figure S1). At each prediction time point, associations between demographic (age and sex), clinical (disease duration and annualised relapse rate (ARR), number of relapses in the previous year, proportion of time on DMTs pre- and post-baseline, annualised EDSS slope and frequency of visits during the post-baseline period) and paraclinical variables (qualitative MRI and CSF information) and the subsequent conversion to SPMS were evaluated (definitions of the variables are given in Online Supplement).

### Study end points

The outcome of interest was objectively defined conversion to SPMS (Box 1).<sup>3</sup> The date of SPMS conversion was the date of the first EDSS increase that eventually led to the definition of SPMS being reached; patients could only reach this outcome once. Patients who did not meet this outcome were censored at the last recorded visit with non-zero probability of SPMS conversion (i.e. for which one subsequent EDSS and functional scores  $\geq 3$  months later were recorded).

**Box 1.**

The used objective definition of SPMS:<sup>3</sup> EDSS  $\geq 4$  disability progression by  $\geq 1$  (where EDSS  $\leq 5.5$ ) or  $\geq 0.5$  EDSS points (where EDSS  $\geq 6$ ) confirmed after  $\geq 3$  months and in the absence of a relapse pyramidal functional system score of  $\geq 2$ .

*Statistical analysis*

Statistical analysis was performed using R version 3.2.4. The association between each variable and the outcome was assessed using univariate Cox proportional hazards models. A series of multivariable marginal Cox proportional hazards models were then constructed using the covariates potentially associated with the outcome at  $\alpha = 0.20$ . These models were adjusted for study centre, post-baseline DMT exposure and post-baseline visit frequency. To account for multiple entries per patient (and the associated interdependence of these repeated observations), all models were clustered by patient with a robust estimation of variance. The median time to SPMS was estimated with a left- and right-censored proportional hazards model with only one entry per patient allowed. The proportional hazards assumption was confirmed by visual inspection of the Schoenfeld residuals, and where violated, accelerated failure time model with Weibull distribution was used. The best fitted multivariable model was chosen based on Akaike information criterion, least risk of overfitting and most clinically relevant covariates, in descending order of importance.

*Secondary and sensitivity analyses*

In order to assess additional predictive factors, three cohorts with additional data available were studied: (1) MRI brain (to evaluate the association of SPMS with brain MRI status), (2) MRI brain and spinal cord (to evaluate the association of SPMS with spinal MRI status) and (3) MRI brain and CSF (to evaluate the association of SPMS with CSF findings). To assess the robustness of the primary model in sensitivity analyses, two further sub-cohorts were studied, where: (1) more stringent data quality criteria were applied (only centres with the highest quality data were included) or (2) patients were followed up for  $\geq 9$  years (the upper quartile of follow-up time). ‘High quality centres’ were arbitrarily defined as having a data density of  $>44\%$  of the maximum data density,  $<3$  data errors per 100 patient-years and generalisability  $>65\%$  of the maximum generalisability.<sup>5</sup> The analytical methodology used in the primary analysis was applied to secondary and sensitivity analyses.

**Results***Patient characteristics*

We identified 15,717 patients contributing 176,602 visits and 100,573 patient-years of follow-up eligible for inclusion in the primary analysis (Figure 1 and Online Supplement Tables S3 and S4). The characteristics of the examined cohort are provided in Table 1, and those of the excluded cohort in Online Supplement Table S5. A total of 1546 (10%) patients converted to SPMS during their recorded follow-up. The median time to SPMS was 32.4 years (95% confidence interval (95% CI): 31.1–33.7) from disease onset (Figure 2). This was confirmed in a subcohort followed prospectively from  $\leq 10$  years from disease onset ( $n = 11,926$ ), where the proportion of patients with SPMS at 32.4 years was 60%. The dates of the prediction time points ranged from October 1975 to October 2016 with the median date being September 2010. At the time of censoring, 79% of the patients had received injectable DMTs, 24% received oral DMTs and 14% received monoclonal antibody therapy, and 15% of the patients remained untreated. At the time of censoring, patients had been treated with DMTs for a median of 3.9 years (quartiles: 1.3–7.5), having spent a median of 48% (quartiles: 16%–75%) of their disease duration on DMTs.

*Univariate analysis*

The results of the univariate Cox regression are provided in Online Supplement Table S6. Male sex, older age at visit, older age at symptom onset, longer disease duration, a higher number of relapses in the previous year, higher EDSS and faster disability accrual tended to be associated with an increased risk of SPMS. Improving disability, a higher ARR, involvement of multiple central nervous system (CNS) regions and/or spinal cord symptoms at onset and prior proportion of time on DMT tended to be associated with a reduced risk of SPMS in unadjusted univariate models. Visual, brainstem or supratentorial onset symptoms were not associated with SPMS.

*Multivariable analysis*

The results of the primary multivariable regression model are shown in Figure 3. Disease duration and age were considered more relevant than age at symptom onset and were not substantially collinear (Pearson’s  $r = 0.57$ ); they were therefore included in the model. Similarly, ARR and the number of relapses in the previous year were also not substantially collinear (Pearson’s  $r = 0.54$ ) and both were included in the model.

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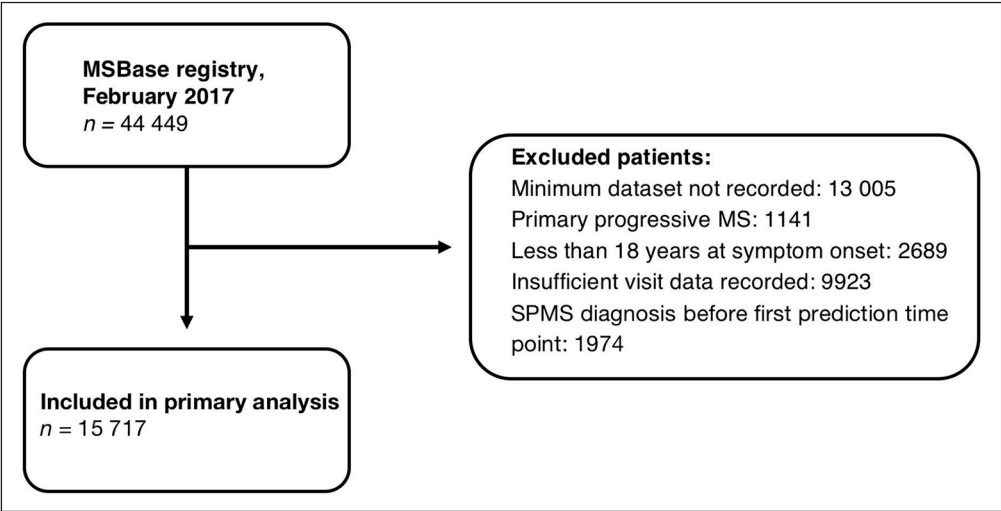
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Online Supplement Table S1.



**Figure 1.** CONSORT flowchart of patient disposition (primary analysis). Patients excluded due to incomplete minimum dataset had at least one of the following information missing: date of birth, gender, centre, disease course, date of first symptom onset and onset symptom phenotype. Patients excluded due to insufficient visit data had less than four visits with EDSS recorded or less than 3 months between the first EDSS score after the initial prediction time point and last visit. EDSS: Expanded Disability Status Scale.

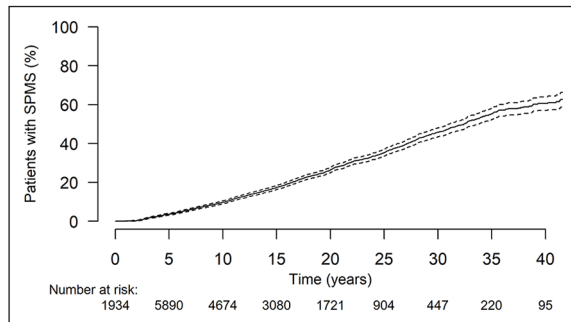
**Table 1.** Characteristics of studied patients at first prediction time point.

	Count (%)	Mean (SD)	Median (quartiles)
Patients (% female)	15,717 (71)		
Age (years)		38.4 (10.4)	37.4 (30.4, 45.4)
Disease duration (years)		6.8 (7.3)	4.1 (1.6, 9.7)
Onset symptoms, patients <sup>a</sup>			
Spinal cord	4368 (28)		
Visual	4295 (27)		
Brainstem	4128 (26)		
Supratentorial	4957 (32)		
Polysymptomatic	1922 (12)		
Disability, EDSS (EDSS step)			2.0 (1.0, 3.0)
Pre-baseline annualised EDSS slope (EDSS steps per year)		0.6 (0.8)	0.4 (0.2, 0.8)
Pre-baseline annualised relapse rate (relapses per year)		0.9 (0.9)	0.6 (0.3, 1.2)
Number of relapses ≤ 12 months prior			1 (0, 1)
Number of patients having received any treatment	10,005 (64)		
Percentage of time on therapy		24.2 (28.6)	10.9 (0, 43.5)
Follow-up time per patient <sup>b</sup> (years)		6.4 (4.9)	5.3 (2.5, 9.1)
Number of prediction time points contributed per patient <sup>b</sup>			8 (3, 15)

SD: standard deviation; EDSS: Expanded Disability Status Scale.  
<sup>a</sup>Patients with multiple onset symptoms were counted both in the phenotype of the symptoms they experienced and again in the polysymptomatic group.  
<sup>b</sup>Calculated over the entire length of patient follow-up.

A higher EDSS score (HR: 1.30, 95% CI: 1.25–1.35), worsening disability trajectory at a rapid rate (HR: 2.82, 95% CI: 2.07–3.84), a greater number of relapses in the previous year (HR: 1.07, 95% CI: 1.02–1.13), longer disease duration (HR: 1.01, 95% CI: 1.00–1.02) and older age (HR: 1.02, 95% CI: 1.01–1.02) were all independently associated with the risk of SPMS conversion. A greater proportion of time spent on DMTs (HR: 0.71, 95% CI: 0.55–0.91) and an improving disability trajectory (HR: 0.62, 95% CI: 0.39–0.98) were associated with a lower risk of SPMS. Sex, overall ARR and phenotype of onset





**Figure 2.** Time to SPMS from disease onset.

The median time to SPMS from disease onset was estimated with a left- and right-censored proportional hazards model with only one entry per patient allowed. Of the 15,717 patients evaluated, 1546 (10%) fulfilled the definition of SPMS after a median of 32.4 years (95% confidence limits: 31.1–33.7 years). SPMS: secondary progressive multiple sclerosis.

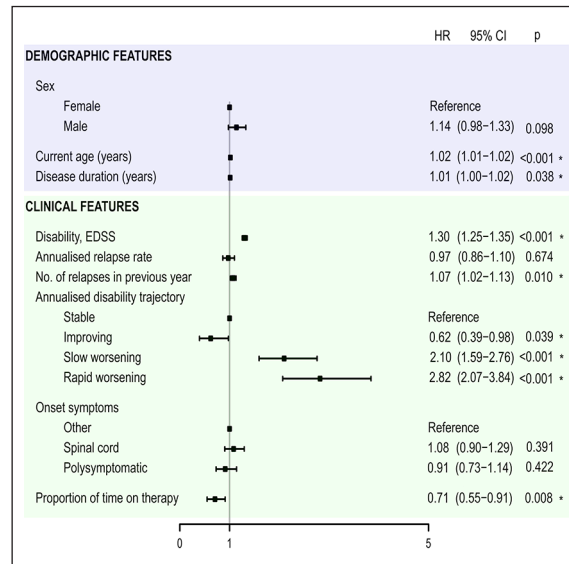
symptoms were not independently associated with the risk of SPMS.

### Secondary analyses

The results of the secondary analyses are shown in Figure 4. In the first analysis, where MRI brain data were analysed (Figure 4(a)), 6145 patients were included, contributing 35,340 visits and 39,360 patient-years of follow-up. At the time of censoring, patients had been treated with DMTs for a median of 2.8 years (quartiles: 1.1, 5.9), having spent a median of 49% (quartiles: 18%–75%) of their time from disease onset on DMTs. This analysis largely confirmed the results of the primary analysis. Of note, in this cohort, MRI evidence of disease activity in the brain, a greater number of relapses in the previous year and time spent on DMTs were not independently associated with the risk of becoming secondarily progressive.

The second secondary analysis investigated MRI spinal cord parameters (fitted with Weibull distribution;  $n = 1748$ ; Figure 4(b)). It highlighted that having radiological evidence of spinal cord lesions at any time does not independently influence the risk of SPMS (HR: 1.14, 95% CI: 0.67–1.93). While the results largely confirmed those of the primary analysis, in this cohort male sex was associated with higher risk of SPMS (HR: 1.91, 95% CI: 1.19–3.06).

The analysis investigating the impact of CSF markers (fitted with accelerated failure time model;  $n = 3105$ ; Figure 4(c)) did not find an association between the presence of oligoclonal bands at any time and risk of SPMS (HR: 0.83, 95% CI: 0.48–1.44). It otherwise largely confirmed the results of the primary analysis.



**Figure 3.** Primary analysis: risk factors of secondary progressive multiple sclerosis.

Fitted with a multivariable Cox model. Of the 15,717 patients included in the analysis, 1546 (10%) became secondarily progressive. ‘Annualised disability trajectory’ is the annualised EDSS slope categorised into: stable (gradient  $-0.05$  to  $0.05$  EDSS steps per year), improving ( $<-0.05$ ), slow worsening ( $0.05$ – $0.24$ ) and rapid worsening ( $>0.24$ ). ‘Proportion of time on therapy’ is the length of time spent on any disease-modifying therapy in the pre-baseline period divided by the time from disease onset to the prediction time point.

95% CI: 95% confidence interval; EDSS: Expanded Disability Status Scale; HR: hazard ratio.

\*Significant to the 0.05 level.

### Sensitivity analyses

The results of the sensitivity analyses are given in Figure 5. All sensitivity analyses were fitted with an accelerated failure time model. The sensitivity analysis conducted in centres with the best data quality ( $n = 8090$ ; number of centres = 19; Figure 5(a)) confirmed that higher EDSS, older age, more relapses in the previous year and a worse disability trajectory were associated with a greater risk of SPMS, while an improving disability course and greater proportion of time on DMTs were associated with a lower risk.

Finally, when a minimum follow-up of 9 years ( $n = 4018$ ; Figure 5(b)) was required, a longer disease duration, higher EDSS score, higher ARR and greater proportion of time on DMTs were associated with increased risk of SPMS, while an improving disability course was associated with a lower risk of SPMS.

### Discussion

In this study that used repeated observations in a clustered survival model, an objective definition of SPMS

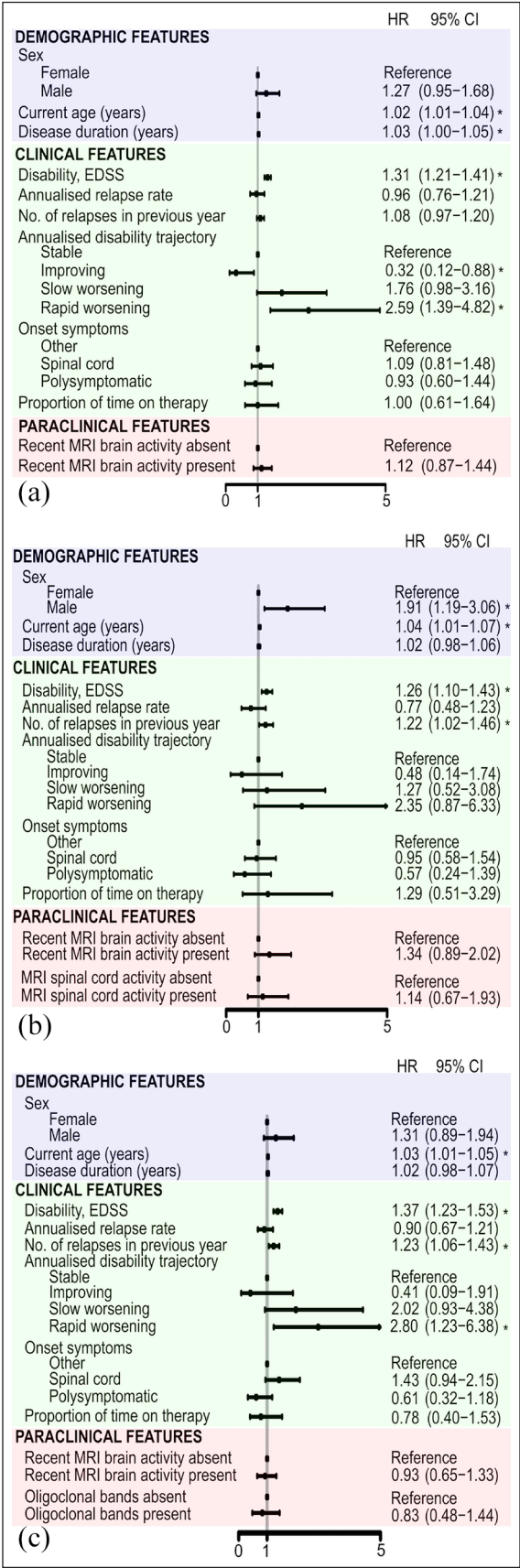


Figure 4. (Continued)

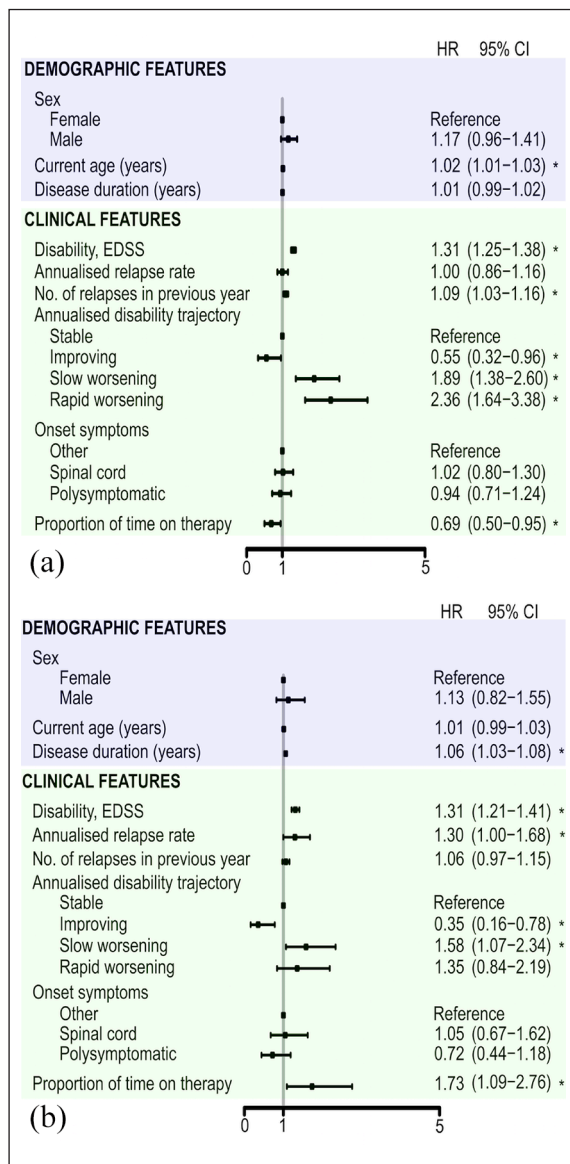
**Figure 4.** Secondary analyses: risk factors of secondary progressive multiple sclerosis. Conducted in cohorts: (a) with MRI brain data required ( $n=6145$ ), (b) with MRI brain and spine data required ( $n=1748$ ) and (c) with MRI brain and CSF data required ( $n=3105$ ). Fitted with multivariable, marginal Cox regression models. Analyses b and c were fitted with a Weibull distribution. ‘Annualised disability trajectory’ is the annualised EDSS slope categorised into: stable (gradient  $-0.05$  to  $0.05$  EDSS steps per year), improving ( $<-0.05$ ), slow worsening ( $0.05-0.24$ ) and rapid worsening ( $>0.24$ ). ‘Proportion of time on therapy’ is the length of time spent on any disease-modifying therapy in the pre-baseline period divided by the time from disease onset to baseline. Recent MRI brain activity is any evidence of new T2 lesions or gadolinium enhancing lesions over the previous 2 years. 95% CI: 95% confidence interval; CSF: cerebrospinal fluid; EDSS: expanded disability status scale; HR: hazard ratio; MRI: magnetic resonance imaging. \*Significant to 0.05 level.

and the multinational MSBase cohort, risk factors heralding conversion of RRMS to SPMS included older age, longer disease duration, greater disability, rapid disability accrual and a greater number of relapses in the previous year. Factors that were associated with a lower risk of SPMS conversion were improvement in disability and potentially also prior exposure to immunotherapies. In contrast, brain MRI activity, spinal MRI disease burden and the presence of oligoclonal bands in the CSF were not associated with SPMS.

Most previous studies have assessed the predictive value of disease and patient characteristics at the beginning of the disease or after 5 years. These studies reported that male sex is associated with an increased risk of SPMS.<sup>9–12</sup> Women are more prone to relapses than men,<sup>13,14</sup> and it is possible that this greater relapse activity may delay the diagnosis of SPMS in women. Our analysis adjusted for the effect of relapses, suggesting that sex is not independently associated with a higher risk of SPMS. In the subset of patients with MRI brain and spine data available, we did find an association between male sex and SPMS; while we cannot reconcile this difference, it should be noted that male sex was trending towards a greater risk of SPMS.

Age at onset is considered one of the best indicators of SPMS conversion.<sup>15–18</sup> In addition, the risk of SPMS increases with older age and longer disease duration,<sup>8,9,19,20</sup> thus confirming that the onset of SPMS is a function of time.<sup>21,22</sup>

Previous studies suggested that the phenotype of onset symptoms may be associated with SPMS conversion.<sup>10,23–25</sup> Our results did not find an evidence of such association. This may be attributed to the fact that in this study, the risk factors were evaluated after a median



**Figure 5.** Sensitivity analyses: risk factors of secondary progressive multiple sclerosis. Conducted in cohorts (a) consisting only of centres with the highest data quality ( $n=8090$ ) and (b) with follow-up greater than 9 years required ( $n=4018$ ).

Fitted with multivariable, marginal Cox regression models. Both analyses were fitted with a Weibull distribution. 'Annualised disability trajectory' is the annualised EDSS slope categorised into: stable (gradient  $-0.05$  to  $0.05$  EDSS steps per year), improving ( $<-0.05$ ), slow worsening ( $0.05-0.24$ ) and rapid worsening ( $>0.24$ ). 'Proportion of time on therapy' is the length of time spent on any disease-modifying therapy in the pre-baseline period divided by the time from disease onset to baseline. 'High quality data centres' were arbitrarily defined as having a data density score of  $>50$  (i.e.  $>44\%$  of the maximum score), error rate of  $<3$  per 100 patient-years and a generalisability score  $>14$  (i.e.  $>65\%$  of the maximum score).<sup>5</sup>

95% CI: 95% confidence interval; EDSS: Expanded Disability Status Scale; HR: hazard ratio.

\*Significant to 0.05 level.

of 4.1 years from disease onset, when other time-dependent variables (such as age and disability) would become relatively more important. The association between greater disability and a risk of SPMS is rather trivial, as to fulfil the objective definition of SPMS, patients must achieve an EDSS score of 4 or greater.

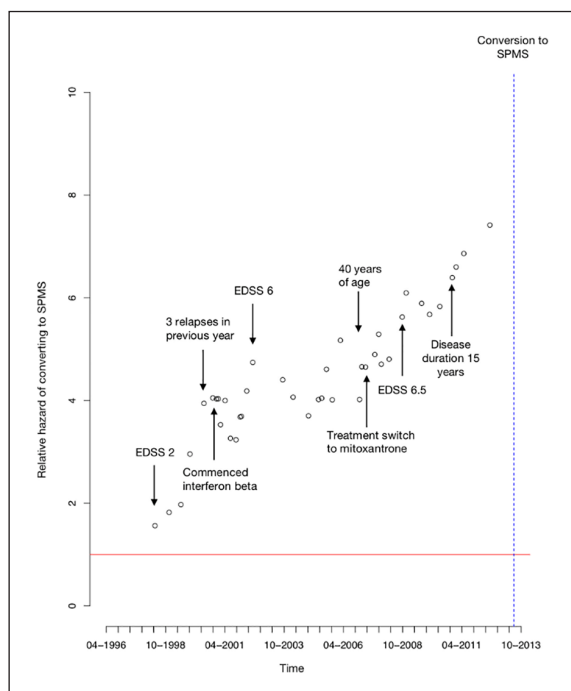
Early relapses are thought to increase the likelihood of developing SPMS,<sup>9,22,26,27</sup> while later relapses are of lesser importance.<sup>9,20</sup> This study showed this association for the number of relapses in the previous year. Interestingly, in the cohort followed for  $\geq 9$  years, the more important predictor was the overall ARR. Thus, inflammatory activity may contribute to SPMS conversion, but the information about prior cumulative relapse activity is more relevant when acquired over an extended time.

While some studies have found no association between DMT use and SPMS,<sup>28,29</sup> the results of this study, in line with work by others,<sup>30–32</sup> suggest that DMTs may delay the onset of SPMS. Interestingly, over the course of almost two decades, the reported median time from MS onset to SPMS has increased from just under 15 years<sup>33</sup> to over 30 years.<sup>34</sup> This increasing trend was again demonstrated in this study. These reported long-term trends do not provide a direct evidence of the effect of DMTs on the onset of SPMS and can be influenced by the differences in the used definitions. However, they are in keeping with our recently completed study, which demonstrated that DMTs, in particular higher-efficacy therapies, reduce the risk of SPMS conversion.<sup>1</sup>

Paraclinical features such as abnormal MRI findings and presence of oligoclonal bands in the CSF are associated with a greater risk of developing MS.<sup>35</sup> This association is expected, as these features are also diagnostic of MS.<sup>7</sup> However, the observed lack of prognostic value of simple MRI and CSF markers with respect to SPMS conversion is not surprising, given that these markers are assessed in the context of established RRMS.

Previous studies have suggested that the number<sup>36</sup> and location<sup>37</sup> of cerebral MRI lesions may provide some information about SPMS conversion. This study did not confirm this observation; however, MSBase MRI data are relatively sparse and only contain limited information about lesion topography.

Unlike most of the previous studies, our design does not restrict the analyses to predictions during early MS. Instead, our results represent the average predictive



**Figure 6.** Individual risk of a patient converting to SPMS, relative to the study cohort. The relative hazard ratios are derived from the results of Cox regression model used in the primary analysis. The vertical dashed line represents the time at which the patient fulfilled the definition of SPMS. The horizontal red line indicates the average risk of conversion to SPMS in the studied MSBase cohort (relative hazard=1).

In 1995, Ms R experienced her first symptoms of multiple sclerosis as acute optic neuritis, at age 28. Over the course of her disease, she experienced 17 relapses and a rapid accumulation of disability. From October 2000 until December 2006 she was treated with interferon beta, and in January 2007 she was switched to mitoxantrone for 6 months. In June 2013, 18 years after her initial diagnosis, she became secondarily progressive at age 47. It can be seen that the patient's hazard of conversion to SPMS increases with disease duration, age and disability milestones, until the patient ultimately becomes secondarily progressive after 18 years of disease.

SPMS: secondary progressive multiple sclerosis.

value of a factor over the course of RRMS. This approach allowed us to integrate change in the associations between the prognostic markers and the risk of SPMS over time (e.g. for relapse count<sup>9</sup>). This is illustrated by the example presented in Figure 6, which also demonstrates the change in the risk of SPMS in response to the change in patient's characteristics.

The main limitation of this study is its observational design and the inherent risk of confounding.<sup>38</sup> Its effect on the results has been minimised by the use of the broadly adjusted multivariable models, including adjustment for centre-specific confounding. Furthermore, the SPMS definition and several risk

factors rely on EDSS; hence, the study carries the limitations intrinsic to the use of this measure. The impact of the rater-dependent variability in EDSS has been minimised by the use of Neurostatus certification. The impact of the non-linearity of EDSS has been minimised through stratification of the requirements for EDSS progression according to the pre-existing disability level.<sup>3</sup> Comparability between the existing studies is difficult owing to the differences in methodologies used, ascertainment bias (introduced by restricting this study to patients treated in tertiary hospitals), as well as the lack of objective definition of SPMS in the previous studies. The objective definition of SPMS used here has only been applied in a limited number of cohorts. Only 10% of our examined cohort reached the study endpoint, which reduced our power. This could be partially attributed to the inclusion criteria, which excluded patients who were diagnosed with SPMS before their first recorded visit. The inclusion of only prospectively fulfilled definition of SPMS may have inflated our reported median time to SPMS; it is therefore reassuring that the time to SPMS was not shorter in the subgroup followed from  $\leq 10$  years from disease onset. The impact of detection bias has been reduced by adjusting for the frequency of post-baseline visits. Data errors were reduced by implementing data quality procedures.<sup>5</sup> Finally, MRI and CSF variables were recorded by treating physicians, potentially introducing reporting bias.

On the contrary, this study is so far the largest study to evaluate clinical, demographic and simple para-clinical markers of SPMS conversion in a global cohort of patients treated in a modern context. In addition, our analysis allows repeated evaluations of associations over time, which accounts for the changing risk of SPMS, which is particularly important in a treated cohort. It also allows for individualised estimation of risk over the course of a patient's disease. Broad generalisability of its results is implied from the multicentre, multinational source of patient data and was assured in a sensitivity analysis restricted to centres with high generalisability of the included cohorts. The main strength of this study lies in the use of an objective SPMS definition, which has mitigated inter-rater variability and will improve reproducibility of the results.<sup>1,3</sup>

## Conclusion

Studying a global RRMS cohort, we have confirmed that the risk of SPMS increases with age, duration of illness, worsening disability and higher number of recent relapses and decreases with better recovery from disability. In keeping with our previous study,<sup>1</sup>



our results confirm that DMTs help delay conversion to SPMS. Therefore, it has become important that clinicians are able to identify those patients at a high risk of secondary progression. Minimising the risk of SPMS should constitute an additional therapeutic target, alongside preventing CNS inflammation and disability accrual.

### Author contributions

A.F. conducted and interpreted the analysis, and drafted and revised the manuscript. T.K. conceptualised and designed the study, interpreted the analysis and edited the manuscript. V.J., D.H., E.K.H., M.T., A.P., M.G., P.D., A.L., G.I., F.G.M., P.G., P.S., D.F., R.A., M.T., R.H., C.B., J.L.-S., E.P., R.B., V.V.P., S.O., F.G., R.T., G.I., D.S., P.M., C.S., M.S., R.A., A.S., T.P., J.L.S.-M., F.V., J.P., Y.S., B.V.W., S.V., E.C., M.L.S., N.D., M.B., J.O., F.M., O.S., O.G., Y.F., B.Y., C.S., B.S., N.S., S.H., A.A., T.A.-H., T.C., B.T., J.H., J.-K.J., A.vd.W., T.S. and H.B. contributed substantially to data acquisition, interpretation of the analysis and have revised and approved the manuscript. A.F. and T.K. had full access to the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

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### Supplemental material

Supplemental material for this article is available online.

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