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ORIGINAL RESEARCH ARTICLE

Preserving Neurological Function in People at High and Low Risk of Aggressive Multiple Sclerosis: An Observational Cohort Study

Izanne Roos · Sifat Sharmin · Serkan Ozakbas · Raed Alroughani · Sara Eichau · Francois Grand'Maison, et al. ***[full author details at the end of the article]***

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Abstract

Background and Objectives Patients aged ≥ 35 years at multiple sclerosis (MS) symptom onset with an Expanded Disability Status Scale (EDSS) score ≥ 3 within the first year are at highest risk of developing aggressive MS (EDSS ≥ 6 within 10 years). Patients without these features are at lowest risk. This study aimed to evaluate whether high-efficacy disease-modifying therapy (HE-DMT) reduced the risk of relapse and disability accumulation in individuals at high risk of aggressive MS, and whether treatment benefit varied by MS severity.

Methods This observational cohort study used longitudinal data from two registries: MSBase (international) and OFSEP (France). Adults with relapse-onset MS and an EDSS score recorded within 12 months of symptom onset were included. Patients were classified into high-risk or low-risk groups for aggressive MS based on the above strata; those at intermediate risk were excluded. A pseudo-cohort framework compared periods of continuous HE-DMT (fingolimod, cladribine, monoclonal antibodies) with periods of non-HE-DMT states (on lower-efficacy DMTs or untreated) within each aggressive MS risk stratum. Marginal structural models with repeated adjustment for time-varying confounders of treatment and censoring were used to estimate counterfactual cumulative hazards of relapses and 6-month confirmed disability worsening and improvement. An interaction between MS risk stratum and treatment strategy was tested. A secondary analysis evaluated patients who received an HE-DMT during the study period.

Results In total, 10,405 people (2021 high risk, 8384 low risk) were included. Continuous HE-DMT reduced the risk of relapse in both high-risk and low-risk groups. There was no evidence of a difference in disability outcomes between treatment approaches. There was no evidence of an interaction between aggressive MS risk and treatment effect. In stratified analyses, lowest relapse risk was observed in the low-risk group treated with HE-DMT (hazard ratio [HR] 0.75, 95% CI 0.69–0.80). Treatment with HE-DMT was associated with relapse risk comparable to that observed in the low-risk group not treated with HE-DMT (HR 0.99, 0.87–1.13). In a secondary analysis restricted to patients who receive HE-DMT during the study timeframe, treatment with HE-DMT reduced the risk of disability worsening in the high-risk group (HR 0.75, 0.58–0.99), to the level observed in the low-risk group (HR 0.80, 0.70–0.92).

Conclusions HE-DMTs reduced the risk of relapse in people at both high and low risk of aggressive MS, with no evidence of differential treatment benefit. In the overall population, no evidence of a difference in disability outcomes between HE-DMT-treated and HE-DMT-untreated time was observed. However, among patients ever exposed to HE-DMT, disability worsening was less common while treated with HE-DMT.

1 Introduction

Multiple sclerosis (MS) is a heterogeneous disease with a spectrum of disease severity and associated disability. Six percent of people with MS (pwMS) have an aggressive MS course, defined as requiring ambulatory assistance (Expanded Disability Status Scale [EDSS] score of 6) within 10 years of MS onset [1, 2]. A longitudinal cohort study from MSBase identified that pwMS ≥35 years at MS symptom onset with an EDSS of ≥3 within the first year have a 21% rate of developing aggressive MS [2]. In contrast, those without these features are at lowest risk of aggressive MS (rate: 1.4%). Therefore, pwMS can be stratified into high and low risk groups as early as the first year from MS symptom onset.

MS treatment has shifted toward widespread high-efficacy (HE) disease-modifying therapy (DMT) use, backed by growing evidence of its role in reducing disability accumulation and progression to secondary progressive MS [3–6].

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Key Points

It is uncertain whether the need for high-efficacy disease-modifying therapy (HE-DMT) differs between patients at highest and lowest risk of developing severe forms of multiple sclerosis (MS).

This observational cohort study provides evidence that although some people with MS are at low risk of aggressive MS, they benefit from high-efficacy therapies to prevent relapses to a similar extent as people with MS at high risk of aggressive MS.

Among patients who qualified for treatment with HE-DMT, HE-DMT exposure reduced disability accumulation.

While HE-DMTs are intuitively preferred over escalation for pwMS at high risk of aggressive MS, this group is small and underrepresented, limiting direct evidence [7]. Additionally, it is uncertain whether there is a differential benefit of HE-DMTs, and whether this approach is necessary for pwMS at the lowest risk of developing aggressive MS. Given the potential risks associated with HE-DMTs, it is crucial to determine if it is reasonable or necessary to treat all pwMS with HE-DMTs regardless of their risk of developing aggressive MS [8].

We present a study from two longitudinal MS cohorts with the aim of quantifying differences in relapse and disability outcomes between periods treated with HE-DMT and periods not treated with HE-DMT (i.e., treated with lower-efficacy DMTs or untreated) and among patients with predicted aggressive and mild course of MS. Comparisons of observational data between periods in HE-DMT and non-HE-DMT states are complicated by reverse causality. To address this, the study employed causal inference methods, specifically marginal structural models with inverse probability weighing, to estimate the causal effect of remaining in HE-DMT versus non-HE-DMT states over time [9–11].

2 Materials and Methods

2.1 Study Design

We designed an observational cohort study using data from two large non-overlapping MS registries: MSBase (an international MS registry, ACTRN12605000455662) [12] and OFSEP (Observatoire Français de la Sclérose en Plaque, the French national MS registry) [13]. MSBase is an international, prospectively collected cohort including more than 80,000 patients from 150 centres at the time of data extract. OFSEP is the French national MS registry that integrates clinical and imaging data from 33 specialised MS centres across France. The study quantified the effects of remaining in an HE-DMT state in comparison to remaining in a non-HE-DMT state, using a marginal structural model with inverse probability weighting to adjust for time-dependent confounding.

2.2 Study Population

Longitudinal data were extracted from MSBase and OFSEP in May 2023 and May 2022, respectively. PwMS with relapse-onset MS and a first visit within 12 months of MS symptom onset were assessed for inclusion. Further minimum data was ≥ 2 subsequent disability scores ≥ 6 months apart, ≥ 1 disability score per year, and presence of the minimum dataset required to adjust for confounders (see Procedures). PwMS were followed from MS onset to date of the last available visit. The following DMTs were considered HE: sphingosine 1-phosphate inhibitors, cladribine, daclizumab, anti-CD20 therapies, mitoxantrone, natalizumab, and alemtuzumab [4, 5, 14]. All other DMTs were not considered to be HE. PwMS previously in clinical trials or treated with stem cell transplantation were excluded.

2.3 Procedures

The date of the first reported MS symptom was considered the date of MS onset. PwMS aged ≥ 35 years at MS onset with a maximum EDSS score ≥ 3 in the first year were classified at high risk of aggressive MS. PwMS with none of these features (i.e., < 35 years at MS onset and maximum EDSS score < 3 in year 1) were classified as low risk. PwMS not fitting into either group were classified as intermediate risk and were excluded to focus on treatment outcomes at both extremes of aggressive MS risk.

The follow-up time was segmented into 6-month intervals (bins), with potential confounders of treatment effect recorded in each bin (see Statistical Analysis section). Treatment status was updated in each bin. Bins in which a HE-DMT was recorded for ≥ 15 days were classified as "HE-DMT", and all other bins were classified as "not HE-DMT", consistent with prior work [10]. This conservative threshold minimises misclassification by avoiding the assignment of active treatment time to the comparison state, which would bias estimates toward the null. Each patient could therefore contribute to both the HE and not-HE pseudocohorts at different times.

The EDSS was used to quantify disability [15]. Annual disability scores were required. Where no new disability score was available during a 6-month period, the preceding EDSS was carried forward consistent with prior methodology in observational cohorts [10]. This was required in only

30% of time bins, and no score was carried forward more than once. Relapses were defined as new/exacerbation of existing symptoms persisting for ≥ 24 h, in the absence of a concurrent illness/fever and occurring ≥ 30 days after a previous relapse. The presence/absence of new/enlarging T2 hyperintense or contrast-enhancing lesions on MRI brain was reported using institutional protocols. MRI activity was treated as present only when explicitly recorded.

Data were prospectively collected mainly from academic MS centres during routine clinical care and recorded into the MSBase data entry system or European Database for Multiple Sclerosis (EDMUS, OFSEP) [13, 16]. Rigorous data quality assurance procedures were applied (electronic supplementary material [ESM] Table S1) [17].

2.4 Approvals

The study was approved by the Melbourne Health Human Research Ethics Committee and local ethics committees. Written informed consent was provided by patients. Requirements of the French Data Protection Agency were fulfilled.

2.5 Outcomes

Outcomes were separately evaluated in pwMS at high and low risk of reaching aggressive MS. The primary study outcomes were the probabilities of experiencing relapses, disability accumulation, and disability improvement. Disability accumulation was defined as an increase in EDSS by 1 step (1.5 steps if baseline EDSS 0, 0.5 steps if baseline EDSS > 5.5) confirmed over ≥ 6 months (with confirmation occurring in the absence of a relapse in the preceding 30 days) [18]. Disability improvement was defined as a decrease in EDSS by 1 step (1.5 steps if baseline EDSS ≤ 1.5, 0.5 steps if baseline EDSS > 6) confirmed over ≥ 6 months. Carryover EDSS scores were not used as either a baseline or confirmation for confirmed disability endpoints. Reaching EDSS step 6, sustained for the duration of follow-up, was a secondary outcome (only pwMS with EDSS ≤ 6 at baseline included). The interaction of aggressive MS risk with treatment strategy was evaluated.

2.6 Statistical Analysis

Statistical analyses were performed using R. To mitigate confounding between treatment allocation and disease outcomes, marginal structural models were used to compare the counterfactual cumulative hazards of events between patients who had versus those who had not initiated and continuously taken HE-DMTs over follow-up [19, 20].

Stabilised normalised inverse probability of treatment weights were calculated in each 6-month bin based on the inverse of each person's probability of receiving HE-DMT conditional on their baseline, time-dependent, and stabilising variables [20, 21]. Treatment status, age, sex, MS course and duration, relapses (number in the preceding 0–12 months and total number since MS onset), disability score (EDSS), EDSS change in the past year, and MRI activity in the prior 12 months (defined as the number of MRI brain scans showing new/enlarging T2 lesions or gadolinium-enhancing lesions) were included as time-dependent variables. Birth date, country, and date of first MS symptom were included as stabilising variables. To account for censoring, stabilised normalised inverse probability of censoring weights were calculated using the same variables [22]. The final weight was calculated by multiplying the inverse probability of treatment and censoring weights within each bin and then cumulatively across all preceding bins. Weights were truncated at the 1st and 99th percentiles to reduce the influence of extreme values; however, no trimming was applied. Covariate balance was assessed by standardised mean differences.

Weighted Andersen-Gill marginal structural models were used to compare the cumulative hazards of relapses, disability accumulation, and disability improvement events, among pseudocohorts who were hypothetically always versus never treated with HE-DMTs [23]. Weighted marginal structural Cox models were used to compare the cumulative hazards of reaching EDSS 6 between these pseudo cohorts. To assess the potential influence of unmeasured confounding, we calculated *E*-values for the hazard ratios of all primary outcomes [24].

An additional analysis included an interaction term between HE treatment status and predicted aggressive MS risk to evaluate the differential effect of HE-DMTs on the above outcomes across the two risk groups.

Models were clustered by patient to account for within-subject correlation. The weighted models were adjusted for additional variables if the standardised mean difference between weighted groups exceeded 0.2, and for visit density for disability outcomes. The proportional hazards assumption was evaluated using global and covariate-specific Schoenfeld residuals. Because treatment status was the primary exposure, violations were defined based on the treatment-specific residuals. In the event of a violation, we fitted a treatment-by-time interaction term and conducted time-stratified Cox models for the periods before and after the point of violation.

A secondary analysis was performed, including only pwMS who were treated with an HE-DMT during the recorded follow-up, reflecting individuals for whom HE-DMT was considered a clinically realistic treatment [14].

Sensitivity analyses were performed to further explore the impact of geographic variability, treatment effects during 6-month periods, and variable missingness: (1) evaluating differential treatment effects between registries, (2)

excluding partially treated bins, and (3) because MRI activity was missing in 43% of periods, we conducted a multiple-imputation analysis using an expectation–maximisation with bootstrapping framework to impute MRI activity as a time-varying covariate [25]. Twenty imputed datasets were generated using all variables predictive of MRI activity or missingness.

3 Results

3.1 Study Population

Of 52,804 pwMS with a visit within 12 months of MS onset, the risk of aggressive MS was estimated in 14,869 patients (Fig. 1). A total of 2021 pwMS aged ≥ 35 years at MS onset with EDSS ≥ 3 within the first year were at high risk of aggressive MS. Conversely, 8384 pwMS with none of these features were at low risk of aggressive MS. Excluded patients were older and had shorter prospective follow-up than those who were included (ESM Table S2). There were no substantial differences among the included cohorts stratified by registry (ESM Table S3).

The median time from MS onset to first visit was 5 months (Table 1). EDSS measurements were available in 70% of all 6-month periods. Completeness was slightly higher during periods on high-efficacy therapy (73%) compared with non-HET periods (68%), although distributions overlapped substantially. Data on brain MRI from the previous 12 months was available for 52% of the study periods. Descriptive checks showed no consistent pattern of demographic or clinical characteristics associated with MRI missingness. PwMS at high risk of aggressive MS had a mean age at MS onset of 45 years, and a maximum EDSS of 3.5 in year 1. Of the 561 pwMS at high risk of aggressive MS with ≥ 10 years' follow-up, 128 (22.8%) reached an EDSS score of ≥ 6 within 10 years since MS onset, therefore fulfilling the definition of aggressive MS.

PwMS at low risk of aggressive MS had a mean age at MS onset of 27 years, and a maximum EDSS of 1.5 in year 1. Of the 2423 pwMS at low risk of aggressive MS with ≥ 10 years' follow-up, 94 (3.9%) fulfilled the definition of aggressive MS.

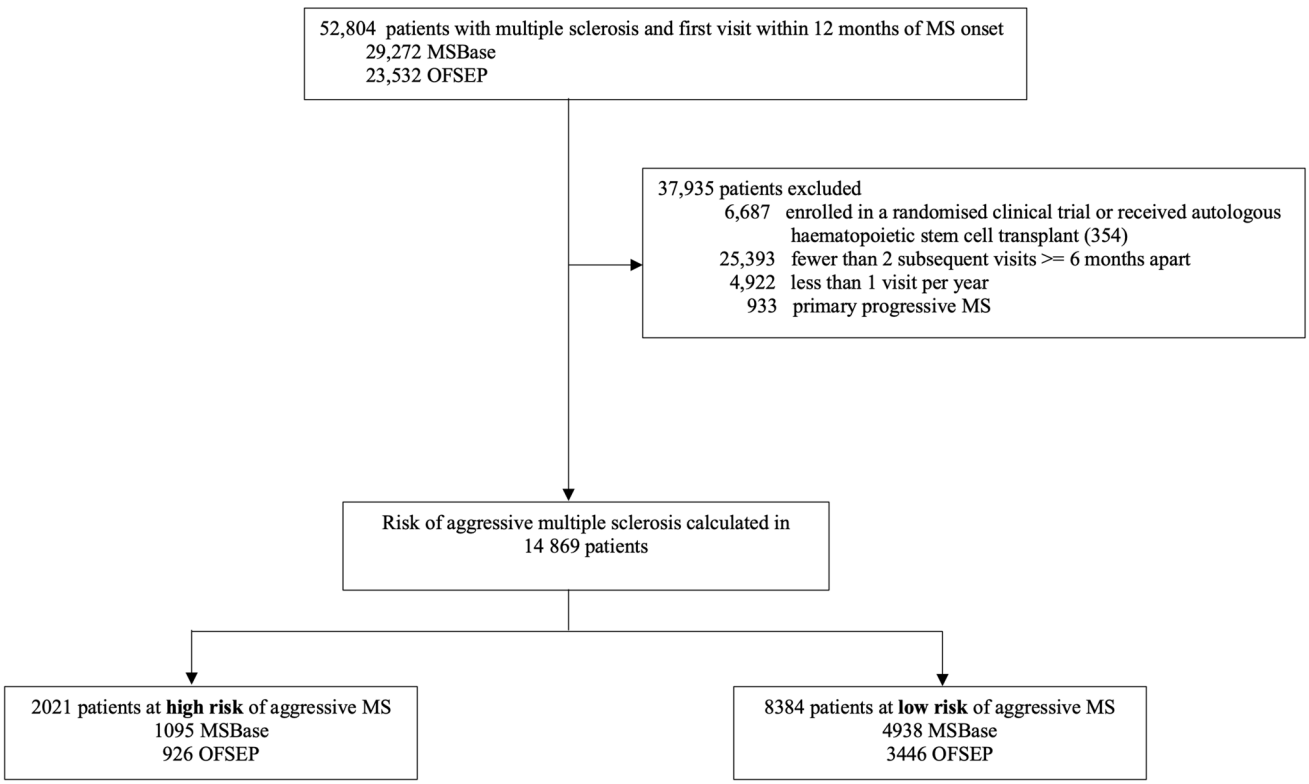

Fig. 1 Consort diagram of patient disposition. High-efficacy therapies: sphingosine 1-phosphate inhibitors, cladribine, daclizumab, anti-CD20 therapies, mitoxantrone, natalizumab and alemtuzumab. Patients at high risk of aggressive MS are aged ≥ 35 years at MS onset and have a maximum EDSS ≥3 within the first year of MS onset. Patients at low risk of aggressive MS have neither of these characteristics. All other patients are at intermediate risk of MS and are excluded from the analysis. *EDSS* Expanded Disability Status Scale, *MS* multiple sclerosis

3.2 Inverse Probability of Treatment and Censoring Weights

Stabilised normalised inverse probability of treatment and censoring weights for each patient at each 6-monthly period were calculated based on the probability of receiving HE-DMT at any period, conditional on patients' demographic information, MS history, and previous treatment exposure. The weights followed an expected distribution, indicating good model specification (ESM Figure S1, ESM Table S4). Acceptable covariate balance (<0.2) was maintained overall (Fig. 2), and at most 6-monthly bins (ESM Figure S2).

Table 1 Characteristics of the study cohort

	Aggressive MS risk	
	High	Low
Patients, *n* (%)	2021	8384
Female	1398 (69.2)	6025 (71.9)
Male	623 (30.8)	2359 (28.1)
Registry, *n* (%)		
MSBase	1095 (54.2)	7289 (39.9)
OFSEP	926 (45.8)	3446 (41.1)
Age, years	45 (7)	27 (5)
Disease duration (first visit), years	0.5 [0.3, 0.8]	0.5 [0.4, 0.8]
Disability (first visit), EDSS	3.0 [2.8, 4.0]	1.0 [0.0, 2.0]
Maximum disability in first year, EDSS	3.5 [3.0, 4.5]	1.5 [1.0, 2.0]
Disability (last visit), EDSS	3.5 [2.0, 5.5]	1.0 [0.0, 2.0]
MS course at first visit		
Clinically isolated syndrome	1367 (67.6)	5630 (67.2)
Relapsing–remitting	654 (31.5)	2753 (32.8)
Visit interval, months	6.4 [4.8, 8.4]	6.6 [5.0, 8.5]
Prospective follow-up, years	6.1 [3.6, 10.7]	6.5 [3.7, 10.8]
Patients with MRI recorded, *n* (%)	1953 (97)	8203 (98)
Proportion of follow-up time on, (%)		
High-efficacy DMTs	23 [0, 55]	24 [0, 48]
Not on high-efficacy DMTs	77 [45,100]	76 [52, 100]
No DMTs	16 [0, 60]	15 [0, 44]
Treatment strategy at any time during follow-up, no. of patients (%)		
Alemtuzumab[(H)]	32 (2)	176 (2)
Natalizumab[(H)]	383 (19)	1499 (18)
Mitoxantrone[(H)]	114 (6)	138 (2)
Ocrelizumab/rituximab/ofatumumab[(H)]	255 (13)	907 (11)
Daclizumab[(H)]	1 (0)	9 (0)
Cladribine[(H)]	41 (2)	225 (3)
Fingolimod/ozanimod[(H)]	358 (18)	1910 (23)
Siponimod[(H)]	7 (0)	4 (0)
Dimethyl fumarate	250 (12)	1396 (17)
Teriflunomide	242 (12)	977 (12)
Interferon beta/glatiramer acetate	1091 (54)	5463 (65)
Untreated	1452 (72)	5969 (71)
Number of DMTs during follow-up	1 [0, 1]	1 [0, 2]
Year of baseline	2012 [2006, 2015]	2012 [2007, 2016]

Data are presented as mean (SD) or median [quartiles] as appropriate

[(H)]High-efficacy disease-modifying therapy

DMT disease-modifying therapy, *EDSS* Expanded Disability Status Scale, *MRI* magnetic resonance imaging, *MS* multiple sclerosis

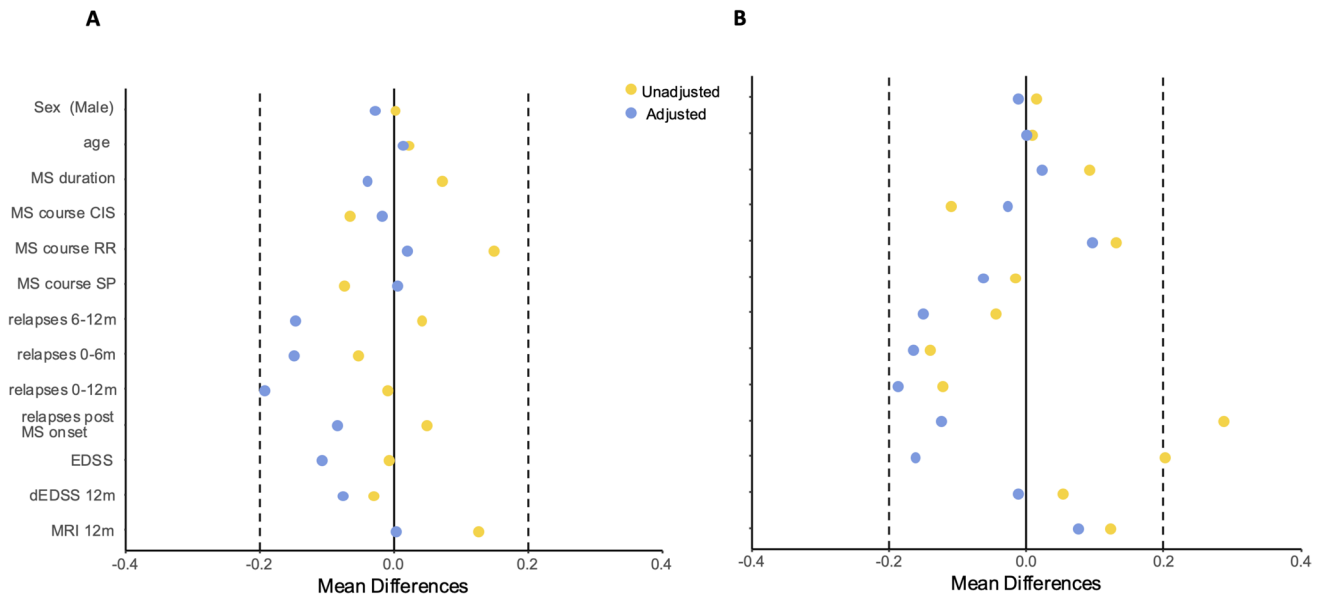

Fig. 2 Overall covariate balance in people at (**A**) high risk of aggressive MS and (**B**) low risk of aggressive MS. This figure shows the average covariate balance over the entire follow up. Covariate balance over years is shown in the electronic supplementary material. *CIS* clinically isolated syndrome, *dEDSS* difference in EDSS, *MS* multiple sclerosis, *SP* secondary progressive

3.3 Disease Outcomes

We first estimated treatment effects within the high risk and low risk of aggressive MS groups separately, followed by a combined stratified analysis including a treatment-by-risk interaction term to enable comparison across the two groups.

3.3.1 High Risk of Developing Aggressive Multiple Sclerosis (MS)

Among pwMS at high risk of developing aggressive MS, the pseudo cohort remaining continuously in HE-DMT states was less likely to experience relapses than the pseudo cohort not in HE-DMT states (annualised relapse rate [ARR] 0.20 vs 0.28; hazard ratio [HR] 0.78, 95% confidence interval [CI] 0.70–0.86; Fig. 3A). There was no evidence for a difference in cumulative hazards of disability accumulation (HR 0.93, 95% CI 0.77–1.12; Fig. 3B), disability improvement (HR 0.87, 95% CI 0.74–1.02; Fig 3C) or the probability of reaching EDSS step 6 (HR 1.16, 95% CI 0.87–1.54; ESM Figure S3A) between treatment approaches.

3.3.2 Low Risk of Developing Aggressive MS

Among pwMS at low risk of developing aggressive MS, the pseudo cohort remaining continuously in HE-DMTs states was less likely to experience relapses than the pseudo cohort not in HE-DMT states (ARR 0.18 vs 0.28; HR 0.72, 95% CI 0.67–0.77; Fig. 3D). There was no evidence for a difference in the cumulative hazards of disability accumulation (HR1.08, 95% CI 0.96–1.22; Fig. 3E), disability improvement (HR 1.01, 95% CI 0.86–1.18; Fig. 3F), or the probability of reaching EDSS step 6 (HR 1.10, 95% CI 0.77–1.56; ESM Figure S3B) between treatment approaches.

3.3.3 Robustness to Unmeasured Confounding

Outcomes showed moderate robustness to unmeasured confounding (ESM Table S5).

3.3.4 Interactions Between the Risk of Aggressive MS and High-Efficacy Therapy

There was no evidence of interactions between treatment with HE-DMTs and the risk of aggressive MS: relapses (HR 0.96, 95% CI 0.85–1.10), disability accumulation (HR 0.87, 95% CI 0.70–1.06), disability improvement (HR 0.82, 95% CI 0.66–1.01), and reaching an EDSS of 6 (HR 0.98, 95% CI 0.63–1.52).

In pwMS at high risk of aggressive MS, HE-DMT states reduced the risk of relapses to the risk observed in pwMS at low risk of aggressive MS not on HE-DMTs (Table 2). The cumulative risk of relapses was lowest in pwMS at low risk of aggressive MS treated with HE-DMTs (HR 0.75, 95% CI 0.69–0.80; reference: low-risk not in HE-DMT states). Lack of treatment with HE-DMTs exposed pwMS at high risk of aggressive MS to a higher risk of relapse (HR 1.37, 95% CI 1.25–1.51).

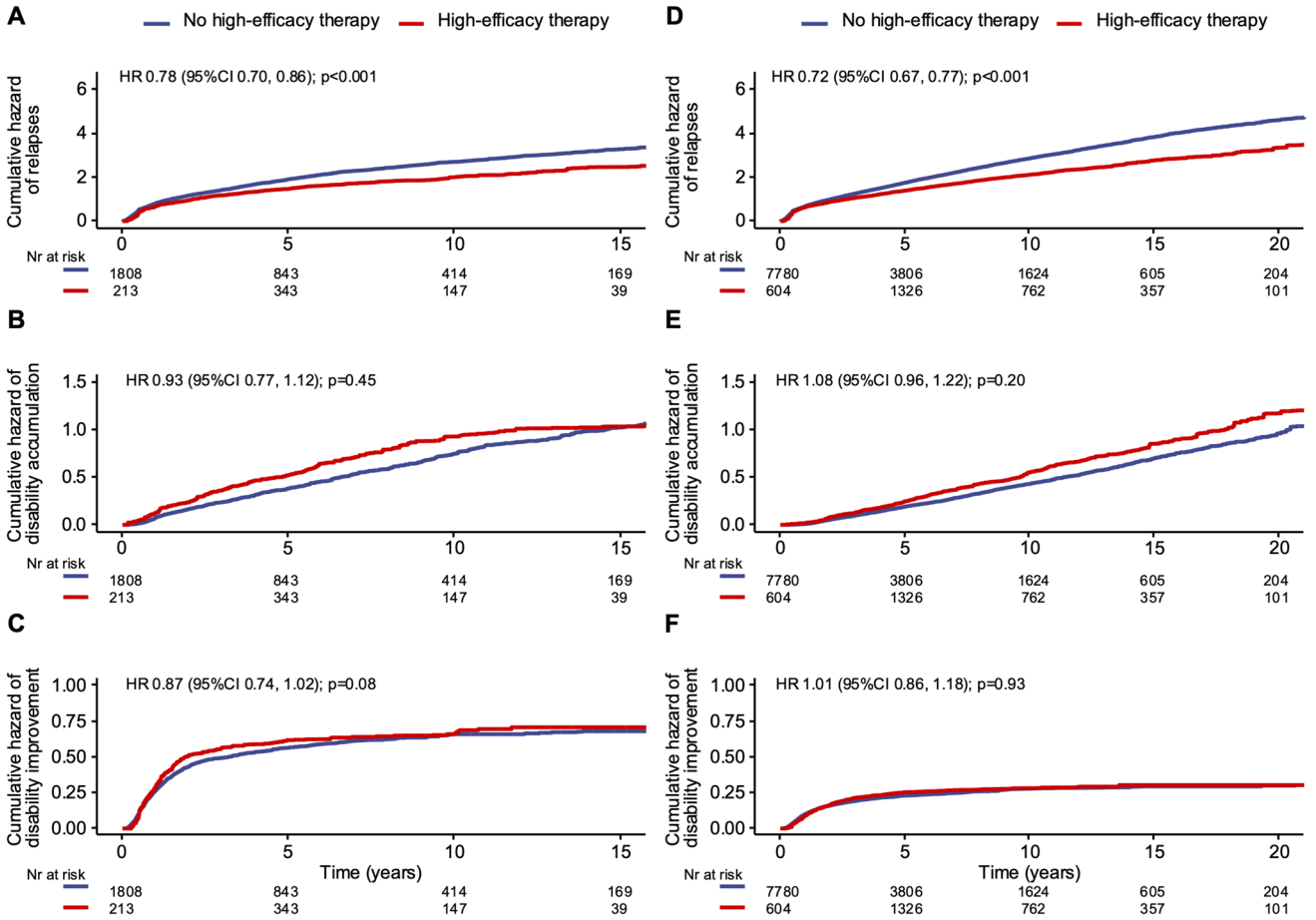

Fig. 3 Study outcomes. Comparison of cumulative hazards of relapses (**A**, **D**), disability accumulation (**B**, **E**), and disability improvement (**C**, **F**) comparing pseudocohorts in the high-efficacy therapy versus non-high-efficacy therapy treatment states. People at high risk of aggressive MS are in **A**, **B**, **C**. Patients at low risk of aggressive MS are in **D**, **E**, **F**. *MS* multiple sclerosis

Table 2 Outcomes stratified by aggressive MS risk and HE-DMT treatment states

		Relapses HR (95% CI)	Disability accumulation HR (95% CI)	Disability improvement HR (95% CI)	Time to EDSS 6 HR (95% CI)
Low risk of aggressive MS	No HE-DMT state	*Ref.*	*Ref.*	*Ref.*	*Ref.*
	HE-DMTs state	**0.75 (0.69–0.80)**	1.10 (0.98–1.25)	0.98 (0.84–1.14)	1.19 (0.86–1.64)
High risk of aggressive MS	No HE-DMT state	**1.37 (1.25–1.51)**	1.15 (0.97–1.36)	**1.82 (1.54–2.16)**	**1.58 (1.04–2.39)**
	HE-DMTs state	0.99 (0.87–1.13)	1.10 (0.88–1.39)	**1.47 (1.19–1.82)**	1.84 (0.95–2.94)

Bold formatting indicates statistical significance

CI confidence interval, *EDSS* Expanded Disability Status Scale, *HE-DMT* high-efficacy disease-modifying therapy, *HR* hazard ratio, *MS* multiple sclerosis, *Ref.* reference

There was no evidence of a difference in the risk of disability accumulation stratified by aggressive MS risk and HE-DMT state.

While the probability of disability improvement was higher in pwMS at high risk of aggressive MS, the observed risk of disability improvement did not differ between treatment approaches. There was no evidence for a difference in the risk of disability improvement in pwMS at low risk of aggressive MS who were versus were not in HE-DMT states.

The risk of reaching an EDSS of 6 was highest in pwMS at high risk of aggressive MS, particularly when not in HE-DMT states (HR 1.58, 95% CI 1.04–2.39; reference: low risk not in HE-DMT states).

3.3.5 Secondary Analysis Within the Subgroup Exposed to High-Efficacy Disease-Modifying Therapy (HE-DMT)

A total of 893 patients at high risk of aggressive MS and 3667 patients at low risk of aggressive MS were treated with HE-DMT during the study period (ESM Table S6). Overall covariate balance was acceptable (ESM Figure S4). Standardised mean differences exceeded 0.2 in some 6-month bins for relapse and EDSS covariates in the high-risk group, and for relapse covariates in the low-risk group, and models were adjusted accordingly.

The results for relapse outcomes confirm those of the primary analysis (ESM Table S7A and Table 7B). Among pwMS at high risk of developing aggressive MS, the pseudocohort remaining continuously in HE-DMT states was less likely to experience relapses than the pseudocohort not in HE-DMT states (ARR 0.21 vs 0.40; HR 0.61, 95% CI 0.54–0.69). Among pwMS at low risk of developing aggressive MS, the pseudocohort remaining continuously in HE-DMT states was less likely to experience relapses than the pseudo cohort not in HE-DMT states (ARR 0.19 vs 0.41; HR 0.59, 95% CI 0.55–0.63).

The results for disability accumulation however differed from the primary analysis (ESM Table S7A and 7B). Pseudocohorts in HE-DMT states had a lower probability of disability accumulation in both the high-risk (HR 0.72, 95% CI 0.59–0.89) and the low-risk (HR 0.79, 95% CI 0.70–0.91) of aggressive MS risk groups. Furthermore, the low-risk of developing aggressive MS strata had a lower probability of reaching an EDSS step of 6 in HE-DMT states (HR 0.79, 95% CI 0.70–0.91). HE-DMTs reduced the hazard of disability accumulation in the high-risk of aggressive MS group below the hazard in the low-risk group not treated with HE-DMTs (HR 0.75, 95% CI 0.58–0.98).

3.3.6 Sensitivity Analyses

There was no evidence of effect modification by registry for any outcome in either risk group (ESM Table S8). Sensitivity analyses excluding partially treated bins, and using multiple imputation of missing MRI data, yielded treatment-effect estimates consistent with the primary analyses (ESM Table S9).

4 Discussion

This study of pwMS from two large MS registries (MSBase and OFSEP) demonstrates that the association between HE-DMT and reduced relapse risk is consistent across prognostic MS subpopulations. Continuous time spent on HE-DMTs reduces the risk of relapses compared with time spent in non-HE-DMT states (i.e., lower-efficacy therapies or untreated) among pwMS at both high and low risk of developing aggressive MS. Furthermore, treatment with HE-DMTs is associated with a marked attenuation of the excess relapse risk observed in the high-risk stratum to the risk observed in pwMS at low risk of aggressive MS not treated with HE-DMTs. Overall, no evidence of a difference in disability outcomes between treatment approaches was detected. However, among a subgroup of patients who required HE-DMT during the follow-up, HE-DMT reduced the risk of disability accumulation in pwMS at high risk of aggressive MS to or below the risk observed in pwMS at low risk of aggressive MS.

Prognostication of MS disease severity, particularly with the aim of identifying pwMS at greatest risk of rapid disease progression and significant accumulation of disability over a short period is a clinical priority. Among several proposed definitions of aggressive MS, reaching an EDSS score of ≥6 within 10 years since disease onset is most commonly used, with a population risk of 6% [1, 2, 26]. The Barcelona inception cohort showed that pwMS with ≥20 T2 lesions and ≥2 Gd+ lesions on MRI brain at the time of the first demyelinating event have a 20% chance of developing aggressive MS [1]. A previous study from MSBase (conducted in a partially overlapping cohort) identified that 21% of pwMS older than 35 years at MS onset, with an EDSS ≥ 3 within the first year, develop aggressive disease [2]. Our study, in a combined dataset from MSBase and OFSEP, identified a similar risk (22.8%) of fulfilling the definition of aggressive MS among pwMS with these characteristics. In contrast, 3.9% of pwMS with none of these characteristics developed aggressive MS. This observation underscores the high discrimination ability of the present predictive model of aggressive MS. For this study, we have simplified the prediction of the risk of aggressive MS to two accessible clinicodemographic characteristics. However, we acknowledge that the trajectory of aggressive MS risk is complex and may change over time. In this study, predicted risk of aggressive MS was used solely to stratify the cohort, allowing assessment of treatment response at both risk extremes while excluding intermediate-risk cases.

Studies on the comparative effectiveness of HE-DMT in populations enriched with people with aggressive MS are scarce. People with aggressive MS are underrepresented in contemporary trials [7], and observational comparisons

typically focus on common treatment scenarios rather than prognostic subgroups [27]. The present work provides a novel perspective by comparing two hypothetical approaches to MS therapy—remaining in an HE-DMT state versus remaining in a non-HE-DMT state—at both extremes of aggressive MS risk. While we recognise that these two extremes are rarely encountered in contemporary practice, they allow us to estimate the net therapeutic benefit that HE-DMTs can offer. We found that treatment with HE-DMT was effective at reducing the risk of relapses across pwMS at both high and low risk of aggressive MS, and that pwMS at high risk of aggressive MS not treated with HE-DMT were more likely to reach significant disability (EDSS 6) than those at low risk. Improvement in disability outcomes was confined to patients who warranted treatment with HE-DMT during follow-up. In this subgroup, treatment with HE-DMTs led to a lower risk of disability accumulation in pwMS at high risk of aggressive MS (approximately 25% of the patients), similar to the 20% reduction observed in pwMS at low risk of aggressive MS compared with patients in the non-HE-DMT state. This suggests that while some pwMS are at low risk of requiring a gait aid within 10 years from MS onset, they are still at risk of relapse and disability accumulation. Reassuringly, this risk can be effectively mitigated by proactive choice of therapy. These findings complement a 30-year observational study of patients with 'benign MS', defined as an EDSS ≤ 3 ten years after MS onset, whose risk of subsequent disability accrual was not negligible and could not be accurately predicted [28]. The improvement in disability outcomes among the patients treated with HE-DMT during follow-up warrants cautious interpretation. This subgroup represents individuals whose treatment course included escalation to HE-DMT, with escalation decisions influenced by evolving disease activity and clinical trajectory. While treatment effects are estimated by contrasting periods on and off HE-DMT in both analyses, restricting analysis to patients who escalated during follow-up conditions the analysis on treatment trajectory and limits generalisability. As such, disability findings in this subgroup should be interpreted as exploratory.

Disability improvement was observed more frequently among pwMS at high risk of aggressive MS, regardless of treatment state. This likely reflects a greater burden of relapse-associated and potentially reversible disability in this group. In pwMS at lower risk of aggressive MS, and therefore by definition with lower baseline disability, opportunities for measurable improvement are more limited.

This study has several limitations. First, the main limitation of this study is its observational nature. However, data were collected from two large, non-overlapping multicentre cohorts, increasing the generalisability of the findings. All data underwent rigorous quality control procedures [29]. Marginal structural models enable us to repeatedly rebalance groups for time-varying confounders, which helps mitigate the risk of measured confounding. However, the risk of unmeasured confounding remains, particularly in relation to MRI measures. However, we, and others, have previously shown that the inclusion of MRI does not change the results of comparative effectiveness studies [10, 30]. While treatment effect estimates using imputed MRI data were consistent in magnitude and direction with the subgroup analysis, indicating that the conclusions were robust to the handling of MRI missingness, extensive missing MRI data remain a potential source of unmeasured confounding, and this should be considered when interpreting the findings. While EDSS scores were carried forward for a single interval in 29% of bins, these values were not used to define or confirm disability outcomes. We have achieved acceptable overall balance of all included covariates, and have accounted for informed censoring by weighting on the inverse probability of censoring. In the subgroup analysis requiring treatment with HE-DMTs, residual covariate imbalance (SMD >0.2) occurred at isolated intervals, predominantly in variables closely linked to treatment escalation decisions (e.g., short-term relapse activity), and may reduce the strength of causal interpretation. Conclusions should be interpreted with this context in mind. Second, all included pwMS had a first recorded visit within 12 months of MS onset (to accurately stratify aggressive MS risk). PwMS with the mildest forms of MS may therefore have been excluded from the main analysis. Third, safety data were insufficient to include a safety comparison in the present analysis. The clinical application of these findings should be considered in the context of the established safety profiles of HE-DMTs. Fourth, this study compared outcomes between periods in the HE-DMT treatment state and periods in the non-HE-DMT state. Periods when pwMS were either untreated or received therapies other than HE-DMTs were grouped together, which may have obscured differential effects between these categories. Importantly, a median of only 15–16% of follow-up time was spent untreated. Fifth, this study utilises a counterfactual framework to model the overall magnitude of the effect of continuous treatment with HE-DMTs rather than the timing of HE therapies or comparative effectiveness of high-efficacy versus low-efficacy DMTs in this population. It was therefore not designed to evaluate specific treatment sequences, escalation strategies, or individual HE-DMTs.

5 Conclusion

In this study, we used a causal inference framework to show that continuous treatment with HE-DMTs, compared with periods not on HE-DMTs, is associated with a substantially lower risk of relapse in pwMS at both high and low risk

of aggressive MS. Relapse-reducing benefits are consistent across prognostic strata, indicating that patients at low predicted risk of aggressive disease derive comparable protection against relapses to those at high risk. In contrast, no evidence of a difference in disability outcomes was observed at the population level; however, among patients who warrant treatment with HE-DMT, HE-DMT reduces the risk of disability worsening. Overall, our findings support the use of HE-DMTs for effective relapse control across prognostic MS strata, while disability outcomes appear more dependent on treatment context. The decisions concerning personalised choice of therapy remain complex, involving not only treatment efficacy, but also safety, accessibility, and acceptability, and require a holistic approach and clinical judgement.

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Declarations

Conflict of interest Izanne Roos has served on scientific advisory boards, received conference travel support and/or speaker honoraria from Roche, Novartis, Merck, Neuraxpharm and Biogen. Sifat Sharmin did not declare any competing interests. Serkan Ozakbas did not declare any competing interests. Raed Alroughani received honoraria as a speaker and for serving on scientific advisory boards from Bayer, Biogen, GSK, Merck, Novartis, Roche and Sanofi-Genzyme. Sara Eichau has received speaker honoraria and consultant fees from Biogen Idec, Novartis, Merck, Janssen, Bristol-Meyers, Bayer, Sanofi Genzyme, Roche and Teva. Francois Grand'Maison received honoraria or research funding from Biogen, Genzyme, Novartis, Teva Neurosciences, and ATARA Pharmaceuticals. Cavit Boz received conference travel support from Biogen, Novartis, Bayer-Schering, Merck and Teva, and has participated in clinical trials by Sanofi Aventis, Roche and Novartis. 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contributed to data acquisition and interpretation, provided methodological oversight, and critically revised the manuscript for important intellectual content. SS contributed to study design, interpretation of results, and manuscript review. SV contributed to study design, data acquisition, interpretation of results, and manuscript editing. SO, RA, SE, FG, CB, JLS, KB, AP, SJK, PG, AVdW, YB, MF, AS, MB, JP, MT, OG, RM, MJS, DS, GL, VvP, NJ, EC, RG, DM, CR, SH, MS, PM, JG, JLSM, AA, AGK, EL, VS, BVW, BW, TCT, BT, GM, ELP, JDS, AR, PC, EB, HZ, AK, JPel, TM, PL, JC, CLF, CP, GD, DAL, ET, BS, EM, AAK, BB, OC, ADS, JPC, KH, AW, PCa, OH, CPo, SM, LM, CLab, and ID contributed to data acquisition and/or participant recruitment and reviewed and edited the manuscript. All authors have read and approve the final version of the manuscript and agree to be accountable for the work.

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Consent to Participate Written informed consent was provided by patients. Requirements of the French Data Protection Agency were fulfilled.

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Authors and Affiliations

Izanne Roos[1,2] · Sifat Sharmin[2] · Serkan Ozakbas[3,4] · Raed Alroughani[5] · Sara Eichau[6] · Francois Grand'Maison[7] · Cavit Boz[8] · Jeannette Lechner-Scott[9,10] · Katherine Buzzard[11,12] · Alexandre Prat[13] · Samia J. Khoury[14] · Pierre Grammond[15] · Anneke van der Walt[16,17] · Yolanda Blanco[18] · Matteo Foschi[19,20] · Aysun Soysal[21] · Michael Barnett[22] · Julie Prevost[23] · Murat Terzi[24] · Oliver Gerlach[25,26] · Richard Macdonell[27] · Maria Jose Sa[28,29] · Daniele Spitaleri[30] · Guy Laureys[31] · Vincent van Pesch[32,33] · Nevin John[34,35] · Elisabetta Cartechini[36] · Riadh Gouider[37,38] · Davide Maimone[39] · Cristina Ramo-Tello[40] · Suzanne Hodgkinson[41] · Mark Slee[42] · Pamela McCombe[43] · Justin Garber[44] · Jose Luis Sanchez-Menoyo[45,46] · Abdullah Al-Asmi[47] · Allan G. Kermode[48,49,50,51] · Emmanuelle Lapointe[52] · Vahid Shaygannejad[53] · Bart Van Wijmeersch[54,55] · Barbara Willekens[56,57,58] · Tamara Castillo-Triviño[59] · Bruce Taylor[60,61] · Guillaume Mathey[62,63] · Emmanuelle Le Page[64] · Jerome De Seze[65,66] · Aurelie Ruet[67] · Pierre Clavelou[68,69] · Eric Berger[70] · Helene Zephir[71] · Arnaud Kwiatkowski[72] · Jean Pelletier[73] · Thibault Moreau[74] · Pierre Labauge[75] · Jonathan Ciron[76,77] · Christine Lebrun-Frenay[78] · Caroline Papeix[79] · Gilles Defer[80] · David Axel Laplaud[81] · Eric Thouvenot[82,83] · Bruno Stankoff[84] · Elisabeth Maillart[85] · Abdullatif Al-Khedr[86] · Bertrand Bourre[87] · Olivier Casez[88] · Amélie Dos Santos[89] · Jean-Philippe Camdessanche[90] · Karolina Hankiewicz[91] · Abir Wahab[92] · Philippe Cabre[93] · Olivier Heinzlef[94] · Corinne Pottier[95] · Solène Moulin[96] · Laurent Magy[97] · Céline Labeyrie[98] · Inès Doghri[99] · Sandra Vukusic[100,101,102,103] · Tomas Kalincik[1,2] on behalf of the MSBase and OFSEP Study Groups

✉ Tomas Kalincik
tomas.kalincik@unimelb.edu.au

[1] Department of Neurology, Neuroimmunology Centre, Royal Melbourne Hospital, L7 635 Elizabeth Street, Melbourne, VIC 3002, Australia

[2] CORe, Department of Medicine, University of Melbourne, Melbourne, Australia

[3] Medical Point Hospital, Izmir University of Economics, Konak/Izmir, Turkey

[4] Multiple Sclerosis Research Association, Izmir, Turkey

[5] Division of Neurology, Department of Medicine, Amiri Hospital, Sharq, Kuwait

[6] Department of Neurology, Hospital Universitario Virgen Macarena, Sevilla, Spain

[7] Neuro Rive-Sud, Greenfield Park, QC, Canada

[8] Department of Neurology, KTU Medical Faculty Farabi Hospital, Trabzon, Turkey

[9] Hunter Medical Research Institute, University Newcastle, Newcastle, Australia

[10] Hunter New England Health, John Hunter Hospital, Newcastle, NSW, Australia

[11] Department of Neurosciences, Box Hill Hospital, Melbourne, Australia

[12] Eastern Health Clinical School, Monash University, Box Hill, Australia

[13] CHUM MS Center and Universite de Montreal, Montreal, Canada

[14] Nehme and Therese Tohme Multiple Sclerosis Center, American University of Beirut Medical Center, Beirut, Lebanon

[15] CISSS Chaudière-Appalache, Levis, Canada

[16] Department of Neurology, The Alfred Hospital, Melbourne, Australia

[17] Department of Neuroscience, School of Translational Medicine, Monash University, Melbourne, Australia

[18] Service of Neurology, Center of Neuroimmunology, Hospital Clinic de Barcelona, Barcelona, Spain

[19] Neurology Unit, Department of Neuroscience, MS Center, S. Maria delle Croci Hospital of Ravenna, Ravenna, Italy

[20] Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy

[21] Bakirkoy Education and Research Hospital for Psychiatric and Neurological Diseases, Istanbul, Turkey

[22] Brain and Mind Centre, University of Sydney, Sydney, Australia

[23] CSSS Saint-Jérôme, Saint-Jerome, Canada

[24] Medical Faculty, 19 Mayis University, Samsun, Turkey

[25] Academic MS Center Zuyd, Department of Neurology, Zuyderland Medical Center, Sittard-Geleen, Netherlands

[26] School for Mental Health and Neuroscience, Department of Neurology, Maastricht University Medical Center, Maastricht, Netherlands

[27] Austin Health, Melbourne, Australia

[28] Department of Neurology, Centro Hospitalar Universitario de Sao Joao, Porto, Portugal

[29] FP-I3ID, Instituto de Investigação, Inovação e Desenvolvimento Fernando Pessoa, Porto, Portugal

[30] Azienda Ospedaliera di Rilievo Nazionale San Giuseppe Moscati Avellino, Avellino, Italy

[31] Department of Neurology, Universitary Hospital Ghent, Ghent, Belgium

[32] Department of Neurology, Cliniques Universitaires Saint-Luc, Brussels, Belgium

[33] Université Catholique de Louvain, Louvain-la-Neuve, Belgium

[34] Department of Medicine, School of Clinical Sciences, Monash University, Melbourne, Australia

[35] Department of Neurology, Monash Health, Clayton, Australia

[36] Neurology Unit, P O Unico Macerata, AST Macerata, Macerata, Italy

[37] Department of Neurology, LR 18SP03, Clinical Investigation Centre Neurosciences and Mental Health, Razi University Hospital, Tunis, Tunisia

[38] Faculty of Medicine of Tunis, University of Tunis El Manar, Tunis, Tunisia

[39] Centro Sclerosi Multipla, UOC Neurologia, Azienda Ospedaliera per l'Emergenza Cannizzaro, Catania, Italy

[40] Department of Neuroscience, Hospital Germans Trias i Pujol, Badalona, Spain

[41] Immune Tolerance Laboratory, Ingham Institute and Department of Medicine, UNSW, Sydney, Australia

[42] College of Medicine and Public Health, Flinders University, Adelaide, Australia

[43] Department of Neurology, University of Queensland, Brisbane, Australia

[44] Department of Neurology, Westmead Hospital, Sydney, Australia

[45] Department of Neurology, Hospital de Galdakao-Usansolo, Galdakao, Spain

[46] Biocruces-Bizkaia Health Research Institute, Barakaldo, Spain

[47] College of Medicine and Health Sciences, Sultan Qaboos University, Al-Khodh, Oman

[48] Perron Institute for Neurological and Translational Science, University of Western Australia, Nedlands, Australia

[49] Centre for Molecular Medicine and Innovative Therapeutics, Murdoch University, Perth, Australia

[50] Institute for Immunology and Infectious Diseases, Murdoch University, Perth, WA, Australia

[51] Sir Charles Gairdner Hospital, University of Western Australia, Nedlands, Australia

[52] Medicine, Division of Neurology, Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, Canada

[53] Isfahan University of Medical Sciences, Isfahan, Iran

[54] University MS Centre, Hasselt/Pelt, Belgium

[55] Noorderhart, Rehabilitation and MS, Pelt and Hasselt University, Hasselt, Belgium

[56] Department of Neurology, Antwerp University Hospital, Edegem, Belgium

[57] Translational Neurosciences Research Group, Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium

[58] Laboratory of Experimental Hematology, Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium

[59] Hospital Universitario Donostia, San Sebastián, Spain

[60] Royal Hobart Hospital, Hobart, Australia

[61] Menzies Institute for Medical Research, University of Tasmania, Hobart, Australia

[62] Department of Neurology, Nancy University Hospital, Nancy, France

[63] Université de Lorraine, APEMAC, Nancy, France

[64] Pontchaillou, CIC1414 INSERM, Rennes, France

[65] Department of Neurology, CHU de Strasbourg, Strasbourg, France

[66] INSERM 1434, Strasbourg, France

[67] Department of Neurology, University Hospital of Bordeaux, Bordeaux, France

[68] Department of Neurology, CHU Clermont-Ferrand, Clermont-Ferrand, France

[69] Université Clermont Auvergne, Inserm, Neuro-Dol, Clermont-Ferrand, France

[70] Service de Neurologie, CHU de Besançon, Besançon, France

[71] CHU Lille, CRCSEP Lille, Univ Lille, Lille, France

[72] GHICL, Department of Neurology, Université catholique de Lille, Lille, France

[73] Aix Marseille Univ, APHM, Hôpital de la Timone, Pôle de Neurosciences Cliniques, Marseille, France

[74] Department of Neurology, CHU de Dijon, Dijon, France

[75] Neurology Department, Montpellier University Hospital, Montpellier, France

[76] Department of Neurology, CHU de Toulouse, Toulouse, France

[77] Université de Toulouse, Inserm, CNRS, Toulouse, France

[78] CRCSEP, Service de Neurologie, Université Nice Cote d'Azur, Nice, France

[79] Department of Neurology, Fondation Rotschild, 75000 Paris, France

[80] Department of Neurology, Caen University Hospital, Caen, France

[81] Nantes Université, CHU Nantes, INSERM, Center for Research in Transplantation and Translational Immunology, UMR 1064, CIC INSERM 1413, Service de Neurologie, 44000 Nantes, France

[82] Department of Neurology, University Hospital of Nimes, Nimes, France

[83] CESP, Univ Montpellier, INSERM, Montpellier, France

[84] Sorbonne Universités, UPMC Paris 06, Brain and Spine Institute, ICM, Hôpital de la Pitié Salpêtrière, Inserm UMR S 1127, CNRS UMR 7225, and Department of Neurology, AP-HP, Saint-Antoine Hospital, 75000 Paris, France

[85] Department of Neurology, Hôpital Pitié-Salpêtrière, Paris, France

[86] Department of Neurology, CHU d'Amiens, 80000 Amiens, France

[87] Department of Neurology, CHU de Rouen, Rouen, France

[88] CHU Grenoble Alpes, Department of Neurology, Neurology MS Clinic Grenoble, Grenoble Alpes University Hospital, La Tronche T-RAIG, TIMC-IMAG, Grenoble Alpes University, 38700 Grenoble, France

[89] Department of Neurology, CHU La Milétrie, Hôpital Jean Bernard, 86000 Poitiers, France

[90] Department of Neurology, CHU Saint-Etienne, Saint-Étienne, France

[91] Department of Neurology, Hôpital Pierre Delafontaine, Centre Hospitalier de Saint-Denis, 93200 Saint-Denis, France

[92] Department of Neurology, APHP, Hôpital Henri Mondor, 94000 Créteil, France

[93] Department of Neurology, CHU de la Martinique, 97200 Fort-de-France, France

[94] Hôpital de Poissy Saint-Germain-en-Laye, Poissy, France

[95] Department of Neurology, CH de Pontoise, Hôpital René Dubos, Pontoise, France

[96] Department of neurology, CHU de Reims, CRC-SEP, 51092 Reims Cedex, France

[97] Department of Neurology, CHU de Limoges, Hôpital Dupuytren, 87000 Limoges, France

[98] Department of neurology, CHU Bicêtre, 94275 Le Kremlin Bicêtre, France

[99] Hôpital Bretonneau, CRC SEP and Department of Neurology, CHU de Tours, 37000 Tours, France

[100] Service de Neurologie, sclérose en plaques, pathologies de la myéline et neuro-inflammation, Hospices Civils de Lyon, Lyon, France

[101] Observatoire Français de la Sclérose en Plaques, Centre de Recherche en Neurosciences de Lyon, Inserm 1028, Lyon, France

[102] University of Lyon, Lyon, France

[103] Eugène Devic EDMUS Foundation Against Multiple Sclerosis, Lyon, France