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ORIGINAL RESEARCH ARTICLE

Treatment De-escalation in Relapsing-Remitting Multiple Sclerosis: An Observational Study

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Abstract

Background In relapsing-remitting multiple sclerosis (RRMS), extended exposure to high-efficacy disease modifying therapy may increase the risk of side effects, compromise treatment adherence, and inflate medical costs. Treatment de-escalation, here defined as a switch to a lower efficacy therapy, is often considered by patients and physicians, but evidence to guide such decisions is scarce. In this study, we aimed to compare clinical outcomes between patients who de-escalated therapy versus those who continued their therapy.

Methods In this retrospective analysis of data from an observational, longitudinal cohort of 87,239 patients with multiple sclerosis (MS) from 186 centers across 43 countries, we matched treatment episodes of adult patients with RRMS who underwent treatment de-escalation from either high- to medium-, high- to low-, or medium- to low-efficacy therapy with counterparts that continued their treatment, using propensity score matching and incorporating 11 variables. Relapses and 6-month confirmed disability worsening were assessed using proportional and cumulative hazard models.

Results Matching resulted in 876 pairs (de-escalators: 73% females, median [interquartile range], age 40.2 years [33.6, 48.8], Expanded Disability Status Scale [EDSS] 2.5 [1.5, 4.0]; non-de-escalators: 73% females, age 40.8 years [35.5, 47.9], and EDSS 2.5 [1.5, 4.0]), with a median follow-up of 4.8 years (IQR 3.0, 6.8). Patients who underwent de-escalation faced an increased hazard of future relapses (hazard ratio 2.36 and 95% confidence intervals [CI] [1.79–3.11], $p < 0.001$), which was confirmed when considering recurrent relapses (2.43 [1.97–3.00], $p < 0.001$). It was also consistent across subgroups stratified by age, sex, disability, disease duration, and time since last relapse.

Conclusions On the basis of this observational analysis, de-escalation may not be recommended as a *universal* treatment strategy in RRMS. The decision to de-escalate should be considered on an individual basis, as its safety is not clearly guided by specific patient or disease characteristics evaluated in this study.

1 Introduction

Significant progress has been made in the treatment of relapsing-remitting multiple sclerosis (RRMS), with licensing of over 20 disease modifying therapies (DMTs) to date [1]. Despite these strides, multiple sclerosis (MS) remains an incurable condition that necessitates long-term treatment in most patients.

Clinicians have traditionally favored starting treatment with a low-efficacy, low-risk DMT, and switching to higher efficacy DMTs in the event of disease activity. However, recent studies suggest that initiating treatment with high-efficacy DMTs early in the disease course yields better long-term outcomes [2–5]. This shift in treatment strategy has led to an increasing number of young patients being exposed to high-efficacy therapies early in their disease. However, guidance is lacking on the optimal long-term management of such patients. Prolonged exposure to DMTs may pose challenges, such as an increased risk of side effects [6–8], compromised treatment adherence [9, 10], and inflated medical costs per patient [11, 12]. Studies on treatment *discontinuation*, which refers to a complete cession of DMT, have shown inconclusive results [13–16], with disease reactivation being observed to begin approximately 4–6 weeks after stopping fingolimod and 8 weeks after stopping natalizumab [17].

Treatment *de-escalation*, here defined as treatment switch to a lower efficacy therapy, is often considered as a strategy to taper off high-efficacy DMTs and reduce associated risks while still maintaining some protection from potential (rebound) disease activity. However, evidence on the

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Key Points

There is limited evidence on the concept of treatment de-escalation in relapsing-remitting multiple sclerosis (RRMS) and on whether it is associated with an increased risk of future disease reactivation compared with treatment continuation.

This observational study provides evidence that treatment de-escalation is associated with a higher risk of future relapses and 6-month confirmed Expanded Disability Status Scale worsening compared with treatment continuation.

These findings suggest that treatment de-escalation may not be *universally* recommendable in patients with RRMS. The decision to de-escalate should be carefully considered, as patient eligibility is not clearly guided by specific thresholds of patient or disease characteristics evaluated in this study.

effectiveness of this approach, as well as on disease characteristics that may support patient eligibility, is scarce. In this work, we aimed to compare clinical outcomes of patients who de-escalated treatment to those who maintained their treatment regimen, using data from a longitudinal international MS cohort study.

2 Methods

2.1 Database

We used data from MSBase, a longitudinal MS cohort study involving 186 centers across 43 countries. In this database, patient-level demographic and clinical data have been continuously entered since 1 July 2004 (including the possibility to enter retrospective data), using a secure online data entry system. For this study, we extracted data on 22 July 2023. Prior to the analysis, data underwent rigorous quality control procedures (eMethods 1, in the Supplementary Material).

2.2 Standard Protocol Approval, Registrations, and Patient Consents

This study received ethics approval from the Melbourne Health Human Research Ethics Committee and the local institutional review board in all centers. Written informed consent was obtained from all patients.

2.3 Inclusion and Exclusion Criteria

We included patients with clinically definite MS [18], aged ≥ 18 years, who met a minimum data completeness requirement (including sex, date of birth, date of clinical onset, and dates of relapses), and had ≥ 3 documented clinical visits including Expanded Disability Status Scale (EDSS) assessments (of which 1 visit occurred within 6 months prior, and ≥ 2 visits occurred after baseline, the latter spanning ≥ 6 months). We excluded patients with clinically isolated syndrome, progressive MS forms, and patients treated with alemtuzumab, cladribine, mitoxantrone or stem cell transplantation at any time during follow-up. For patients who transitioned to secondary progressive MS (SPMS, as diagnosed by the treating neurologist), we assessed the follow-up until diagnosis of SPMS.

2.4 Study Design

This retrospective analysis of prospectively collected cohort data was designed to compare clinical outcomes of patients who underwent treatment de-escalation with matched patients who continued their treatment regimen. The null hypothesis stated that there is no difference in clinical outcomes between the groups.

DMTs were classified into three groups [1]: (a) high-efficacy DMTs: ocrelizumab, rituximab, and natalizumab; (b) medium-efficacy DMTs: fingolimod, dimethyl fumarate, siponimod, ozanimod, and daclizumab; and (c) low-efficacy DMTs: interferon beta-1a or -1b, peginterferon beta-1a, glatiramer acetate, and teriflunomide. Treatment de-escalation was defined as a switch from (a) to (b), from (a) to (c), or from (b) to (c) after being on the pre-de-escalation DMT for at least 6 months, and starting the post-de-escalation DMT within 30 days after the end of the expected biological effect of the pre-de-escalation DMT (Supplementary Table 1) [17, 19]. For de-escalators, baseline was defined as the date of treatment switch (the date of the last pre-switch treatment administration). For non-de-escalators, baseline was identified through propensity score matching (as defined below, Fig. 1). Patients were censored at the last recorded visit, at transition to SPMS, at death, at DMT discontinuation, or at treatment switch (including subsequent de-escalations, switches within DMT efficacy groups or re-escalations for the de-escalation group), whichever came first.

2.5 Clinical Outcomes

The following clinical endpoints were studied: (I) relapses, defined as new/exacerbating neurological symptom that

persisted for ≥ 24 hours, in absence of concurrent fever, occurring ≥ 30 days after a previous relapse [20]; (II) ≥ 6-month confirmed EDSS worsening, defined as an increase of ≥ 1.5 points if baseline EDSS was 0, ≥ 1 points if baseline EDSS was 1.0–5.5, and ≥ 0.5 points if baseline EDSS was ≥ 6 (using R package MSoutcomes) [21].

2.6 Statistical Analysis

2.6.1 Matching

To balance the groups for their baseline characteristics, we estimated the propensity score of treatment de-escalation using a multivariable logistic regression model with treatment allocation as the outcome variable. Independent (matching) variables were age, sex, country of origin, EDSS at baseline, duration of MS at baseline, last DMT prior to baseline, number of previous DMTs, time on previous DMT,

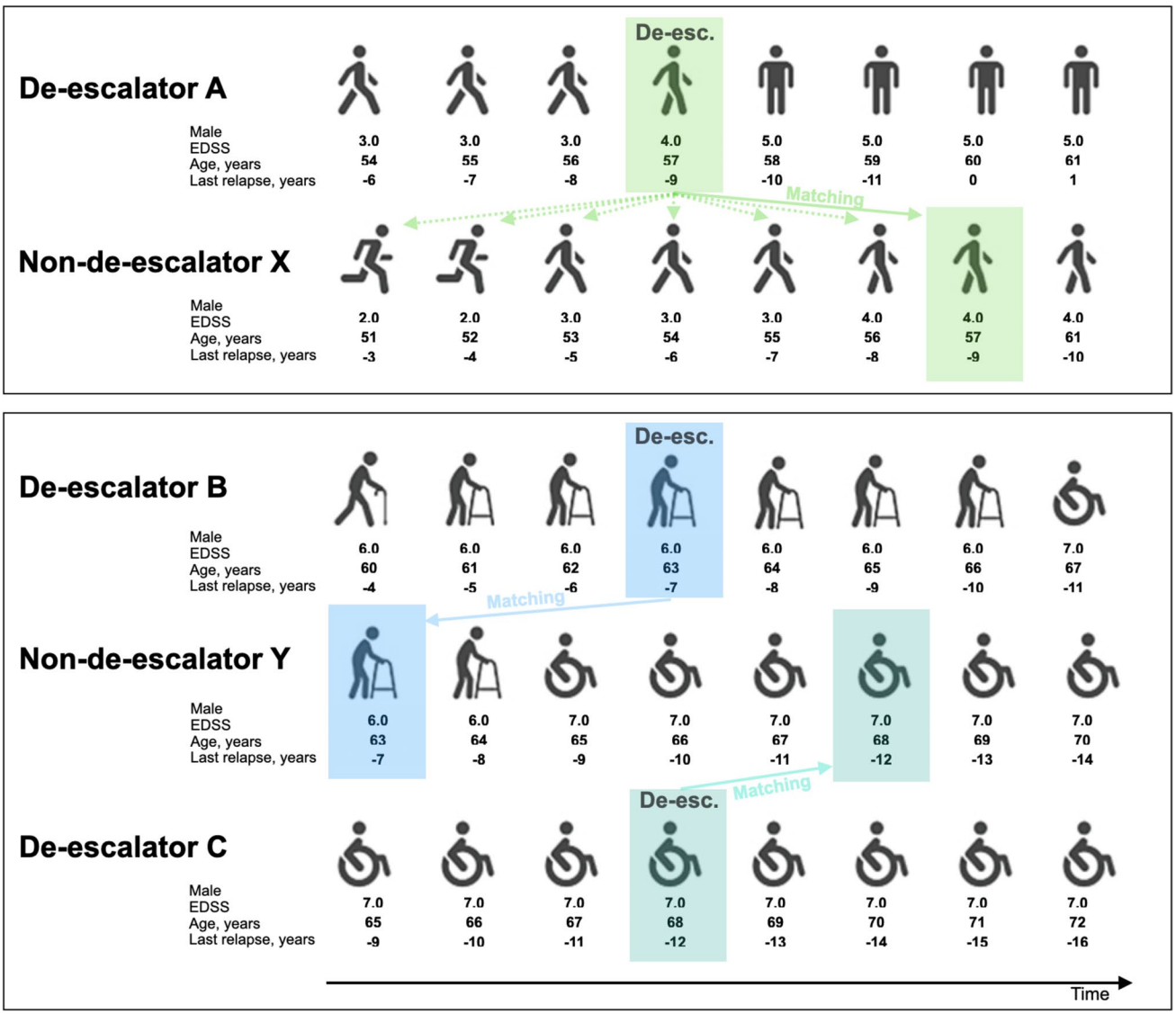

Fig. 1 Matching procedure of three exemplary de-escalating patients (De-escalator A, De-escalator B, and De-escalator C). Sex, EDSS, age, and last relapse represent 4 examples of the 11 matching variables, given for multiple visits over time. For de-escalating patients, baseline was defined as the date of treatment switch. For non-de-escalating patients, baseline was determined through propensity score matching, selecting the visit that most closely matched the baseline of the de-escalating patients (green line, upper panel) out of all available visits (green dashed lines, upper panel) of all patients. Matched baselines are indicated by matching color-coded boxes. In the lower panel, note that one non-de-escalating patient (Non-de-escalator Y) was matched to two separate de-escalating patients (De-escalator B and De-escalator C, respectively) at two different timepoints. *EDSS* Expanded Disability Status Scale

most effective previous DMT, time since last relapse, and number of relapses in the previous year (Supplementary Fig. 1). Each de-escalation was considered a new baseline, allowing patients who underwent multiple de-escalations to be matched multiple times (i.e., at each de-escalation separately). For non-de-escalating patients, since there was no specific de-escalation date, any visit that met the following criteria could serve as matching time-point (Fig. 1) [2]: (a) patient was aged ≥ 18 years at visit, (b) patient was treated with the same DMT for ≥ 6 months before the visit, (c) patient experienced no relapse in the 30 days before the visit, and (d) the patient's record had at least 1 prior and 2 following visits, the latter at least 6 months apart. Non-de-escalating patients could therefore be matched at multiple eligible timepoints (Fig. 1, lower panel). We then matched de-escalation episodes to visits of non-de-escalating patients, on the basis of the propensity score, in a 1:1 ratio using nearest neighbor matching within a caliper of 0.1 standard deviations of the propensity score, with replacement. Variations of these parameters are presented in Supplementary Table 7. Balance after matching was assessed using standardized mean differences (SMD), and an SMD < 0.2 was considered a sign of acceptable balance [22].

2.6.2 Statistical Analyses

Clinical outcomes were analyzed using conditional Cox proportional hazard models, describing the proportion of patients that were free of relapses or EDSS worsening. For recurrent events, the cumulative hazard was assessed with conditional proportional hazard models with robust estimation of variance and a cluster term for matched pairs.

Analyses were weighted to adjust for matching with replacement (calculated as the inverse of the number of times an individual was matched, e.g., if a patient was matched four times, its weight was set to 0.25). Analyses of EDSS worsening were additionally adjusted for visit density, calculated per patient, as the number of visits per follow-up time. Patients were pairwise censored, with the follow-up time determined as the shorter follow-up within matched pairs [23]. The proportional hazards assumption was assessed using the Schoenfeld global test. Kaplan–Meier curves were censored at the latest point at which each group contained ≥ 10 patients. We compared the annualized relapse rate (ARR), using negative binomial models, with cluster term for patient pair and time to censoring as offset.

Patient characteristics potentially relevant to treatment de-escalation [10, 13, 24, 25] were evaluated in separately matched subgroups, using clinically applicable cut-off values: sex (female or male); age (< 40, 40–50, or > 50 years); EDSS (< 1.5, 2.0–3.5, 4–5.5, or ≥ 6); disease duration (< 5, 5–10, 10–15, or > 15 years), and time since last relapse (< 2, 2–5, or > 5 years). The significance threshold was set at the 95% confidence level. For subgroup analyses involving more than two strata, we report the two-sided *p*-value after adjustment for false discovery rate (FDR) using the Benjamini–Hochberg procedure [26].

2.6.3 Sensitivity Analyses

We performed the following exploratory sensitivity analyses: (I) using an "intention-to-treat" approach, including all subsequent events irrespective of subsequent treatment decisions; (II) including only de-escalation episodes with an overlapping effect of the pre-de-escalation DMT at start of the post-de-escalation DMT, thereby avoiding any untreated period (versus a 30-day period that was considered acceptable in the primary analysis); (III) excluding all patient pairs that were censored within 1 year after de-escalation, focusing on outcomes that are likely unaffected by immediate rebound disease activity; and (IV) including only patients for whom the reason for treatment de-escalation was documented.

2.7 Data Availability

The MSBase registry is a data processor and warehouses data from individual principal investigators who agree to share their datasets on a project-by-project basis. Data access to external parties can be granted on reasonable request at the sole discretion of the principal investigators, who need to be approached individually for permission.

3 Results

3.1 Cohort Description

A total of 87,239 patients were assessed for eligibility; 873 de-escalating and 55,413 non-de-escalating patients fulfilled the inclusion criteria. Among the latter group, 30,734 timepoints were eligible for matching (Supplementary Fig. 2).

3.2 Matching

The matching procedure yielded 876 well-balanced pairs (SMD < 0.2 for all matching variables), composed of 856 de-escalating (20 patients were matched twice owing to multiple de-escalation episodes) and 547 non-de-escalating patients (174 patients were matched at multiple eligible timepoints; Table 1, Fig. 1; characteristics of unmatched eligible patients are given in Supplementary Table 6). These patients were drawn from 71 centers in 23 countries.

The median (IQR) individual follow-up was 4.8 (3.0, 6.8) years, corresponding to a cumulative follow-up of 9019 patient-years.

3.3 Primary Analysis

Over a median [IQR] pairwise-censored follow-up of 1.0 [0.4, 2.2] year, a total of 292 relapses occurred (199 in de-escalating, 93 in non-de-escalating patients). Competing censoring events included transition to SPMS: de-escalating $n = 10$, non-de-escalating patients $n = 9$; death: de-escalating: $n = 1$, and non-de-escalating patients $n = 1$. Patients who de-escalated therapy were at a higher risk of relapse (HR 2.36 [1.79–3.11], $p < 0.001$, Fig. 2A) and had a higher ARR than non-de-escalating patients (mean [SD], 0.27 [0.44] versus 0.13 [0.28], incidence rate ratio 1.48, $p < 0.001$). De-escalation episodes were associated with a higher cumulative hazard of relapses than treatment continuation (1094 events, of which 751 were in de-escalators and 343 were in non-de-escalators; HR 2.43 [1.97–3.00], $p < 0.001$).

Regarding 6-month confirmed EDSS worsening, with a median [IQR] time to pairwise censoring of 1.25 [0.61, 2.30] years, a higher hazard was observed among de-escalation episodes (101 events, hereof 66 in de-escalating, 35 in non-de-escalating patients; HR 1.54 [1.02–2.34], $p = 0.04$, Fig. 2B). In regards to recurrent events, the results did not reach statistical significance (259 events, HR 1.08 [0.82–1.40], $p = 0.6$).

3.4 Sensitivity Analyses

3.4.1 Intention-to-Treat Approach

The results of the primary analysis including the 876 matched pairs were confirmed when applying an intention-to-treat approach (Supplementary Table 2).

3.4.2 Patients with Overlap of Pre- and Post-de-escalation DMT

The results were confirmed when exclusively assessing the 443 de-escalation episodes with an overlap of pre- and post-de-escalation DMT effect, and their matched non-de-escalating patients (Supplementary Fig. 3A; median [IQR], overlap 29 [17, 40] days, compared with a median [IQR] treatment gap of 7 [−22, 14] days in the primary cohort).

3.4.3 After Exclusion of Patient Pairs that Are Censored within 1 Year after De-escalation

The results of the primary analysis were confirmed when considering only events that occurred >1 year after de-escalation (matched pairs, $n = 426$; Supplementary Fig. 3B and Supplementary Table 3A).

3.4.4 Patients in Whom the Reason for De-escalation Was Reported

The reason for treatment de-escalation was reported in 309 out of 876 de-escalation episodes (Table 1), of which 307 were matched to non-de-escalating patients. The results of the primary analysis were confirmed when considering recurrent events (307 matched pairs, 98 relapses, HR 3.65 [2.22–5.99], $p < 0.001$; 59 EDSS worsenings, HR 1.77 [1.04–3.01], $p = 0.04$). Analyses stratified by de-escalation reason (where available) are given in Supplementary Table 4.

3.5 Subgroup Analyses

Owing to the paucity of EDSS worsening events, the following subgroup analyses were restricted to relapse outcomes (Fig. 3).

3.5.1 Stratification by Age

The risk of relapse was higher in de-escalating patients in all age groups (< 40 years: 406 matched pairs, mean [SD], age 32.24 [5.36] years versus 32.47 [5.11] years, HR 3.43 [2.29–5.15], $p < 0.001$; age 40–50 years: 255 matched pairs, age 44.42 [2.88] years versus 44.61 [2.96] years, HR 2.65 [1.54–4.56], $p < 0.001$; and age > 50 years: 174 matched pairs, age 56.14 [4.52] years versus 56.08 [4.53] years, HR 2.34 [1.19–4.59], $p = 0.01$).This was confirmed when considering recurrent events (age < 40 years: HR 2.17 [1.74–2.76], age 40–50 years: 2.59 [1.72–3.91] and > 50 years: 2.56 [1.56–4.31], respectively, all $p < 0.001$)

3.5.2 Stratification by Time since Last Relapse

In patients who experienced their last relapse within 2 years prior to baseline (408 matched pairs, mean [SD], time since last relapse 1.00 [0.50] versus 1.02 [0.60] years) and those with a relapse in the 2–5 years prior (326 matched pairs, 3.03 [0.77] versus 3.08 [0.80] years prior), we observed higher hazards of relapse in de-escalators than non-de-escalators (HR 2.50 [1.69–3.68] and 2.49 [1.61–3.86], respectively, both $p < 0.001$). For patients whose last relapse was > 5 years prior (119 matched pairs, 8.32 [3.34] versus 8.36 [3.74] years prior), there were higher relapse hazards in de-escalating patients, but the low number of events led to increased uncertainty in the parameter estimate, hereby widening the 95% CI (28 events, HR 5.40 [1.83–15.93], $p = 0.002$, confirmed when considering recurrent events: 76 events, 7.62 [3.17–18.31], $p < 0.001$).

Table 1 Demographic and clinical characteristics of matched patients

	Characteristics of patients at first matched de-escalating episode		Characteristics of all matched de-escalating episodes		
	Non-de-escalators	De-escalators	Non-de-escalators	De-escalators	SMD
N	547	856	876	876	
Age, years, median [IQR]	40.2 [34.2, 47.2]	40.3 [33.6, 48.8]	40.8 [35.5, 47.9]	40.2 [33.6, 48.8]	0.038
Female Sex, *n* (%)	386 (70.6)	624 (72.9)	640 (73.1)	636 (72.6)	0.010
EDSS, median [IQR]	2.5 [1.5, 4.0]	2.5 [1.5, 4.0]	2.5 [1.5, 4.0]	2.5 [1.5, 4.0]	0.030
Disease duration, years, median [IQR]	9.3 [5.9, 14.8]	9.7 [5.7, 15.2]	10.3 [6.6, 15.4]	9.7 [5.6, 15.3]	0.016
Reason for de-esc, *n* (%)					n.a.
Disease Activity	n.a.	125 (14.6)	n.a.	126 (14.4)	
AE	n.a.	87 (10.2)	n.a.	90 (10.3)	
Scheduled	n.a.	34 (4.0)	n.a.	35 (4.0)	
Pregnancy	n.a.	32 (3.7)	n.a.	32 (3.7)	
Patient wish	n.a.	26 (3.0)	n.a.	26 (3.0)	
NA	n.a.	552 (64.5)	n.a.	567 (64.7)	
DMT before de-esc, *n* (%)					0.097
Natalizumab	387 (70.7)	644 (75.2)	675 (77.1)	650 (74.2)	
Ocrelizumab	4 (0.7)	10 (1.2)	10 (1.1)	10 (1.1)	
Rituximab	4 (0.7)	8 (0.9)	5 (0.6)	9 (1.0)	
Fingolimod	89 (16.3)	99 (11.6)	109 (12.4)	109 (12.4)	
Dimethyl fumarate	63 (11.5)	95 (11.1)	77 (8.8)	98 (11.2)	
DMT after de-esc (%)					3.184
Natalizumab	387 (70.7)	0 (0.0)	675 (77.1)	0 (0.0)	
Ocrelizumab	4 (0.7)	0 (0.0)	10 (1.1)	0 (0.0)	
Rituximab	4 (0.7)	0 (0.0)	5 (0.6)	0 (0.0)	
Fingolimod	89 (16.3)	447 (52.2)	109 (12.4)	452 (51.6)	
Ozanimod	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)	
Siponimod	0 (0.0)	5 (0.6)	0 (0.0)	5 (0.6)	
Dimethyl fumarate	63 (11.5)	68 (7.9)	77 (8.8)	68 (7.8)	
Glatiramer acetate	0 (0.0)	124 (14.5)	0 (0.0)	129 (14.7)	
Teriflunomide	0 (0.0)	120 (14.0)	0 (0.0)	126 (14.4)	
Peginterferon beta-1a	0 (0.0)	10 (1.2)	0 (0.0)	10 (1.1)	
Interferon beta-1a	0 (0.0)	69 (8.1)	0 (0.0)	72 (8.2)	
Interferon beta-1b	0 (0.0)	12 (1.4)	0 (0.0)	13 (1.5)	
Time between end of pre-de-escalation DMT efficacy and start of post-de-escalation DMT, days, median [IQR]	n.a.	7 [−22, 14]	n.a.	7 [−22, 14]	n.a.
No. of DMTs prior to de-esc, mean (SD)	1.9 (1.3)	2.3 (1.0)	2.3 (1.4)	2.3 (1.0)	0.035
Highest effective DMT prior to de-esc, *n* (%)					0.083
Natalizumab	412 (75.3)	667 (77.9)	705 (80.5)	685 (78.2)	
Ocrelizumab	12 (2.2)	24 (2.8)	26 (3.0)	24 (2.7)	
Rituximab	6 (1.1)	8 (0.9)	7 (0.8)	8 (0.9)	
Fingolimod	70 (12.8)	84 (9.8)	83 (9.5)	86 (9.8)	
Dimethyl fumarate	47 (8.6)	73 (8.5)	55 (6.3)	73 (8.3)	
Time on DMT prior to de-esc, years, mean (SD)	2.0 (1.6)	2.5 (1.6)	2.4 (1.8)	2.5 (1.6)	0.048
Relapse in the past 12 months, yes, *n* (%)	125 (22.9)	190 (22.2)	183 (20.9)	196 (22.4)	0.036
Time since last relapse, years, mean (SD)	2.8 (2.7)	2.9 (3.1)	2.9 (2.8)	2.9 (3.1)	0.009
No. of relapses in the past 12 months, mean (SD)	0.18 (0.60)	0.22 (0.53)	0.18 (0.66)	0.22 (0.53)	0.069
New/enhancing lesions, *n* (%)					0.607
no	130 (23.8)	188 (22.0)	197 (22.5)	191 (21.8)	
yes	140 (25.6)	44 (5.1)	222 (25.3)	45 (5.1)	
NA	277 (50.6)	624 (72.9)	457 (52.2)	640 (73.1)	

The table displays patient characteristics at the first matched event (left two columns) as well as characteristics of all matched baselines (right two columns)

AE adverse events, *de-esc* de-escalation, *DMT* disease modifying therapy, *EDSS* expanded disability status scale, *IQR* interquartile range, *NA* not

Table 1 (continued)

available, *n.a.* not applicable, *no.* number, *SD* standard deviation, *SMD* standardized mean difference (a *SMD* < 0.2 is considered as a sign of adequate balance).

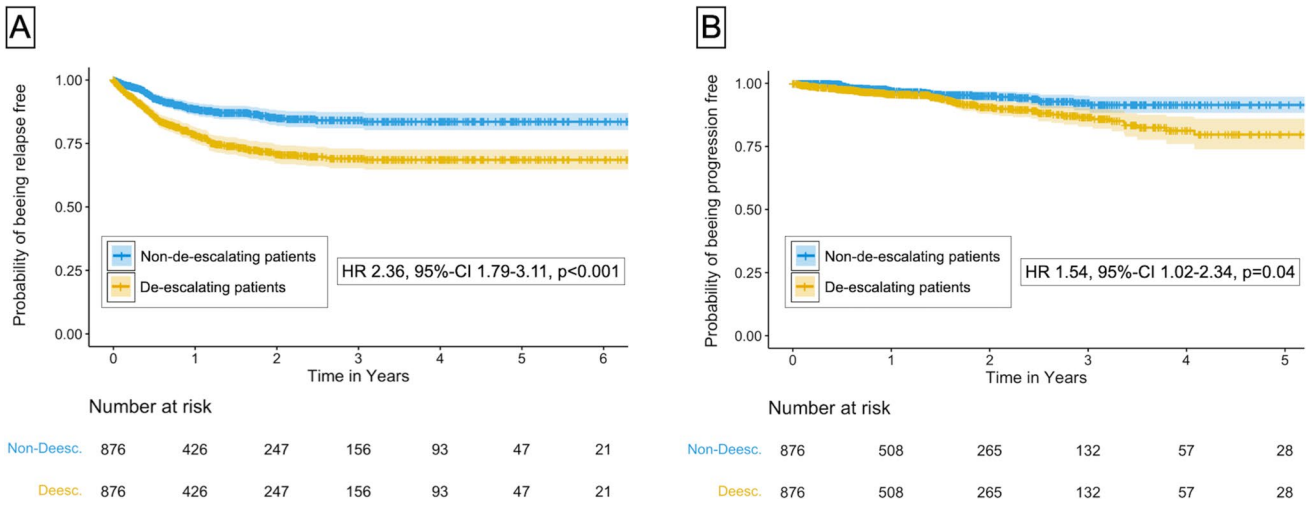

Fig. 2 Risk of being free from (**A**) relapses, and (**B**) 6-month confirmed EDSS worsening. Kaplan–Meier curves and numbers at risk. *HR* hazard risk, *95% CI* 95% confidence interval

3.5.3 Stratification by Age and Time since Last Relapse

Figure 4A, B provides a perspective of the cumulative hazard of relapses among patients stratified by age and time since last relapse into 9 and 4 subgroups, respectively (Supplementary Fig. 4 shows the results for patients free from relapses). Among patients of age < 40 or < 50 years, respectively, we observed higher hazards of relapses, regardless of the time since last relapse. No clear threshold was identified after which de-escalation would not be associated with an increased risk of relapse.

3.5.4 Stratification by Sex, EDSS or Disease Duration

There were higher HRs for relapses in de-escalating patients of all subgroups, as stratified by their sex, EDSS, or disease duration (Supplementary Table 5; confirmed when considering recurrent events).

3.5.5 Stratification by DMT groups

Patients de-escalating from high- to medium- or from high- to low-efficacy DMTs showed higher relapse hazards than patients continuing with high-efficacy DMTs (HR 2.54 [1.78–3.64] and 3.68 [1.86–7.28], respectively, both $p < 0.001$; Fig. 5; confirmed when considering recurrent relapses). There was a higher hazard in patients switching from medium- to low-efficacy DMT than those who continued medium-efficacy therapy, but this was not statistically significant (HR 1.70 [0.93–3.1]; confirmed when considering recurrent events: 184 events, HR 1.37 [0.91–2.06]).

4 Discussion

In this cohort study, we demonstrated that treatment de-escalation is associated with an elevated risk of clinical reactivation of multiple sclerosis, as measured by both relapses and disability accumulation. This elevated risk was present regardless of age, sex, EDSS, disease duration, or time since the last relapse, manifested both early and late (more than 1 year after) after de-escalation, and was consistent across multiple analytical approaches.

To date, limited evidence exists on treatment de-escalation, mostly derived from small cohorts. In an observational study on seven patients who de-escalated from natalizumab to glatiramer acetate, five patients experienced disease reactivation within 12 months [27]. Following natalizumab, disease reoccurrence was reduced by de-escalation to fingolimod ($n = 26$), compared with stopping all DMT ($n = 10$) [28]. In a retrospective single-arm study of 506 patients de-escalating from natalizumab to dimethyl fumarate, relapse frequency more than doubled after de-escalation [29]. Our study confirms the observation of an increased risk of disease reactivation after de-escalation within a relatively larger

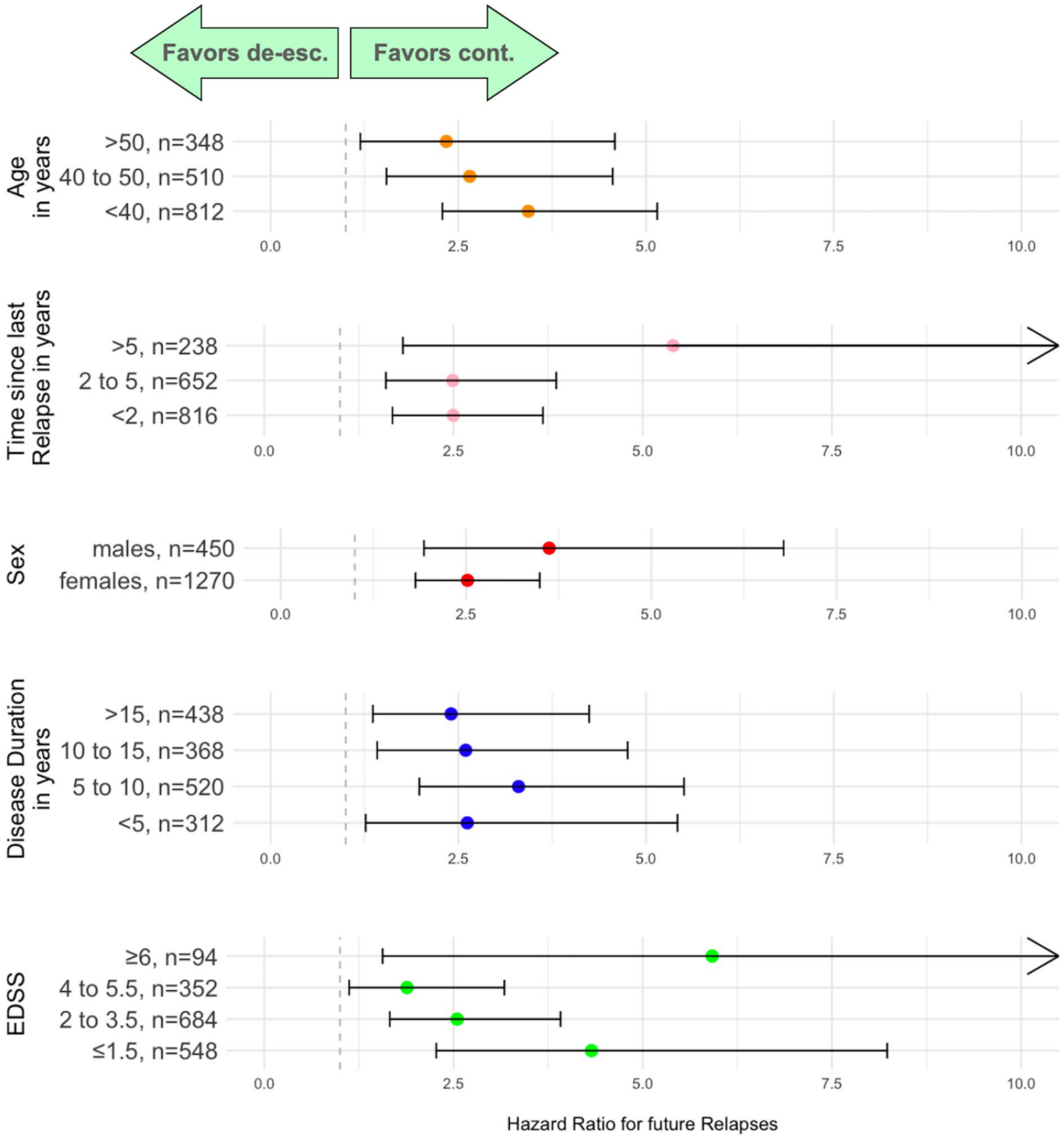

Fig. 3 Subgroups stratified by age, time since last relapse, gender, disease duration and EDSS. Forrest plot displaying hazard ratios and 95% confidence intervals. *EDSS* Expanded Disability Status Scale, *HR* hazard ratio

study sample. We included non-de-escalating patients as an appropriate control group and addressed the absence of a de-escalation date in these patients by employing a matching approach in which every visit of non-de-escalators was considered a potential matching point. This approach expanded the matching pool to 30,734 potential matching time points of non-de-escalating patients, enabling us to identify optimal matching partners for each de-escalating patient despite employing an extensive matching framework that included 11 clinically relevant variables.

Our results remained consistent when analyzing matched subgroups, stratified by age, sex, EDSS, disease duration, or time since the last relapse. Although our results indicated a potential association of age and the risk of disease reactivation (Fig. 4), the data did not allow us to identify a clear threshold at which de-escalation would be considered safe. Similar associations were evident after stratification

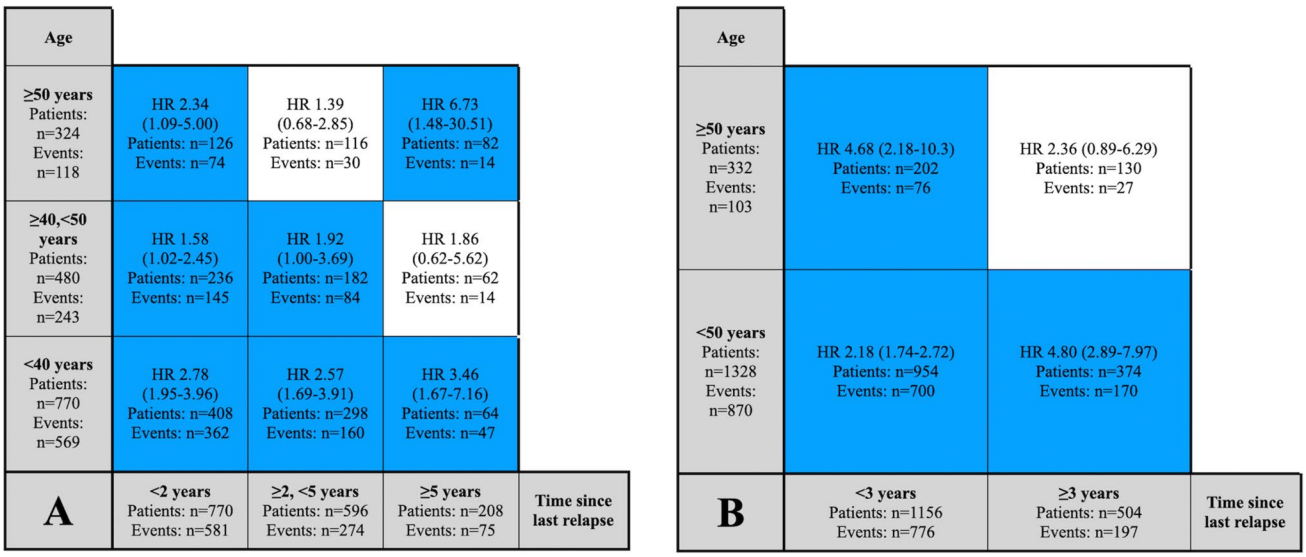

Fig. 4 The risk of relapses among patients stratified by age and time since last relapse. HR and confidence intervals derive from conditional hazard models capturing recurring outcome events during the entire follow-up period. Results from the Cox proportional hazards model are given in Supplementary Fig. 4. (**A**) The data is stratified into nine separately matched groups, providing higher granularity, while acknowledging the limitation of small sample sizes and numbers of outcome events, and (**B**) stratification is performed for four separately matched groups, enhancing statistical power and sample size, sacrificing granularity. Stratified groups with HR confidence intervals crossing the threshold "1" are highlighted in blue. *HR* hazard ratio

by time since last relapse or by both age *and* time since last relapse. However, subgroups of older age, higher EDSS, and longer time since last relapse were hampered by within-group variability and small sample sizes, which may explain the difference between our results and previous studies on DMT cessation, which have identified these factors as significant determinants of disease reactivation [8, 10, 13, 30]. Nevertheless, our subgroup analyses indicated that certain groups, such as those undergoing scheduled de-escalation or de-escalation due to patient preference or pregnancy, may be more suitable candidates for a de-escalation strategy. It is important to note, however, that these subgroups constituted the smallest cohorts in our study, and while their point estimates still suggested potential benefits of treatment continuation, these observations did not reach the level of statistical evidence.

Studies on DMT cessation have reported disease reactivation particularly in the first 2 months after stopping anti-cell trafficking agents, such as natalizumab and fingolimod [17]. Our results first indicate that de-escalation from natalizumab to medium-efficacy DMTs may not be capable to fully prevent this early disease reactivation, even when starting the post-de-escalation DMT very promptly, while still benefiting from the biological effect of the pre-de-escalation DMT (sensitivity analysis II). Second, our results suggest that the disease reactivation after de-escalation extends beyond a mere rebound phenomenon. This is supported by the analysis of events occurring more than 1 year after de-escalation (sensitivity analysis III), a timeframe which most clinicians would consider beyond the immediate rebound phase.

Intriguingly, in patients de-escalating from medium- to low-efficacy DMTs, there were higher hazards of relapse after de-escalation, but this result did not reach statistical significance. This finding might be partly attributed to a lower disease activity in patients de-escalating from medium-efficacy DMTs including fingolimod, making the loss of disease control less noticeable if it were to occur, compared with a de-escalation from high-efficacy DMTs, including natalizumab.

Our study has several limitations. First, given its non-randomized observational design, it is unable to establish a causal relationship between treatment de-escalation and subsequent disease reactivation. Second, observational studies are prone to systematic bias [31] such as attrition bias (arising from differences in follow-up duration and informed censoring), detection bias (arising from informed differences in EDSS assessment frequencies), and immortal time bias (arising from time-dependent exposure misclassification), which we attempted to mitigate with pairwise censoring, adjustment for visit density, and alignment of the baseline with the last administration of the previous drug, respectively. However, the most important bias is indication bias [32], arising from the nonrandom decision to de-escalate therapy, i.e., patients who are perceived by their MS care providers as "needing" high-effective therapy are less likely to undergo treatment de-escalation. This scenario may lead to an underrepresentation of patients

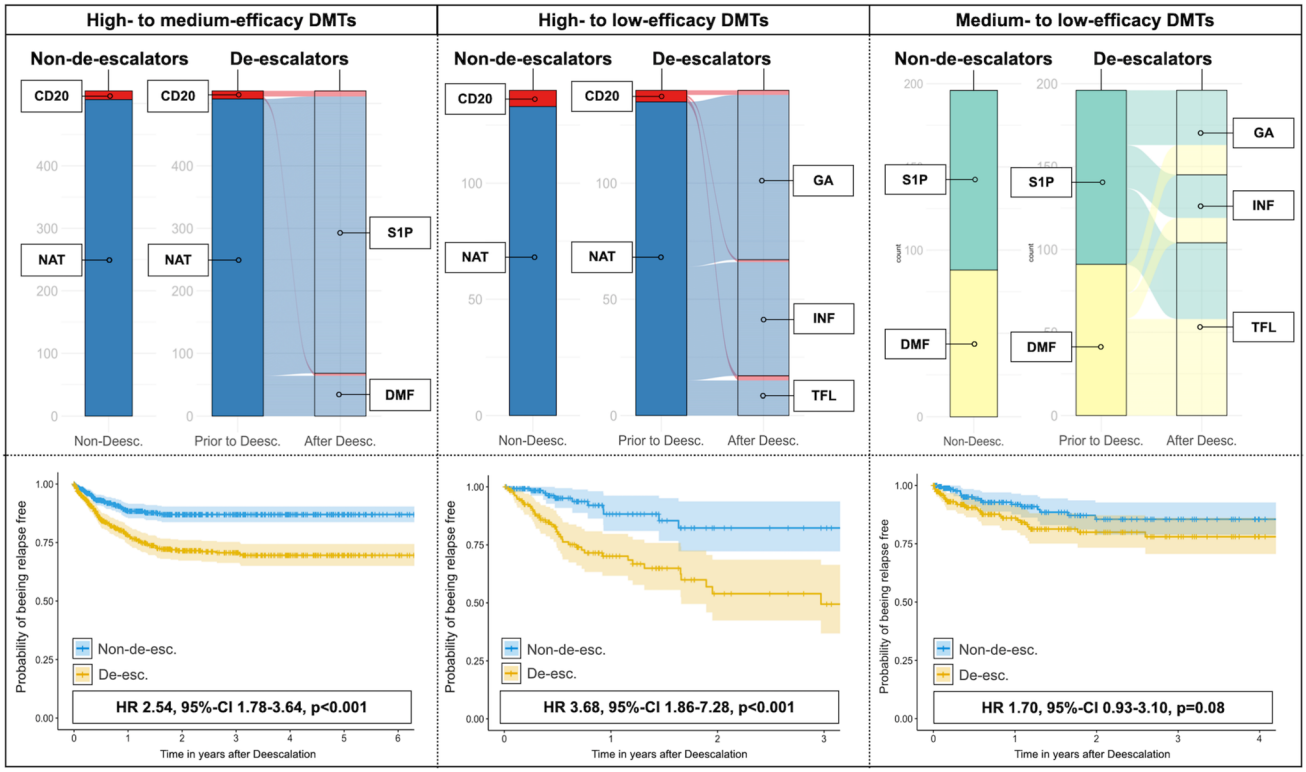

Fig. 5 Subgroup analyses stratified for DMT groups: patients switching from high- to medium- (left panel), high- to low- (middle panel), and medium- to low-efficacy DMTs (right panel). Top panels show DMTs as bar charts of non-de-escalators (left bar), de-escalators prior to de-escalation (middle bar), and de-escalators after de-escalation (right bar). Lower panels show Kaplan–Meier curves of the groups under consideration (non-de-escalators versus de-escalators). *CD20* *anti* CD20-antibodies (encompassing rituximab and ocrelizumab), *DMF* dimethyl fumarate, *DMTs* disease modifying therapies, *GA* glatiramer acetate, *HR* hazard ratio, *INF* interferon (encompassing interferon beta-1a, interferon beta-1b, and peginterferon beta-1a), *NTZ* natalizumab, *OZA* ozanimod, *S1P* S1P-modulators (encompassing fingolimod, ozanimod, and siponimod), *TFL* teriflunomide, *95% CI* 95% confidence interval

with high disease activity in the de-escalating group or to an overrepresentation of stable patients in the non-de-escalating group. To mitigate this bias, we applied propensity score matching, encompassing a range of variables characterizing patients' disease activity. In addition, we ensured that included individuals had been treated with their pre-existing DMT for at least 6 months immediately prior to matching, thereby emphasizing comparisons during established phases of treatment. Third, we did not assess subclinical disease activity (with magnetic resonance imaging [MRI] or soluble biomarkers), which may guide treatment decisions. Fourth, competing censoring events such as transition to SPMS or death may complicate interpretation of hazard ratios, but the number of these competing events was relatively small and evenly distributed between the two groups, minimizing their potential impact on our findings. Fifth, the small size of treatment subgroups precluded us from conducting detailed analyses of individual DMT de-escalation. Consequently, similar to prior research on DMT discontinuation [16], we grouped DMTs on the basis of their efficacy. Most de-escalating patients were previously on agents that reduce cell trafficking, potentially limiting the generalizability to other modes of action. Sixth, we focused on de-escalation across DMT classes, and did not consider other de-escalation methods such as dose reduction or extension of application intervals. Moreover, the stratification of DMT classes was necessary to ensure adequate subgroup sample size. This approach has excluded minor shifts in treatment efficacy within DMT classes, potentially contributing to the overall low observed de-escalation rate of 1.5%. In addition to these methodological considerations, clinical factors likely play a significant role, reflecting prevailing skepticism toward de-escalation, particularly in absence of overt disease activity or safety concerns. Seventh, we acknowledge that the study does not fully capture the complexity of treatment de-escalation, as this decision is guided by multiple factors, including comorbidities, patient preferences, insurance coverage, and treatment safety or availability (Supplementary Fig. 1). Some of these factors (specifically age, activity prior to de-escalation, and EDSS) could potentially affect both the decision to de-escalate

and the corresponding outcomes of interest, complicating the interpretation of our findings.

5 Conclusions

Our observational study indicates that treatment de-escalation is associated with a considerable risk of clinical reactivation of relapsing-remitting MS across various patient strata. While de-escalation of therapy may be required at times owing to safety and tolerability issues, it may not be recommendable as a *universal* approach, particularly among patients younger than 50 years and those treated with high-efficacy immunotherapy.

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Declarations

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Ethics approval This study received ethics approval from the Melbourne Health Human Research Ethics Committee and the local institutional review boards in all centers.

Consent to participate Written informed consent was obtained from all patients.

Consent for publication Not applicable.

Availability of data and material The MSBase registry is a data processor and warehouses data from individual principal investigators who agree to share their datasets on a project-by-project basis. Data access to external parties can be granted on reasonable request at the sole discretion of the principal investigators, who will need to be approached individually for permission.

Code availability The R package MSoutcomes, which was used for the analyses in this study, is openly available on the Comprehensive R Archive Network (CRAN).

Authors' contributions Conception and design of the study: J.M., S.S., J.L., Ö.Y., C.G., T.D., J.K., L.K., I.R., and T.K. Acquisition and analysis of data: J.M., S.S., D.H., E.K.H., S.E., F.P., P.G., K.B., O.S., A.P., M.G., F.G., R.A., J.L.S., D.S., M.B., E.C., M.J.S., O.G., A.V.W., H.B., J.P., T.C.T., B.Y., S.J.K., I.R., and T.K. Drafting a significant portion of the manuscript or figures: J.M., S.S., J.L., D.H., E.K.H., S.E., F.P., P.G., K.B., O.S., A.P., M.G., F.G., R.A., J.L.S., D.S., M.B., E.C., M.J.S., O.G., A.V.W., H.B., J.P., T.C.T., B.Y., S.J.K., Ö.Y., T.D., C.G., J.K., L.K., I.R., and T.K. All authors have read and approved the final submitted manuscript and agree to be accountable for the work.

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