Supplementary Appendix for *CNS Drugs*

Preserving neurological function in people at high and low risk of aggressive multiple sclerosis: an observational cohort study

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Supplementary table S1: Data quality procedure

- Duplicate patient records were removed.
- Centres with <10 patient records were excluded.
- Patients with missing date of birth were excluded.
- MS onset dates after the data extract date were removed.
- Patients with missing date of the first clinical presentation of MS were excluded.
- The dates of MS onset and the first recorded MS course were aligned.
- Patients with the age at onset outside the 0-100 range were excluded.
- A logical sequence of the MS courses (e.g. clinically isolated syndrome, relapsing-remitting MS, secondary progressive MS) was assured.
- Entries with the initiation of progressive MS prior to its clinical onset of MS were excluded.
- Visits with missing visit date or the recorded date before the clinical MS onset or after the date of data extract were removed.
- EDSS scores outside the range of possible EDSS values were removed.
- Duplicate visits were merged.

- MS relapses with missing visit date or the recorded date after the date of MSBase data extract were removed.
- Duplicate MS relapses were merged.
- Relapses occurring within 30 days of each other were merged.
- Visits preceded by relapses were identified and time from the last relapse was calculated for each visit.
- Therapies were labelled as discontinued or continuing.
- Therapies with erroneous date entries were removed (e.g. commencement date > termination date, commencement after the MSBase data extract date, commencement of disease modifying therapy before the year 1980).
- MS disease modifying therapies were identified and labelled.
- Duplicate treatment entries were removed.
- Where multiple disease modifying therapies were recorded simultaneously, treatment end date of the previous therapy was imputed as the commencement date of the following therapy.

Supplementary table S2: Characteristics of the patients with MS, and a first visit within 12 months of MS onset, who were included and excluded from the study

	Included	**Excluded**
patients, nr (%)	10405	37935
Female	7423 (72.3)	27009 (71.2)
Male	2982 (28.7)	10926 (28.8)
Registry		
MSBase	6033 (38.0)	20105 (53.0)
OFSEP	4372 (42.0)	17290 (47.0)
age, yr	28.9 [24.5, 33.9]	36.0 [26.6, 43.0]
disease duration (1st visit), yr	0.5 [0.4, 0.8]	0.3 [0.1, 0.6]
disability (1st visit), EDSS	1.5 [1.0, 2.0]	1.0 [1.0, 2.0]
maximum disability in first year, EDSS	2.0 [1.0, 2.5]	1.0 [1.0, 2.5]
MS course at first visit		
Clinically isolated syndrome	6812 (65.5)	21790 (57.9)
Relapsing-remitting	3593 (34.5)	15212 (41.1)
Primary progressive	-	933 (2.0)
visit interval, months	6.6 [5.0, 8.5]	6.7 [4.6, 11.9]
prospective follow-up, yr	6.4 [3.7, 10.8]	4.6 [0.9, 9.9]
Number of DMTs during follow-up	1 [0, 2]	1 [0, 2]
Year of baseline	2012 [2007, 2016]	2012 [2006, 2016]

Patients who were excluded from the study had been enrolled in a randomised clinical trial, had fewer than 2 visits after baseline, fewer than 1 visit per year or primary progressive MS.

Supplementary table S3: Characteristics of the study cohort by contributing registry

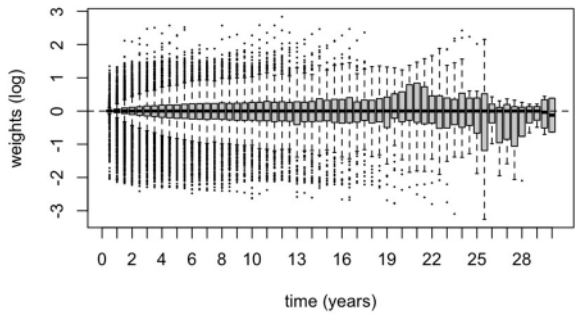
	High Risk Aggressive MS		Low Risk Aggressive MS	
	MSBase	**OFSEP**	**MSBase**	**OFSEP**
patients, nr (%)	1095	926	4938	3446
Female	769 (70.2)	629 (67.9)	3452 (69.9)	2573 (74.7)
Male	326 (29.8)	297 (32.1)	1486 (30.1)	873 (25.3)
	43.2	43.8	27.1	27.4
age, yr	[38.6, 48.6]	[39.0, 49.3]	[23.4, 30.8]	[23.7, 30.9]
	0.5	0.5	0.5	0.5
disease duration (1st visit), yr	[0.3, 0.8]	[0.4, 0.8]	[0.3, 0.8]	[0.4, 0.8]
	3.0	3.3	1.5	1.0
disability (1st visit), EDSS	[2.8, 4.0]	[3.0, 4.0]	[1.0, 2.0]	[0.0, 2.0]
	3.5	4.0	1.5	1.0
maximum disability in first year, EDSS	[3.0, 4.5]	[3.0, 4.5]	[1.0, 2.0]	[0.0, 2.0]
MS course at first visit				
Clinically isolated syndrome	540 (49.3)	827 (89.3)	2248 (45.5)	3382 (98.1)
Relapsing-remitting	555 (50.7)	99 (10.7)	2690 (54.5)	64 (1.9)
	6.3	6.6	6.2	7.1
visit interval, months	[4.7, 8.2]	[5.1, 8.5]	[4.5, 8.2]	[5.7, 8.8]
	6.7	5.6	6.8	5.9
prospective follow-up, yr	[3.9, 10.5]	[3.0, 10.9]	[4.0, 10.8]	[3.2, 10.8]
Treatment strategy at any time during follow-up, nr of patients (%)				
Alemtuzumab[(H)]	28 (1)	4 (0)	152 (2)	24 (0)
Natalizumab[(H)]	196 (10)	187 (9)	765 (9)	734 (9)
Mitoxantrone[(H)]	33 (2)	81 (4)	46 (1)	92 (1)
Ocrelizumab/Rituximab/Ofatumumab[(H)]	136 (7)	119 (6)	528 (6)	379 (5)
Daclizumab[(H)]	1 (0)	-	8 (0)	1 (0)
Cladribine[(H)]	41 (2)	-	221 (3)	4 (0)
Fingolimod/Ozanimod[(H)]	214 (11)	144 (7)	1173 (14)	737 (9)
Siponimod[(H)]	7 (0)	-	4 (0)	-
Dimethyl Fumarate	112 (6)	138 (7)	658 (8)	738 (9)
Teriflunomide	116 (6)	126 (6)	419 (5)	558 (7)
Interferons/Glatiramer Acetate	688 (34)	403 (20)	3564 (43)	1899 (23)
Untreated	754 (37)	698 (35)	3404 (41)	2565 (31)
Number of DMTs during follow-up	1 [0, 1]	1 [0, 1]	1 [0, 2]	1 [0, 2]
Year of baseline	2012 [2008, 2015]	2012 [2004, 2016]	2012 [2007, 2015]	2013 [2007, 2016]

Mean (SD) or median [quartiles] as appropriate

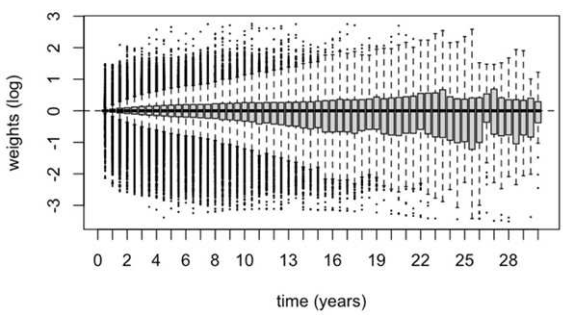
[(H)] High-efficacy disease modifying therapy

Supplementary figure S1: Stabilised weights (therapy * censoring) in patients at **(A)** high risk and **(B)** low risk of aggressive MS

A



B



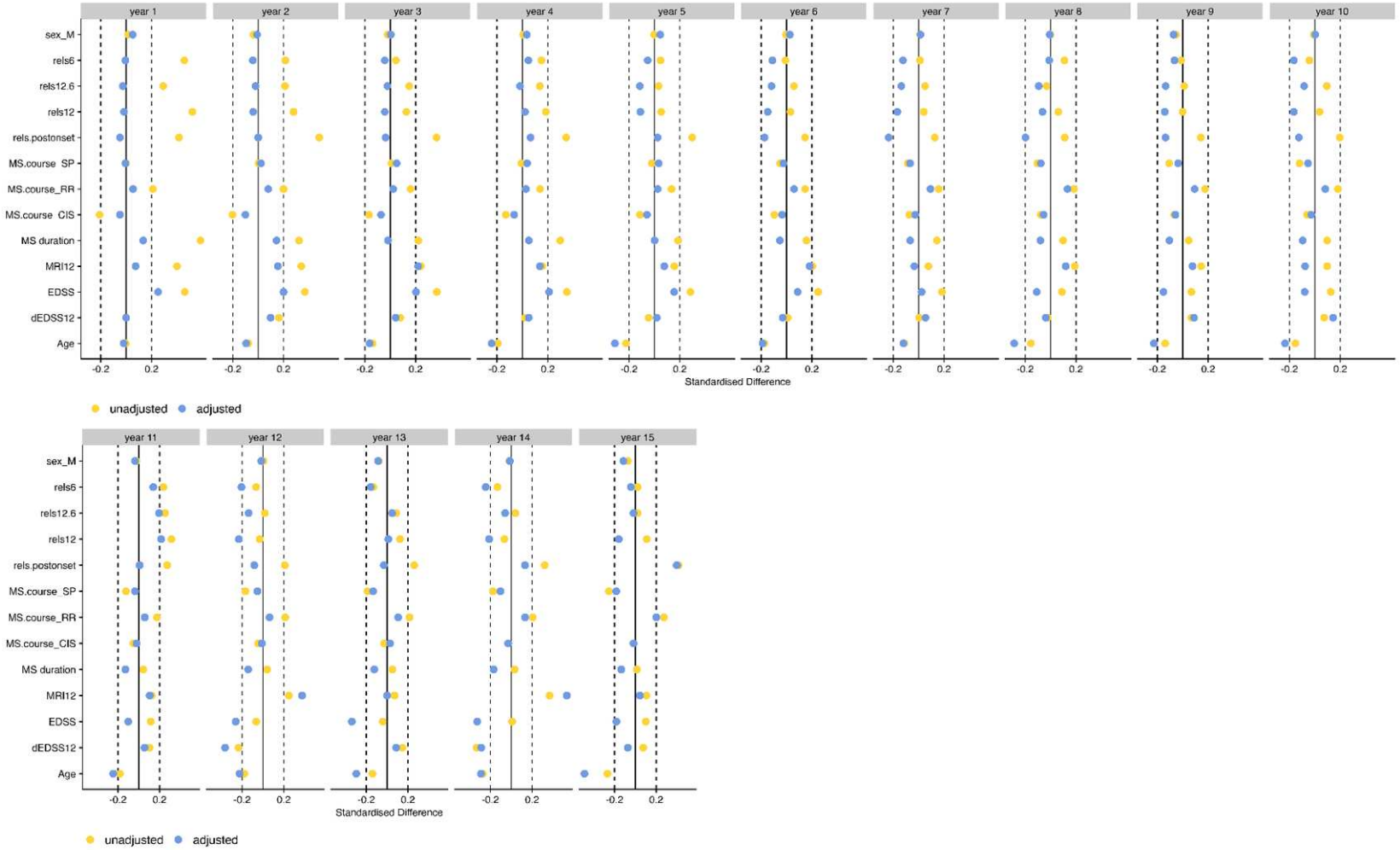
Supplementary table S4: Summary statistics for stabilised inverse probability treatment weights (IPTW) and censoring weights (IPCW) in high-risk and low-risk aggressive MS groups.

Group	Weight Type	Min	1st Qu.	Median	Mean	3rd Qu.	Max
High-risk aggressive MS	IPTW	0.13	0.86	0.96	0.99	1.04	4.01
	IPCW	0.30	0.63	0.76	0.78	0.89	2.28
Low-risk aggressive MS	IPTW	0.09	0.78	0.91	0.95	0.99	4.20
	IPCW	0.23	0.62	0.75	0.76	0.88	2.11

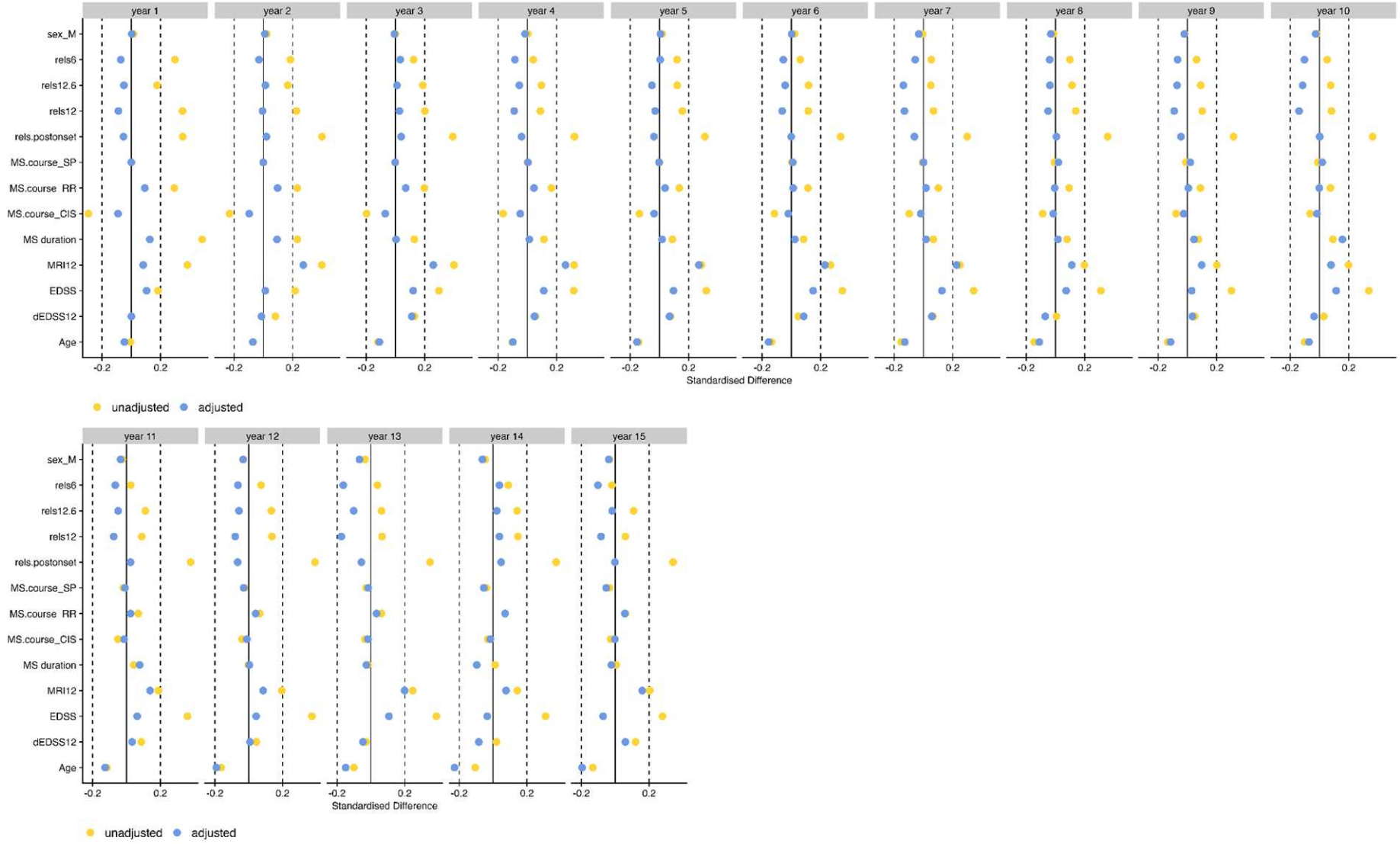
IPTW = inverse probability of treatment weight; IPCW = inverse probability of censoring weight. Stabilised weights were used for all analyses. Weight diagnostics, including distributional plots over time, are shown in Supplementary figure S1.

Supplementary figure S2: Covariate balance over time

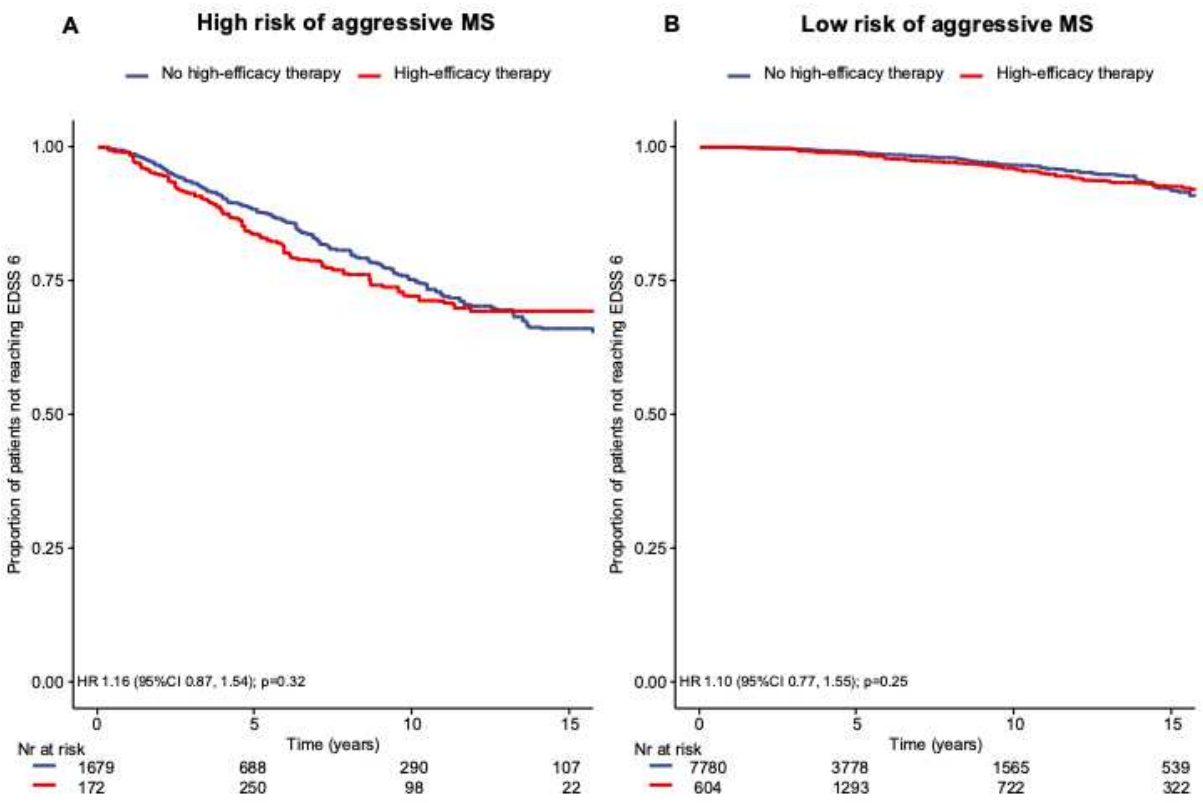
A High risk of aggressive MS



B Low risk of aggressive MS



Supplementary figure S3: Proportion of patients not reaching EDSS 6



Supplementary table S5: E-values for primary outcomes

Outcome	Aggressive MS Risk Stratum	HR (95% CI)	E-value (Point Estimate)	E-value (CI limit closest to null)
Relapse	Low risk	0.72 (0.67-0.77)	1.82	1.69
Disability accumulation		1.08 (0.96-1.22)	1.30	1.00 (CI includes null)
Disability improvement		1.01 (0.86-1.18)	1.09	1.00 (CI includes null)
Relapse	High risk	0.78 (0.70-0.86)	1.67	1.46
Disability accumulation		0.93 (0.77-1.12)	1.28	1.00 (CI includes null)
Disability improvement		0.87 (0.74-1.02)	1.43	1.00 (CI includes null)

E-values represent the minimum strength of association that an unmeasured confounder would need to have with both treatment and the outcome, conditional on measured covariates, to fully explain the observed association.

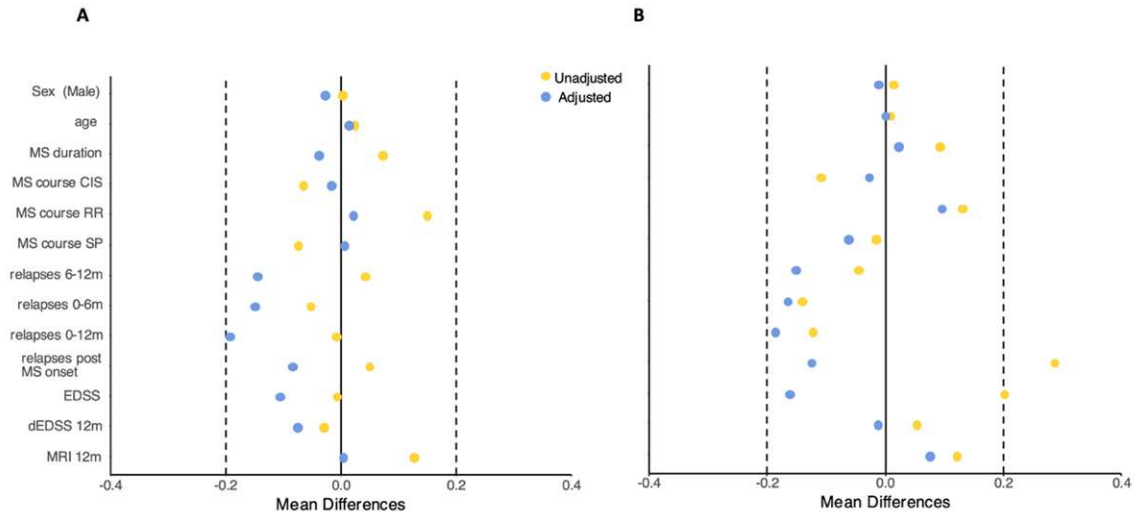
Supplementary table S6: Secondary analysis among a subgroup exposed to HE-DMTs: Cohort demographics

	Aggressive MS Risk	
	High	**Low**
patients, nr (%)	893	3667
Female	635 (71)	2660 (73)
Male	258 (29)	1007 (28)
Registry, nr (%)		
MSBase	492 (55)	2202 (60)
OFSEP	401 (45)	1465 (40)
age, yr	44 (7)	27 (5)
disease duration (1st visit), yr	0.5 [0.4, 0.8]	0.5 [0.4, 0.8]
disability (1st visit), EDSS	3.5 [3.0, 4.0]	1.3 [0.8, 2.0]
maximum disability in first year, EDSS	4.0 [3.0, 5.0]	1.5 [1.0, 2.0]
disability (last visit), EDSS	4.0 [2.5, 6.0]	1.5 [1.0, 2.5]
MS course at first visit		
Clinically isolated syndrome	552 (62)	2282 (60)
Relapsing-remitting	341 (38)	1385 (40)
visit interval, months	6 [5, 8]	7 [5, 8]
prospective follow-up, yr	7.0 [4.2, 11.3]	7.7 [4.5, 12.1]
Patients with MRI recorded, n (%)	858 (96)	3593 (97)
Proportion of follow-up time on		
high-efficacy DMTs	62% [32, 88]	55% [30, 80]
not on high-efficacy DMTs	38% [22, 68]	45% [20, 70]
no DMTs	9% [0, 30]	10% [0, 26]
Treatment strategy at any time during follow-up, nr of		
alemtuzumab$^{(H)}$	32 (4)	176 (5)
natalizumab$^{(H)}$	383 (43)	1499 (41)
mitoxantrone$^{(H)}$	114 (13)	138 (4)
ocrelizumab/rituximab/ofatumumab$^{(H)}$	255 (29)	907 (25)
daclizumab$^{(H)}$	1 (0)	9 (0)
cladribine$^{(H)}$	41 (5)	225 (6)
fingolimod/ozanimod$^{(H)}$	358 (40)	1910 (52)
siponimod$^{(H)}$	7 (1)	4 (0)
dimethyl fumarate	85 (10)	499 (14)
teriflunomide	68 (8)	352 (10)
interferon beta/glatiramer acetate	419 (47)	2280 (62)
untreated	592 (66)	2446 (67)
Number of DMTs during follow-up	1 [1, 2]	2 [1, 3]
Year of baseline	2013 [2008, 2016]	2012 [2008, 2016]

Mean (SD) or median [quartiles] as appropriate

$^{(H)}$ High-efficacy disease modifying therapy

Supplementary figure S4: Secondary analysis among a subgroup exposed to HE-DMTs: Overall covariate balance in people at (A) high risk of aggressive MS and (B) low risk of aggressive MS



Supplementary table S7: Secondary analysis among a subgroup exposed to HE-DMTs: Outcomes

7A – Relapse and disability outcomes in patients with vs without continuous HE-DMTs

	Relapses	**Disability Accumulation**	**Disability Improvement**	**Time to EDSS 6**
			HR (95% CI)	
Low risk of aggressive MS	**0.59 (0.55-0.63)**	**0.79 (0.70-0.91)**	1.09 (0.89-1.32)	**0.52 (0.35-0.77)**
High risk of aggressive MS	**0.61 (0.54-0.69)**	**0.72 (0.59-0.89)**	1.00 (0.81-1.20)	0.84 (0.59-1.20)

7B - Outcomes stratified by aggressive MS risk and treatment with HE-DMTs

		Relapses	**Disability Accumulation**	**Disability Improvement**	**Time to EDSS 6**
			HR (95% CI)		
Low risk of aggressive MS	No HE-DMT state	*Ref.*	*Ref.*	*Ref.*	*Ref.*
	HE-DMTs state	**0.58 (0.54-0.62)**	**0.80 (0.70-0.92)**	1.11 (0.90-1.34)	**0.51 (0.34-0.77)**
High risk of aggressive MS	No HE-DMT state	**1.29 (1.11-1.51)**	1.08 (0.85-1.37)	**1.58 (1.16-2.15)**	1.03 (0.53-1.99)
	HE-DMTs state	**0.73 (0.61-0.87)**	**0.75 (0.58-0.98)**	**1.53 (1.13-2.11)**	0.85 (0.44-1.66)

Supplementary table S8: Treatment Interaction x Registry Estimates.

		Relapses	**Disability Accumulation**	**Disability Improvement**
Sensitivity Analysis	**Aggressive MS Risk Stratum**	*HR (95% CI)*		
Risk of aggressive MS x Registry	Low risk	1.04 (0.92-1.19)	1.09 (0.85-1.40)	1.09 (0.85-1.40)
	High risk	1.24 (0.98-1.58)	0.74 (0.43-1.06)	1.50 (0.95-2.36)

Supplementary table S9: Sensitivity analyses

		Relapses	**Disability Accumulation**	**Disability Improvement**
Sensitivity Analysis	**Aggressive MS Risk Stratum**	*HR (95% CI)*		
Subgroup analysis	Low risk	0.59 (0.55-0.63)	0.79 (0.70-0.91)	1.09 (0.89-1.32)
	High risk	0.61 (0.54-0.69)	0.72 (0.59-0.89)	1.00 (0.81-1.20)
Excluding partially treated bins	Low risk	0.31 (0.28-0.34)	0.62 (0.54-0.71)	1.29 (1.04-1.61)
	High risk	0.37 (0.31-0.44)	0.70 (0.55-0.89)	1.02 (0.79-1.31)
Multiple imputation MRI	Low risk	0.57 (0.53-0.61)	0.73 (0.63-0.85)	1.15 (0.95-1.41)
	High risk	0.60 (0.53-0.68)	0.81 (0.66-0.98)	1.15 (0.96-1.40)