Prognostic Factors of Future Disability Accrual and Improvement in Multiple Sclerosis

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Disclosures

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Objectives and impact

Background

- Knowledge of the clinical and imaging factors that most strongly drive disability worsening or improvement can help inform treatment decisions; however, quantitative evidence is lacking
- The long-term disease trajectory of people living with MS can be improved by initiating efficacious treatment early[1,2]

Objectives

- To investigate the quantitative contributions of demographic as well as clinical and radiological activity / severity markers in driving disability worsening and limiting disability improvement in MS
- To offer insight for updating clinical guidelines in MS

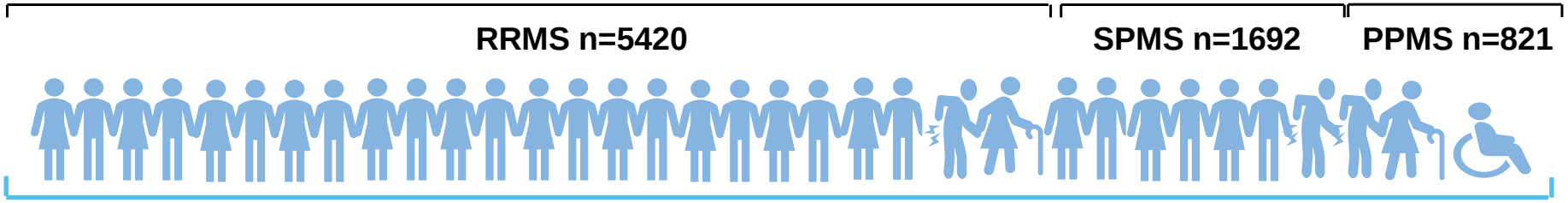
MS, multiple sclerosis

1. Lublin FD, et al. Brain. 2022 Sep 14;145(9):3147-61; 2. He A, et al. Lancet Neurol. 2020 Apr;19(4):307-16.

Novartis-Oxford (NO.MS) MS dataset[1]: Large dataset covering the entire spectrum of MS

9 clinical trials[2]
(Phase 2 and 3 and their extensions)

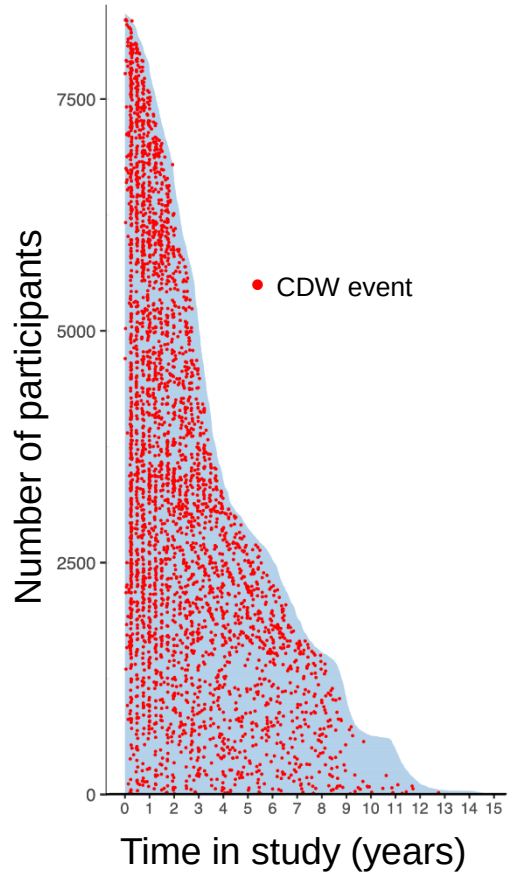
~ 8000 people with MS



Age 10–66 years

~130,000 EDSS assessments

45,000 MRI scans



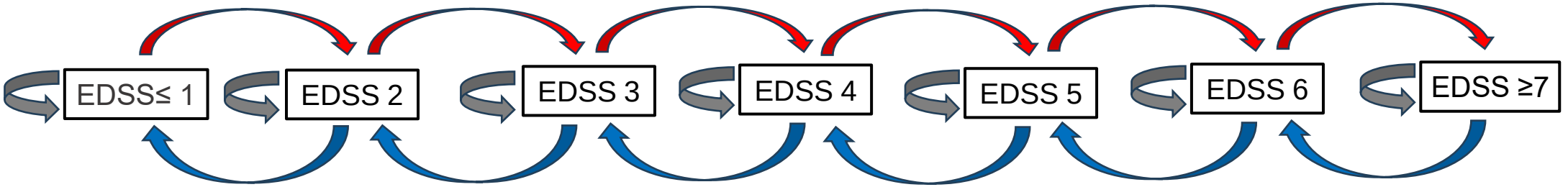
Follow-up ≤ 15 years

CDW, confirmed disability worsening; EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; MS, multiple sclerosis; NO.MS, Novartis-Oxford MS; PPMS, primary progressive MS; RRMS, relapsing-remitting MS; SPMS, secondary progressive MS. 1. Dahlke F, et al.. Multiple sclerosis (Houndmills, Basingstoke, England). 2021 Nov;27(13):2062-76. 2. NCT00333138, NCT00289978, NCT00340834, NCT00731692, NCT00355134, NCT01892722, NCT01665144, NCT02792218, NCT02792231, and their corresponding extensions

Novel approach: Bayesian continuous-time Markov model (CTMM)

Outcome measured:

Improvements and worsenings in disability – i.e. EDSS transitions between two consecutive visits (~3 months)



EDSS assessments:	n=17,883	n=31,834	n=17,451	n=21,447	n=10,172	n=17,022	n=11,275

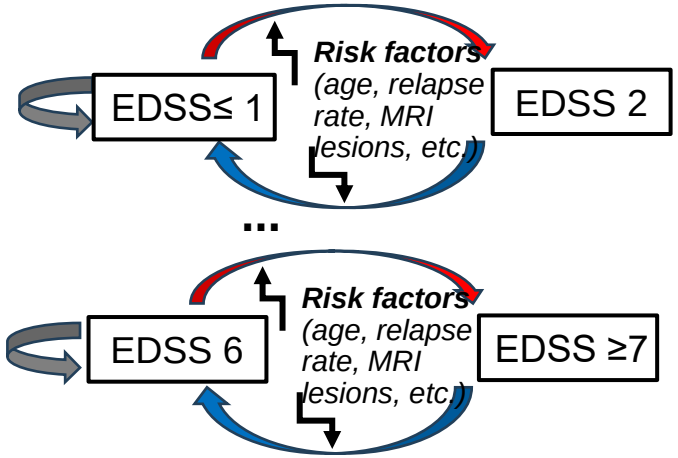
What are the risk factors affecting each EDSS transition?

CTMM; continuous time Markov model; EDSS, Expanded Disability Status Scale. EDSS scores measured during an active relapse were removed

1. Hatami F, Ocampo A, Graham G, Nichols TE, Ganjgahi H. Biostatistics. 2023 Jul 11:kxad012

Advantages of CTMM compared with time-to-event model (TTE)

- **The TTE model, typically used in studies exploring MS prognosis factors[1]:**
  - only assesses factors that affect disability worsening
  - ignores that these factors may vary as the disease evolves
- **The CTMM by contrast[2]:**



Simultaneously models disability improvement and worsening

- *Distinguishes between factors that affect disability worsening and disability improvement*

Assesses risk factors as a function of a patient's current disability level

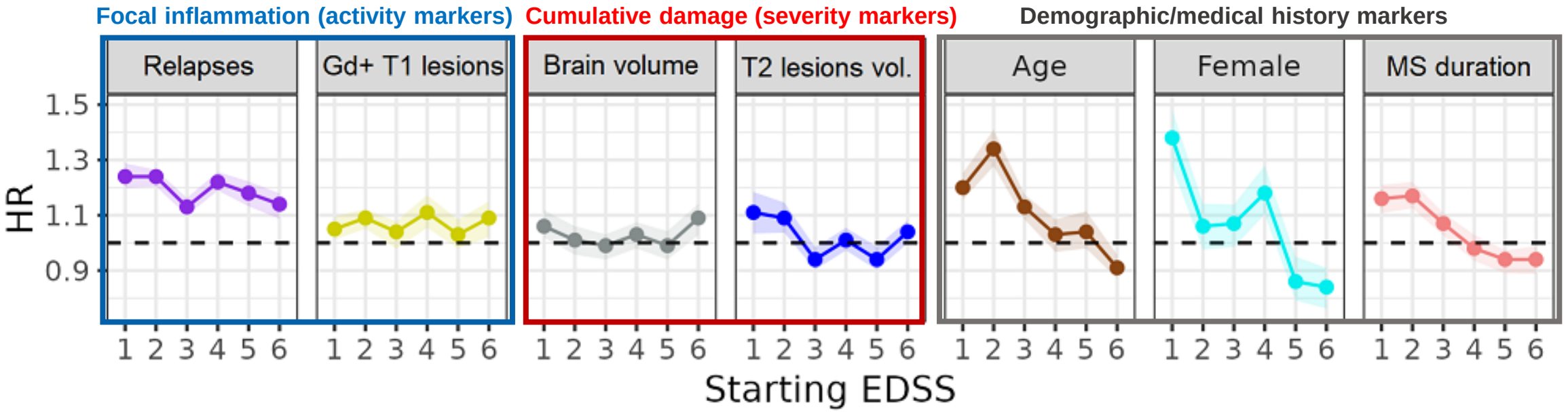
- *Distinguishes between factors that have value early versus later in the disease*

12 estimates for each candidate risk factor vs 1 estimate for a time-to-event model

CTMM; continuous time Markov model; EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging. EDSS scores measured during an active relapse were removed`; MS, multiple sclerosis.

1. Tintore M, et al. MS. Mult Scler. 2020 Nov;26(13):1658-1669. 2. Hatami F, Ocampo A, Graham G, Nichols TE, Ganjgahi H. Biostatistics. 2023 Jul 11:kxad012.

Effects of factors on disability worsening



HR >1 associated with higher probability of worsening (i.e. "drivers of worsening").

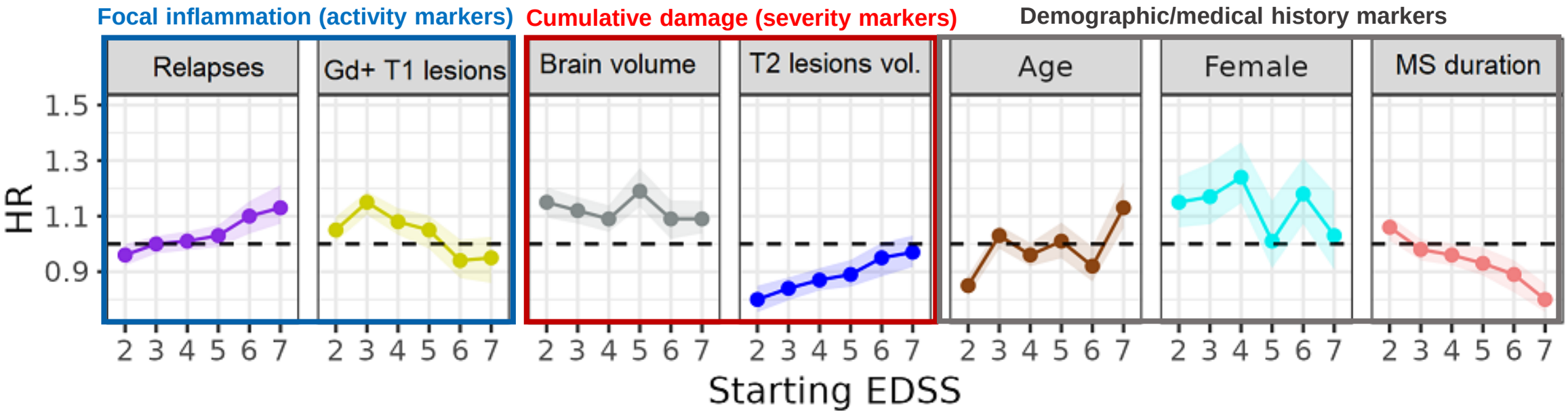
HR <1 associated with lower probability of worsening (i.e. "factors limiting worsening").

Focal inflammation (activity markers) key driver of disability worsening

- The **most consistent** contributor to worsening (i.e., HR consistently >1 over the tested EDSS range) was a higher **number of relapses in the previous year**

Contributing factors to 1-step EDSS disability worsening from a model adjusting for all covariates. Coloured points indicate the estimated HR, the corresponding coloured envelop shaded region represents the 95% CI. Relapses refer to the number of relapses in the previous year; Gd+ T1 lesions are the number of Gadolinium-enhancing T1 lesions (categorized as 0, 1, 2, 3, 4 or more); brain volume is normalised brain volume (cm^3); T2 lesions vol. is T2 lesion volume (mm^3); MS duration is duration since the first MS symptoms. CI, credible interval; EDSS, Expanded Disability Status Scale; Gd+: gadolinium-enhancing; HR, hazard ratio; MS, multiple sclerosis; vol., volume.

Effects of factors on disability improvement



HR >1 associated with higher probability of improvement (i.e. "drivers of improvement").

HR <1 associated with lower probability of improvement (i.e. "factors limiting improvement").

Cumulative damage (severity markers) key limiting factor for the ability to improve

- A **higher normalised brain volume** was the single key factor **consistently** associated with a higher probability of improvement
- A **higher T2 lesion volume** was the single **most consistent** factor limiting disability improvement**, especially at low EDSS scores**

Contributing factors to 1-step EDSS disability improvement from a model adjusting for all covariates. Coloured points indicate the estimated HR, the corresponding coloured envelop shaded region represents the 95% CI. Relapses refer to the number of relapses in the previous year; Gd+ T1 lesions are the number of Gadolinium-enhancing T1 lesions (categorized as 0, 1, 2, 3, 4 or more); brain volume is normalised brain volume (cm^3); T2 lesions vol. is T2 lesion volume (mm^3); MS duration is duration since the first MS symptoms. CI, credible interval; EDSS, Expanded Disability Status Scale; Gd+: gadolinium-enhancing; HR, hazard ratio; MS, multiple sclerosis; vol., volume.

Conclusions

Key findings

- This study based on a very large dataset provides strong evidence that **cumulative MRI disease burden**, as measured by the total T2 lesion volume or the normalised brain volume, **limits the patients' ability to improve** (i.e., to reduce their disability)
- The data also confirm **disease activity** (relapse rates and MRI lesions) as a **key driver of disability worsening**

Clinical impact

- **The accumulation of subclinical disease burden,** as marker of diminished brain reserve capacity, limits a patient's capacity to recover and **should be avoided**
- The importance of achieving optimal control of disease activity with **effective therapies early** – to **protect the patient's brain integrity** and **capability for compensation and recovery** – should be mentioned more explicitly as a treatment target in future MS guidelines

MRI, magnetic resonance imaging; MS, multiple sclerosis

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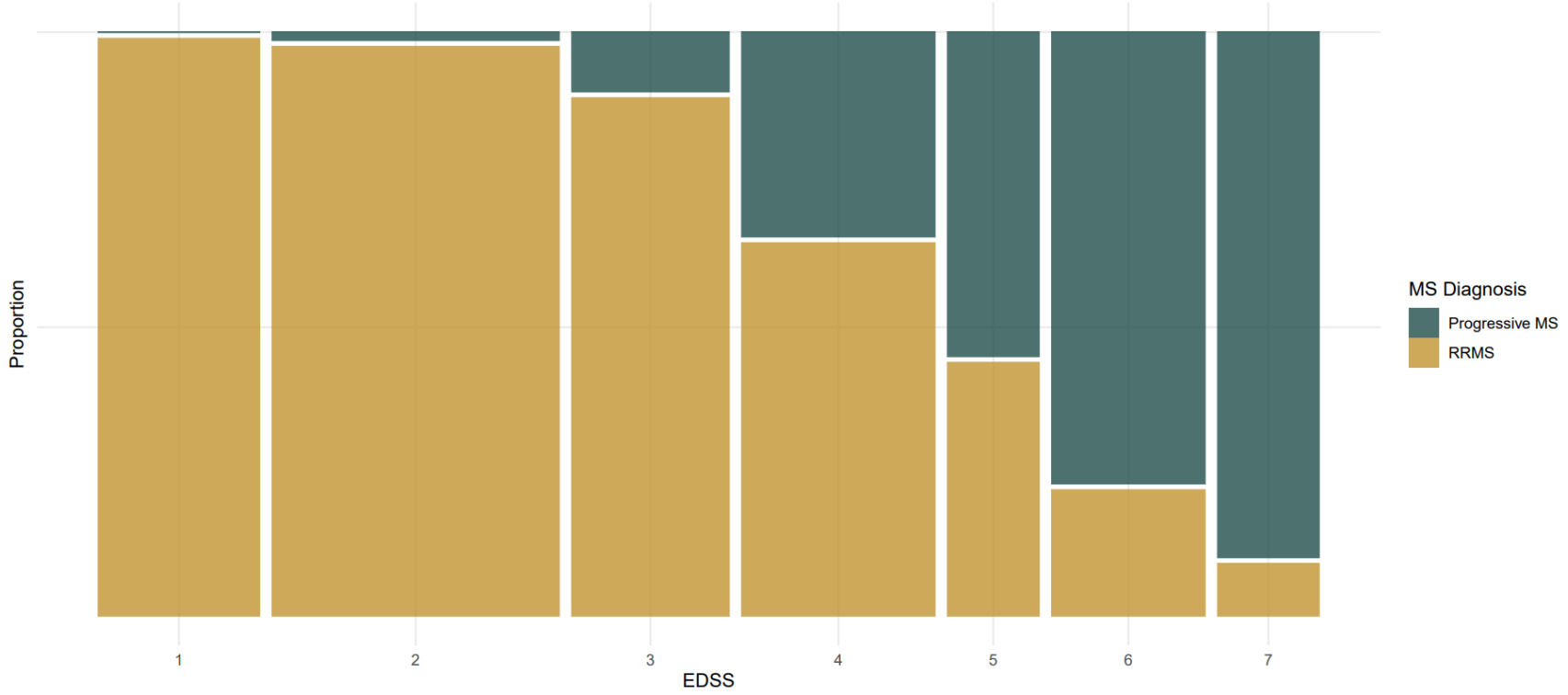
Back up slides

Proportion of EDSS assessments categorized by MS phenotypes for each EDSS state



The height of each colored bar indicates the proportion of EDSS assessments at a given MS phenotype. The width of each bar is proportional to the number of EDSS assessments at the specific disability level. The diagnosis of MS is reported as provided by the investigator. Progressive MS includes both primary progressive and secondary progressive MS. MS, multiple sclerosis; RRMS, relapsing-remitting MS. EDSS, Expanded Disability Status Scale;

Baseline demographic and disease characteristics
(subpopulation of patients from NO.MS[1] with MRI data)

Variable	Total	RRMS	SPMS	PPMS
Total number of patients	7933	5420	1692	821
Age				
n (%)	7933 (100%)	5420 (100%)	1692 (100%)	821 (100%)
Mean (SD)	40.4 (10.7)	36.9 (9.9)	47.8 (8.0)	48.3 (8.4)
[min, max]	[10, 66]	[10, 59]	[20, 63]	[24, 66]
Sex				
n (%)	7933 (100%)	5420 (100%)	1692 (100%)	821 (100%)
Female	5206 (65.6%)	3801 (70.1%)	1009 (59.6%)	396 (48.2%)
Race				
n (%)	7908 (99.7%)	5406 (99.7%)	1681 (99.4%)	821 (100%)
Caucasian	7366 (93.2%)	4973 (92.0%)	1603 (95.4%)	790 (96.2%)
Disease duration (median, years)				
n (%)	7933 (100%)	5420 (100%)	1692 (100%)	821 (100%)
0 to <2	1105 (13.9%)	1095 (20.2%)	5 (0.3%)	5 (0.6%)
2 to <5	1619 (20.4%)	1200 (22.1%)	88 (5.2%)	331 (40.3%)
5 to <10	2196 (27.7%)	1428 (26.4%)	309 (18.3%)	459 (55.9%)
10 to <30	2830 (35.7%)	1632 (30.1%)	1172 (69.3%)	26 (3.2%)
≥30	183 (2.3%)	65 (1.2%)	118 (7.0%)	0
Prior use of a DMT for MS				
n (%)	7932 (99.9%)	5420 (100%)	1962 (100%)	820 (99.9%)
Previously treated with a DMT	4486 (56.6%)	2997 (55.3%)	1318 (77.9%)	171 (20.9%)
Relapses in the past year				
n (%)	7931 (99.9%)	5420 (100%)	1690 (99.8%)	820 (100%)
Mean (SD)	1.0 (0.9)	1.4 (0.8)	0.3 (0.6)	0
EDSS at baseline				
Mean (SD)	3.3 (1.8)	2.4 (1.3)	5.4 (1.1)	4.6 (1.0)
Gd-enhancing T1 lesions (%)				
n (%)	7854 (99.0%)	5384 (99.3%)	1650 (97.5%)	820 (99.9%)
Presence of T1 lesions	2555 (32.5%)	2079 (38.6%)	374 (22.7%)	102 (12.4%)
T2 lesion volume (mm^3) at baseline				
n (%)	7855 (99.0%)	5386 (99.4%)	1651 (97.6%)	818 (99.6%)
Mean (SD)	9773 (12,279)	8055 (10,343)	15,542 (16,173)	9441 (11,369)
Normalized brain volume (cm^3) at baseline[a]				
n (%)	7661 (96.6%)	5222 (96.3%)	1623 (95.9%)	816 (99.4%)
Mean (SD)	1471.6 (106.9)	1484.5 (110.9)	1420.6 (86.4)	1490.7 (84.2)

n (%) refers to the number and proportion of patients with the specific baseline feature evaluated. aBrain volume is normalised for the patient's skull size.). DMT, disease-modifying therapy, EDSS, Expanded Disability Status Scale; Gd, gadolinium; MRI, magnetic resonance imaging; MS, multiple sclerosis; NO.MS, Novartis-Oxford MS; PPMS, primary progressive MS; RRMS, relapsing-remitting MS; SPMS, secondary progressive MS.

1. Dahlke F, et al.. Multiple sclerosis (Houndmills, Basingstoke, England). 2021 Nov;27(13):2062-76.