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Original Research Paper

Age is a critical determinant in recovery from multiple sclerosis relapses

Brittani L Conway, Burcu Zeydan, Uğur Uygunoğlu, Martina Novotna, Aksel Siva, Sean J Pittock, Elizabeth J Atkinson, Moses Rodriguez and Orhun H Kantarci

Abstract

Objective: To evaluate the impact of age on recovery from multiple sclerosis relapses.

Background: Increasing disability in multiple sclerosis is a consequence of progressive disease and incomplete relapse recovery.

Methods: The first and last-ever relapse data (357 relapses in 193 patients) from the Olmsted County population-based multiple sclerosis cohort were systematically reviewed for age, fulminance, location (optic nerve, brainstem/cerebellar, spinal cord), peak deficit, and maximum recovery. Three different relapse-outcome measures were studied both as paired analyses and as an overall group effect: change from peak deficit to maximum recovery in raw functional system score related to the relapse (ΔFSS), a previously published FSS-based relapse-impact model, and change from peak deficit to maximum recovery in Extended Disability Status Scale (ΔEDSS) score.

Results: Older age was linearly associated with worse recovery in the ΔFSS outcome ($p = 0.002$), ΔEDSS outcome ($p < 0.001$), and the FSS-based relapse-impact model ($p < 0.001$). A multivariate analysis of ΔFSS outcome linked poor recovery to older age ($p = 0.015$), relapse location (transverse myelitis or brainstem/cerebellar syndrome; $p < 0.001$), and relapse fulminance ($p = 0.004$).

Conclusion: Multiple sclerosis-relapse recovery declines in a linear fashion with increased age, which should be considered when making treatment decisions.

Correspondence to:
OH Kantarci
Mayo Clinic Center for
Multiple Sclerosis and
Autoimmune Neurology, and
Department of Neurology,
Mayo Clinic College of
Medicine, 200 First Street, SW,
Rochester, MN 55905, USA.
kantarci.orhun@mayo.edu

Brittani Conway
Mayo Clinic Center for
Multiple Sclerosis and
Autoimmune Neurology, and
Department of Neurology,
Mayo Clinic College of
Medicine, Rochester,
MN, USA/ HealthPartners
Neuroscience Center, Saint
Paul, MN, USA

Burcu Zeydan
Mayo Clinic Center for
Multiple Sclerosis and
Autoimmune Neurology, and
Department of Neurology,
Mayo Clinic College of
Medicine, Rochester,
MN, USA/ Department of
Radiology, Mayo Clinic
College of Medicine,
Rochester, MN, USA

Ugur Uygunoğlu
Mayo Clinic Center for
Multiple Sclerosis and
Autoimmune Neurology, and
Department of Neurology,
Mayo Clinic College of
Medicine, Rochester, MN,
USA/ Cerrahpaşa Faculty
of Medicine, Istanbul
University, Istanbul, Turkey

Martina Novotna
Department of Neurology,
Mayo Clinic College of
Medicine and Science,
Rochester, MN, USA/
Polyclinic Medicina Plus,
Prague, Czech Republic

Aksel Siva
Cerrahpaşa Faculty
of Medicine, Istanbul
University, Istanbul, Turkey

Sean J Pittock
Moses Rodriguez
Orhun H Kantarci
Mayo Clinic Center for
Multiple Sclerosis and
Autoimmune Neurology, and
Department of Neurology,
Mayo Clinic College of
Medicine, Rochester, MN,
USA

Introduction

Increasing disability in multiple sclerosis (MS) is a consequence of progressive disease and incomplete recovery from relapses. These processes are not mutually exclusive as poor recovery from early relapses in MS results in earlier onset of progressive disease.[1]

The onset of progressive disease is an age-dependent process that takes place in the fifth decade.[2–5] The same decade also marks a pathological shift from active inflammatory plaques to smoldering plaques[3] and a radiologic shift in high-field, 7-T magnetic resonance imaging (MRI) studies from predominantly shrinking lesions to predominantly expanding lesions with iron rims.[6] Both the expanding lesions in MRI and smoldering lesions in pathological findings are more commonly associated with progressive phase than with relapsing-remitting phase in MS. Imaging evidence further suggests that in otherwise healthy individuals, white-matter integrity plateaus by the third decade and starts to decline by the fourth decade.[7,8]

These findings suggest an age-dependent shift to a progressive phenotype in MS and may also mark a dramatic shift in recovery from relapses. Prior studies have demonstrated that relapse recovery declines with increasing age.[9–13] It remains unclear whether the decline takes place in a linear fashion as opposed to a specific deflection point akin to progressive MS onset. Also the possibility of inherent genetic factors at an individual level must be considered. We tested multiple models of relapse-recovery assessments as a global-population effect and in a paired analysis at the

Elizabeth J Atkinson
Department of Health
Sciences Research, Mayo
Clinic College of Medicine
and Science, Rochester,
MN, USA

individual level by comparing the first and last-ever relapse-recovery metrics in a population-based cohort of patients.

Methods

Standard protocol approvals, registrations, and patient consents

We obtained written informed consent permitting access to the medical record from all patients in accordance with a protocol approved by the Mayo Clinic Institutional Review Board.

Study population

The Olmsted County MS population-based cohort comprises all patients who resided in Olmsted County, were seen originally and followed up at the Mayo Clinic, were diagnosed with MS between December 1991 and December 2002, and re-ascertained in 2010 for additional follow-up with no new patients added at that time.[5,14,15] All patients fulfilled the McDonald diagnostic criteria for MS.[16,17] The original cohort included 210 patients.

History and detailed examinations from periodic clinic visits with MS-trained neurologists served as the primary data source for identification of a relapse and associated peak deficit as well as maximum recovery. Primary care, ophthalmology, and physical medicine and rehabilitation notes provided secondary supplementary information for timing of symptom onset and recovery. Patients with primary progressive multiple sclerosis (PPMS; $n = 15$) were excluded from this study due to inherent overlap of any relapses with progressive disease. In addition, two patients with insufficient data and follow-up were excluded. Ultimately, we studied 193 patients.

Study variables

Two MS-trained and Extended Disability Status Scale (EDSS) score-certified neurologists (B.C., B.Z.) independently reviewed each chart and extracted data. They compared data for each patient for accuracy and jointly reviewed discordant information. A third MS-trained and EDSS-certified neurologist (U.U.) independently reviewed final database discrepancies, and the principal investigator (O.H.K.) arbitrated any disagreement(s). The following information was extracted: sex, age at first- and last ever-recorded relapse, relapse location (hemispheric, optic nerve, brainstem/cerebellar spinal cord, or multifocal), observed peak relapse-related Kurtzke functional

system score (FSS)[18] and peak relapse-related EDSS scores, best observed recovery FSS and EDSS scores, time to maximum recovery (<1 month or ≥ 1 month), stable FSS and EDSS before the last relapse, steroid use during the relapse and final MS disease phase of the patient (relapsing-remitting or progressive) at last follow-up.

Definition of relapse

Relapse was defined as a sudden onset of focal neurologic symptoms lasting more than 24 hours that corresponded to optic neuritis, a new cerebral lesion, a brainstem or cerebellar syndrome, or transverse myelitis. Symptoms had to occur in the absence of an alternative cause (e.g. fever or systemic illness) and at least 30 days from a prior exacerbation. When appropriate, we utilized supportive data to confirm the clinical exacerbation and location (e.g. MRI, somatosensory, or visual evoked potentials).

We defined a fulminant relapse as: (a) reaching a peak FSS[18] of 5 or 6 specific to that relapse or (b) a significant change from baseline in ambulation at the peak of the specific relapse (e.g. being fully ambulatory to needing unilateral assistance, bilateral assistance, wheelchair assistance, or becoming restricted to bed).

Definition of recovery

We defined recovery as the maximal improvement in subjective and objective (examination) findings following the peak deficit of a relapse. We allowed a minimum of 6 months before the recovery determination, since prior publications suggest that most recovery takes place within the first 3 months or less.[12,19,20] We utilized data from an examination within less than 6 months after the relapse if the patient already achieved full recovery status during that time interval.

Outcome models of recovery

Three different recovery outcome models were studied. First two were based on change from peak deficit to maximum recovery in raw FSS related to the relapse. In addition to using a relapse-specific raw change in FSS as outcome ($\Delta FSS = FSS$ relapse peak $-$ FSS maximum recovery), we expanded on our previously published "relapse-impact model" to define patients with good, average, and worst recovery (Figure 1).[21] Accordingly, the model allowed us to account for both the initial impact of the relapse severity ("fulminance") at its peak deficit and the amount of recovery ultimately achieved.
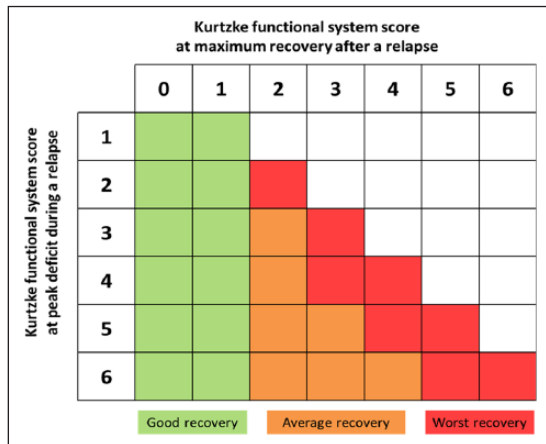
Figure 1. Functional system score (FSS)-based relapse-impact model is illustrated. Good, average, or worst recovery is assigned based on the peak FSS reached during a relapse and the amount of final stabilized recovery FSS reached. Minimum of 6 months is needed to assign the final stabilized recovery FSS except in the case of complete recovery with normalization of FSS attained earlier than 6 months after a relapse.

The third recovery outcome model we used was based on change from peak deficit to maximum recovery in EDSS to assess overall impact of the relapse on disability status of the individual at the time by a change in the peak EDSS score to best recovery EDSS score (ΔEDSS = EDSS relapse peak − EDSS maximum recovery). This model allowed us to quantify the overall disability impact of recovery from the specific relapse (e.g. taking into account the uneven disability contribution of each FSS). In this model, we further accounted for existing pre-relapse disability, calculating peak EDSS gain by a change from stable baseline EDSS. Expectedly, median stable baseline EDSS was irrelevant for the first relapse but relevant for the last relapse (Table 1). We also calculated the recovered fraction of newly accumulated disability [ΔEDSS-R% = 100 × (EDSS maximal recovery − EDSS stable pre-relapse)/(EDSS relapse peak − EDSS stable pre-relapse)]. For poly-symptomatic onset, we used the most devastating clinical syndrome as the FSS of interest. For the EDSS-based models, multiple syndromes relevant to the relapse were included.

Definition of progressive disease course
We defined progressive disease course as a steady, irreversible decline in neurologic function over the course of ≥1 year[22] attributable to MS but occurring independently of relapse-related disability.[5] This most commonly manifested as progressively worsening weakness, spasticity, ataxia, gait difficulty, or bladder dysfunction.

Data analyses
Demographic and clinical data are presented in table format with paired analyses of recovery-outcome models for each individual time point of relapse recovery. For any given measurement, summaries are shown only for subjects that have measurements at both time points. The paired *T*-test or McNemar tests were applied as appropriate to the data. We also presented the first and last relapse recovery data for different models of outcome, both individually and combined, to visualize the relationship of age and relapse recovery.

We only completed multivariable analyses using ΔFSS, since both FSS-based relapse-impact model and EDSS-based recovery models are inherently biased toward the factors such as fulminance or location of a relapse. Mixed-effects models were used to account for the repeated measurements for subjects; all available measurement values were used.

Results
Of the 193 patients eligible for the study, 101 developed progressive MS and 92 remained relapsing-remitting MS at the time of final disease classification. In total, we analyzed 365 first or last relapses with sufficient clinical detail. We excluded eight relapses that occurred after onset of progressive MS because the final diagnostic outcome of progressive MS was one of the variables studied. For the final analyses, 189 first relapses and 168 last relapses were studied with a mean age difference of 15 years between relapse groups (Table 1).

Expectedly, in a historical population-based cohort, if the EDSS was not explicitly stated but detailed examinations and histories were available for FSS components, FSS specific to the relapse was easier to derive than EDSS. Of the 189 patients with first-relapse data, 164 had FSS-based relapse-impact model data, and 161 had EDSS-based relapse-recovery data (Figure 2). Of these, last-relapse data were available for 134 and 130 patients, respectively, to conduct paired first and last relapse-recovery analyses (Figure 2). Hence, for the final paired analyses, we had 85.1% with reliable FSS and 68.8% with reliable global EDSS data to complete our study. Similarly, we were able to reliably calculate ΔEDSS-R% in only 63 patients (33.3% of all eligible patients) for the final paired analyses due to limited availability of data to assign a pre-relapse stabilized EDSS.

Table 1. Demographics, relapse characteristics, and outcome models of the study population based on the paired analysis.

	1st Relapse	1st Relapse (paired)	Last relapse	*p*-value
No. of relapses (in 193 patients)	189	168	168	–
Female %	72.0	72.0	72.0	–
Pre-relapse median stable EDSS (min–max)	0 (0–0)	0 (0–0)	1.5 (0–7.5)	<0.001[a]
Age at relapse (mean ± SD)	30.6 ± 8.8	30.2 ± 8.8	45.0 ± 10.0	<0.001[a]
Relapse location (%)				0.032[b,c]
Hemispheric	3.2	3.0	2.4	0.999[b]
Optic neuritis	21.2	23.2	12.5	0.023[b]
Brainstem-cerebellar	22.8	19.0	31.5	0.005[b]
Transverse myelitis	50.3	52.4	53.0	0.999[b]
Multifocal	2.6	2.4	0.6	0.371[b]
Fulminant relapse (%)	5.5	5.7	12.%	0.066[b]
Treatment of relapse (%)	18.2%	19.0%	47.9%	<0.001[b]
FSS-based recovery outcome				
ΔFSS (mean ± SD)	1.6 ± 1.1	1.7 ± 1.1	1.2 ± 1.2	0.002[a]
FSS-based Relapse-Impact model (good %)	92.1	92.5	56.7	<0.001[b]
EDSS-based recovery outcome				
ΔEDSS (mean ± SD)	1.2 ± 1.3	1.2 ± 1.3	0.6 ± 1.3	<0.001[a]
ΔEDSS-R% (mean ± SD)	65.6 ± 45.2	66.2 ± 45.0	55.5 ± 68.0	0.335[a]
Rapid (within 1 month) recovery (%)	7.2	9.3	7.4	0.789[b]
Remained RRMS at last follow-up (%) (mean disease duration ± SD: 28.7 ± 13.0 years; mean age ± SD: 58.8 ± 12.5 years)	48.1	–	–	–

EDSS: Expanded Disability Status Scale; SD: standard deviation; FSS: functional system score; RRMS: relapsing-remitting multiple sclerosis.

[a]Paired *T*-test.
[b]McNemar test.
[c]Overall test comparing relapse locations.

In the univariate-paired analyses (e.g. first vs last relapse), as the patient aged, recovery worsened in the ΔFSS outcome (mean = 1.7 vs 1.2, *p* = 0.002), ΔEDSS outcome (mean = 1.2 vs 0.6, *p* < 0.001), and the FSS-based relapse-impact model (good = 92.5% vs 56.7%, *p* < 0.001; Table 1). Those subjects with a bad FSS-based relapse-impact model outcome had a much smaller ΔEDSS outcome on average (mean = −0.03) than those with a good FSS-based relapse-impact model outcome (mean = −1.25, *p* < 0.001). The ΔEDSS-R% was not different between the first and the last relapse in paired analyses (mean = 66.2 vs 55.5, *p* = 0.335).

The relationship between age and worsening of recovery was linear without a clear cut-off point regardless of the model used or whether relapses were analyzed separately or combined and smoothed (Figure 3).

Relapse recovery time of <1 month did not differ between the first and last relapse (9.3% vs 7.4%, *p* = 0.789).

The multivariable analyses of ΔFSS outcome yielded an independent effect of older age (*p* = 0.015), relapse location (presence of transverse myelitis or brainstem/cerebellar syndrome; *p* < 0.001), and relapse fulminance (*p* = 0.004), which all consistently correlated with poor recovery. Impact of sex (*p* = 0.786) and time to recovery (*p* = 0.413) on final recovery amount remained insignificant.

More patients received acute relapse-related treatment in last relapse group than the first relapse group (Table 1; first relapse = 19% vs last relapse = 47.9%, *p* < 0.001). Of all relapses, 10.8% without acute treatment versus 1.1% with acute treatment already have
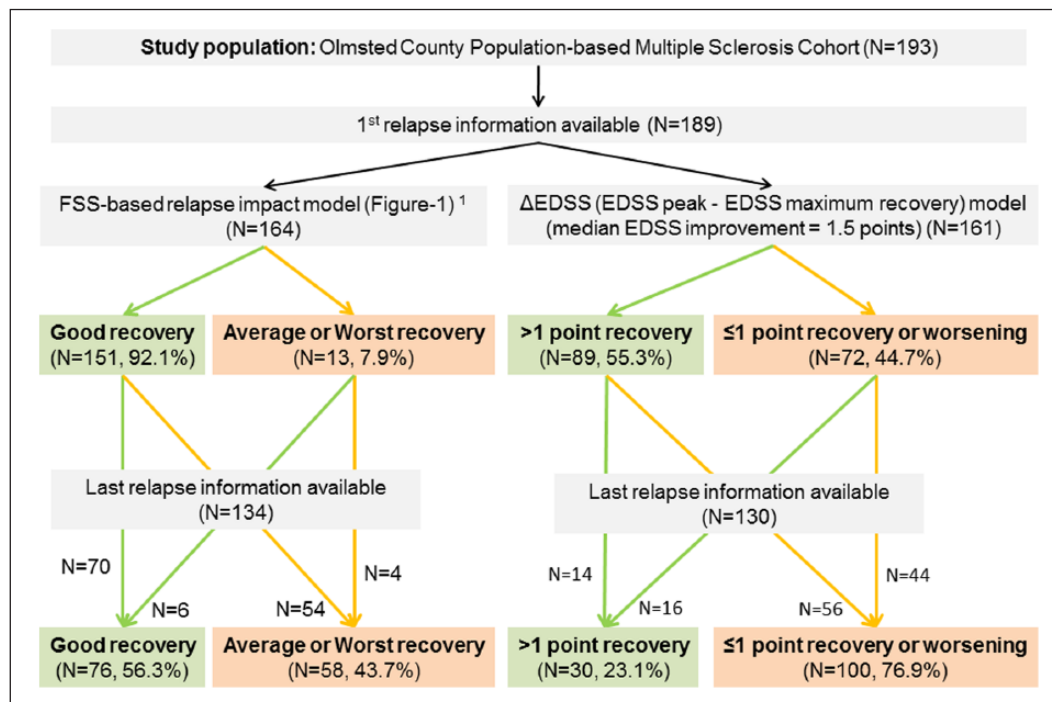
Figure 2. Study population is illustrated with the number of individuals available for each relapse point allowing for pairing for both FSS-based relapse-impact model (Figure 1)[1] and ΔEDSS (EDSS peak – EDSS maximum recovery) model. Colored arrows illustrate the switches between groups of recovery metrics with the absolute number of individuals represented by each arrow shown. Percentages represent the absolute % of patients in the whole group and how they are distributed at each stage of the analyses.

had rapid recovery completed within 1 month ($p = 0.024$). Of all relapses, 83.7% without acute treatment versus 58.8% with acute treatment had good recovery in the FSS-based relapse-impact model though not statistically significant ($p = 0.204$).

A few additional relationships at the individual variable level were highlighted: optic neuritis was more common in the younger first relapse group, while brainstem/cerebellar relapses and fulminant relapses were more common in the older last relapse group (Table 1).

For a final look at the data, we combined the FSS-based relapse-impact model and if a person is above or below the median ΔEDSS recovery metrics to define the patients with "absolute best," "absolute worst," and "intermediate" recovery in both time points ($N = 129$; Figure 4). As expected from the age effect on relapse recovery discussed above, more patients from the first relapse group who originally made "absolute best" recovery shifted to "intermediate" or even "absolute worst" recovery groups in their last relapse. Patients in the "absolute worst" recovery group had a higher likelihood of developing progressive MS than patients in "intermediate" or "absolute

best" recovery groups at the time of last relapse (Figure 4). Of the 12 patients with "absolute best" recovery during the first relapse that continued to have "absolute best" recovery in their last relapse, only two ultimately developed progressive MS. Of the 24 patients with "intermediate" recovery during the first relapse whose recovery remained "intermediate" in their last relapse, 12 patients ultimately developed progressive MS. All four patients with "absolute worst" recovery in their first relapse that remained in the "absolute worst" group during last relapse ultimately developed progressive MS.

Discussion

Our study highlights the importance of aging in recovery from MS relapses in addition to previously demonstrated impact of age on progressive MS onset.[2–5] Our study is unique because the pairing of first and last-ever relapse information in a given individual eliminated individual level of genetic variability as a potential factor in relapse recovery.

We also demonstrated that relapse recovery in a linear fashion declines with age rather than as a significant shift at a certain decade. This differs from what is
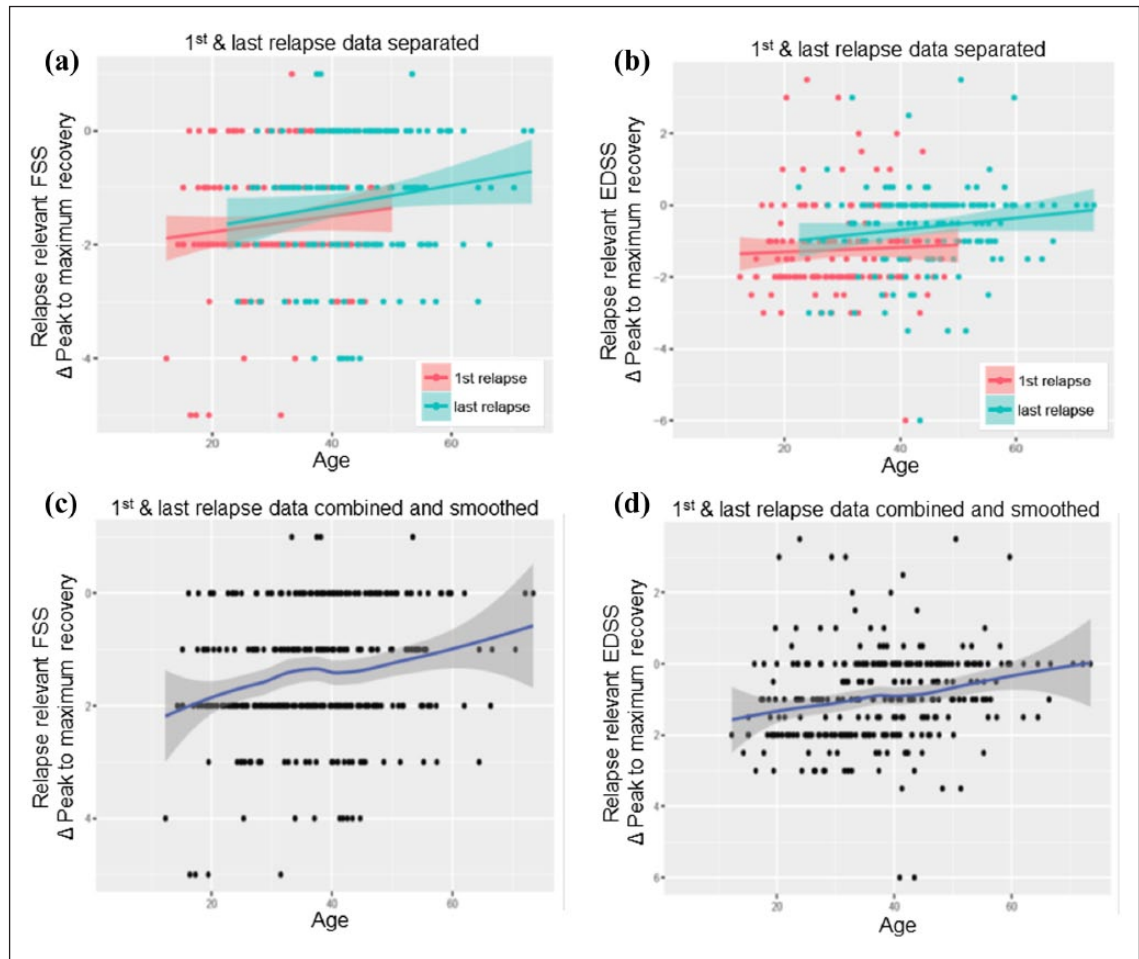
Figure 3. The relationship between age and worsening of recovery. (a) and (c) show the ΔFSS (FSS peak – FSS maximum recovery). (b) and (d) show the ΔEDSS (EDSS peak – EDSS maximum recovery). (a) and (b) show data from first and last relapse separated. (c) and (d) show data from first and last relapse combined and smoothed. Individual relapse points are shown together with the mean recovery and standard deviation from the mean. As patients get older, their ability to recover from relapses declines.

observed at progressive MS onset, in which the fifth decade of life seems to trigger a major shift.[2–5] Instead, patients with relapsing-remitting MS seem to lose recovery potential linearly as they age. However, the decline in the number of relapses may make it difficult to identify a strong shift in the sixth decade and onwards. Also, our study was not specifically enriched for the oldest and youngest (pediatric onset) relapses as evident from the standard error curves in Figure 3.Thus, it remains unclear how early-onset disease might affect the linear decline in relapse recovery. If such a shift exists at a different age group, an extremes analysis would be better suited to determine when the shift occurs.

From a practical perspective, the difference of a relapse at age 20 compared to a relapse at age 60 equals the loss of one full FSS point of potential recovery. Seemingly modest, this incremental loss of one point in recovery, even on a linear and evenly distributed 5- or 6-point scale, is a difference of 17%–20% of measured function. FSS and EDSS steps are not even and are not linear. Therefore, depending on the baseline function of the individual going into a relapse, especially in upper half of the EDSS scale, a one-point change could correspond to an ambulatory patient becoming dependent on a gait aid, or a patient who uses a cane becoming wheelchair-dependent. In contrast, in the lower end of the EDSS, a one-point change may not have a major impact on disability.

Our group had previously shown that a favorable early relapse-recovery in MS delayed the onset of progressive MS.[1] We again illustrated an inherent relationship between relapse recovery, age, and progressive MS. Patients who make good recoveries, despite getting older, rarely develop progressive MS.
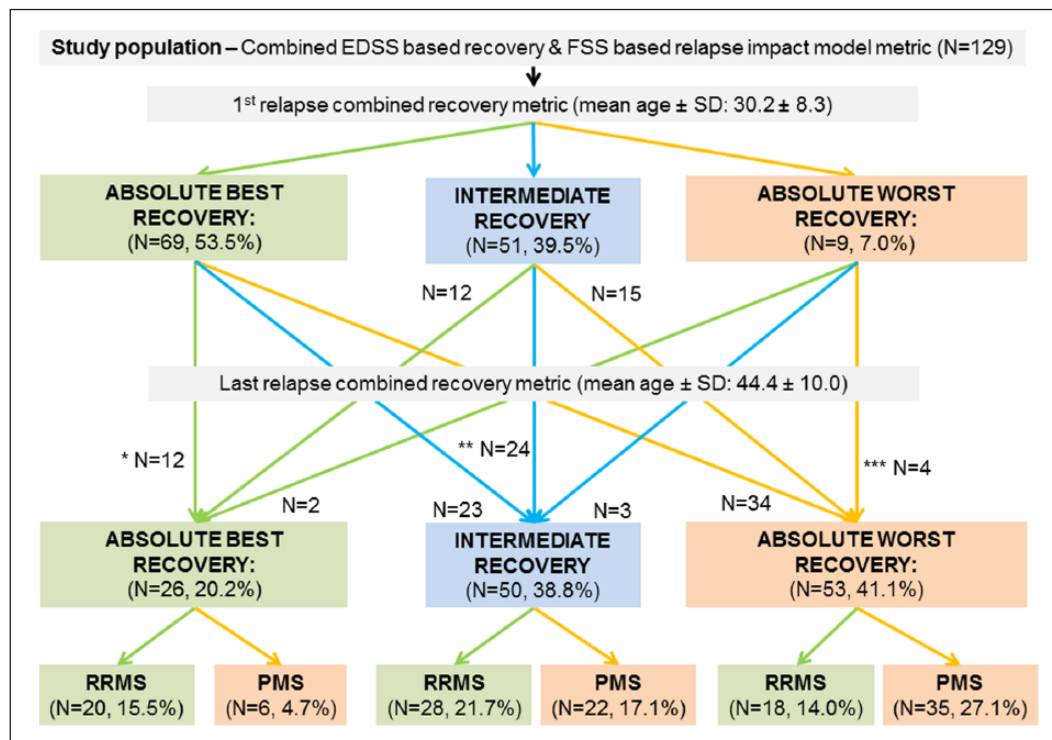
Figure 4. Study population is illustrated with the number of individuals available for each relapse point after combining FSS-based relapse-impact model (Figure 1)[1] and ΔEDSS (EDSS peak − EDSS maximum recovery) model with reclassification as "absolute best" (>1 point recovery in EDSS and good recovery in FSS-based relapse-impact model), "absolute worst" (≤1 point recovery in EDSS and average or worst recovery in FSS-based relapse-impact model), and "intermediate" recovery groups. Colored arrows illustrate the switches between groups of recovery metrics with the absolute number of individuals represented by each arrow shown. Percentages represent the absolute % of patients in the whole group and how they are distributed at each stage of the analyses. *10 of 12 patients with "best" recovery during the first relapse who remained in the "best" recovery group in their last relapse ultimately developed progressive MS. **12 of 24 patients with "intermediate" recovery during the first relapse who remained in the "intermediate" recovery group in their last relapse ultimately developed progressive MS. All of the four patients with "worst" recovery in their first relapse that remained in the "worst" recovery group in their last relapse ultimately developed progressive MS.

We believe this group represents the "clinically benign form of MS." Our study shows that having transverse myelitis, a brainstem/cerebellar syndrome, or a fulminant relapse is associated with a tendency for less sustained recovery independent of aging. This raises the question if aging for unknown reasons increases the severity of deficit from a relapse and the propensity for relapses to happen in more impactful locations than when the patient is younger.

We also show that the impact of age on relapse recovery is evident regardless of the model used, although each model studied has different advantages for future study designs. For example, in a large multivariable study, pure ΔFSS outcome analysis is likely more suitable being the least biased by relative weighting of the relapse location or severity. The FSS-based relapse-impact model used in this, as well as our previous study,[1] would more precisely reflect relapse fulminance and be more appropriate for analyzing

the impact of an aggressive acute treatment approach (e.g. plasma exchange).

For clinical trials, ΔEDSS outcome looks more appropriate when considering the ultimate cumulative disability impact of the relapse. However, we need to be cautious that disability levels accumulated due to previous relapses or progressive disease course will impact the stabilized EDSS preceding the studied relapse. As our results suggest, the impact of a relapse may not be reflected on EDSS outcome if a change from existing baseline disability is accounted for (i.e. ΔEDSS-R% outcome). We also must caution that our available data for ΔEDSS-R% outcome were limited due to the population-based construct of the study relying on available data. It is certainly possible that this outcome model may look different in a more powerful prospective study design such as in clinical trials. However, even then, stabilized pre-relapse EDSS may be the hardest variable to

assess reliably. Therefore, for most relapses recorded after the established diagnosis of MS, an EDSS-based recovery measurement may not reflect the true recovery levels related to a specific relapse compared to an FSS-based recovery measurement. The exception would be the first ever clinical relapse without any baseline disability, making an EDSS-based recovery outcome very suitable for modeling initial impact of and recovery from a clinically isolated syndrome.

We again demonstrated that time to recovery ultimately does not affect the long-term outcome of a relapse.[1] Interestingly, our study would appear to suggest that recovery duration and a relatively good recovery is less common in patients who are treated for a relapse. This of course is a factor of the clinical decision process where patients already rapidly recovering were spared steroids or any other acute relapse-related treatment. Also, last relapses were treated more often than the first relapses in our study. Potential factors that contributed to this clinical decision process are the changing treatment practices over the very long course of this population-based study, a higher tendency to treat a relapse once a diagnosis of MS is established and an older age at last relapse which led to a more severe phenotype lending itself to earlier treatment decisions. If anything, despite significantly more frequent acute treatment of a relapse at an older age, patients recovered worse overall, further confirming the overreaching impact of aging on relapse recovery.

Our study, however, does not implicate avoidance of treatments such as steroids that seemingly shorten the time to recovery and a faster return to a higher quality of post-relapse life. On the contrary, our study raises the hypothesis that an older patient (age > 40) with transverse myelitis, a brainstem/cerebellar syndrome, or a fulminant relapse could potentially be considered for even more aggressive acute treatment (e.g. plasma exchange[23,24]) without delay after steroids or even before steroid initiation. A future study with the right trial construct could determine if such an age-stratified aggressive treatment strategy is justified.

The frequency of relapses declines with age and has been suggested as reason to discontinue disease-modifying treatments at the fifth decade.[25] However, discontinuing these treatments when recovery capacity is diminished may make patients vulnerable to a single, higher-impact relapse. Given our previous findings[26] and current study, we recommend continuation of disease-modifying treatments until late in the sixth decade before considering a stopping trial.

We also demonstrate that while age is a strong determinant of recovery, location of a relapse also has an independent effect on recovery, albeit not as strong as age. It remains unclear if different systems and tracts have different recovery potentials or different reserves to start with. It is possible that the sheer number of past clinical and subclinical insults that might have affected a tract in a patient's lifetime sets the system up for poor outcome by decreasing the reserve. Indeed, this could be a simple factor of length of the tract involved affecting the number of insults. Our study was not powered to address such extensive analyses.

Our study has additional shortcomings. Even though we have a population-based sample of patients, the lack of enough systematic collection of relapse-recovery information led to a loss of informative relapse-related data (1 out of 9 for FSS, 1 out of 3 for EDSS, and 2 out of 3 for ΔEDSS-R% outcomes). Also, we did not analyze every relapse between the first and last to get more linear recovery-related information at an individual level. Thus, our conclusions regarding linearity are at a population level. We also used data collected before many modern disease-modifying drugs (DMD) were available. The paucity of DMDs that prevent relapses (22% of patients used DMDs >3 months) was specifically useful for our study construct as it provided us enough events to reach our conclusions. However, our study cannot elucidate any potential interaction of DMDs with fulminance of or recovery from a relapse. Another note of caution is that we excluded all relapses that happened after progressive disease course ensues. This is reflected also in the low baseline disability accumulated before the last relapse (Table 1) confirming our previous finding that relapses alone contribute significantly less to cumulative disability than progressive disease course.[26] Any further loss of recovery potential due to a clinically evident progressive disease course therefore was not assessed in our study. Finally, our study did not measure any imaging-related recovery metrics because many patients had their first relapses recorded either before MRI was available routinely or the available ones were of very low resolution. It is also unclear which imaging method is currently the best to measure recovery.

interpretation. B.Z. contributed to study concept and design, acquisition of data, and analysis and interpretation. U.U. contributed to acquisition of data. M.N. contributed to acquisition of data. A.S. contributed to critical revision of the manuscript for important intellectual content. S.J.P. contributed to critical revision of the manuscript for important intellectual content. E.J.A. contributed to analysis and interpretation. M.R. contributed to critical revision of the manuscript for important intellectual content. O.H.K. contributed to study concept and design, analysis and interpretation, and study supervision.

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