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**Study Group:** MSBase study group

### Background

Relapse-associated worsening (RAW), defined as disability progression due to incomplete recovery after relapse, is a key determinant of long-term disability in multiple sclerosis (MS). Although relapse frequency declines with age, it is unclear whether risk of RAW increases with age. This has significant implications for the risk-benefit of disease-modifying therapy (DMT) use in older people with MS (pwMS).

### Objectives/Aims

We aimed to examine the effect of age at first relapse on RAW.

### Methods

Using data from the MSBase registry, this multicentre cohort study included pwMS with a recorded relapse and adequate baseline and follow-up EDSS. The primary outcome was RAW at 6 months, with secondary outcomes of RAW at 3 and 12 months and functional system (FS) score worsening.

Mixed-effects logistic regression with random intercept for country was used, with fixed effects for age, sex, disease duration, baseline EDSS, corticosteroid treatment and DMT class.

### Results

5,782 pwMS were included, of whom 1,164, 1,965 and 1,828 had adequate follow-up for RAW assessment at 3, 6 and 12 months respectively.

Mean age was 35.4 ± 10.5 years and 72.3% were female. Spline modelling demonstrated a non-linear relationship between age and RAW, with a disproportionate dose-response increase in risk beyond 50 years.Compared with pwMS aged ≥50, all younger age groups had significantly lower odds of RAW at 6 months: ≤30 years (OR 0.47, 95% CI 0.29–0.75), 31–40 years (OR 0.42, 0.27–0.67), and 41–50 years (OR 0.53, 0.34–0.85). Findings were consistent at 3 and 12 months. Baseline EDSS was inversely associated with RAW at all timepoints (OR 0.77, 95% CI 0.70–0.85).

Corticosteroid treatment was associated with reduced RAW at 6 months (OR 0.67, 95% CI 0.50–0.91), with no significant interaction between steroid use and age. Age was modestly associated with FS worsening at 6 and 12 months (OR 1.16–1.17 per decade).

### Conclusion

Increasing age is associated with a marked non-linear increase in risk of RAW post first relapse in MS. Given that each relapse carries a disproportionately higher risk of persistent disability in older pwMS, these findings challenge the assumption that relapse prevention becomes less relevant with age, and support individualised benefit-risk reassessment of DMT use.

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