A contemporary study of multiple sclerosis disability in south east Wales.

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Key messages

What is already known on this topic: Current data on disability evolution in MS is limited and where available commonly reflects highly selected clinic populations, historic diagnostic criteria, a limited period of observation, and fails to reflect the potential for disability improvement.

What this study adds: This is the first study of disability trajectory in a population-based MS cohort in the UK. In this study, we found that at lower EDSS scores there is greater variability with the probability of improvement being similar to that of worsening, but at EDSS scores of 6.0 and above, disability stabilises with greater time spent at each EDSS level and a smaller chance of improvement than of worsening.

How this study might affect research, practice or policy: The findings of this study provide a detailed contemporary description of disability in MS, which will be useful for patient counselling, design of clinical trials, and to provide a baseline to assess the impact of novel therapeutic interventions.

Abstract

Background: A contemporary understanding of disability evolution in multiple sclerosis (MS) is an essential tool for individual disease management and planning of interventional studies. We have used prospectively collected longitudinal data to analyse disability progression and variation in a British MS cohort.

Methods: Cox proportional hazards regression was used to estimate hazard of EDSS 4.0 and 6.0. A continuous Markov model was used to estimate transitional probabilities for individual EDSS scores. Models were adjusted for age at MS onset, sex, and DMT exposure.

Results: 2135 patients were included (1487 (70%) female, 1922 (89%) relapsing onset). 865 (41%) had used DMTs. Median time to EDSS 4.0 and 6.0 was 18.2 years (95%CI 16.3–20.2) and 22.1 years (95%CI 20.5–24.5). In the Markov model, the median time spent at EDSS scores of <6 (0.40–0.98yr) was shorter than the time spent at EDSS scores of ≥6 (0.87–4.11yr). Hazard of change in EDSS was greatest at EDSS scores <6 (hazard ratio [HR] for increasing EDSS: 1.02–1.33; decreasing EDSS: 0.34–1.27) compared to EDSS scores ≥6 (HR for increasing EDSS: 0.08–0.61; decreasing EDSS: 0.18–0.54).

Conclusions: These data provide a detailed contemporary model of disability outcomes in a representative population-based MS cohort. They support a trend of increasing time to disability milestones compared to historical reference populations, and document disability variation with the use of transitional matrices. Additionally, they provide essential information for patient counselling, clinical trial design, service planning and offer a comparative baseline for assessment of therapeutic interventions.

Introduction

Despite the advent of disease-modifying treatments (DMTs), multiple sclerosis (MS) remains a common cause of non-traumatic neurological disability in young adults, with wide-ranging socioeconomic and health services resource implications.[1] Accumulation of disability at an individual level is unpredictable, particularly in early disease, but usually evolves gradually over several decades. Because of these disease characteristics, changes in disability trajectory are only likely to be apparent in long-term population-based or cohort studies rather than clinical trials. Furthermore although newer DMTs are increasingly effective at subduing or even abolishing early inflammatory disease activity,[2] it remains unclear whether appropriate early intervention will eventually result in a marked long-term reduction in disability, and also whether these long-term trends can be identified and measured in current MS populations.

Long-term disability is commonly measured using the Expanded Disability Status Scale (EDSS[3]). Although the EDSS has well-recognised limitations, it has the important benefit of available historical comparisons. Studies containing EDSS data collected prospectively over many years have already proved invaluable in patient counselling and trial design. However, the earliest studies of this type, including notably, studies from London, Ontario[4], Gothenberg, Sweden[5], and early Norwegian studies[6] describe people with MS from many decades ago before the introduction of DMTs, expansion in specialist services or newer symptomatic interventions and therefore may now have limited contemporary relevance. A number of additional registry studies have subsequently been established, including those from British Columbia (Canada[7–10]), Lyons (France[11,12]), Rennes (France[13]), Lorraine (France[14,15]) and the national MS registries of Sweden,[16] Denmark[17] and Norway[18] which have continued to make significant contributions to our understanding of disability evolution in MS. More recently, research has also focussed on very large datasets collated from routine specialist clinical practice across a number of centres.[19] However, these often

comprise patients on DMTs and in early phase disease and may not be entirely representative of total populations.

As the therapeutic landscape in MS develops to include a wider range of patients[20,21] and the potential for neuroprotective and neuroreparative interventions evolves, it remains essential to have a contemporary understanding of the evolution of disability in a representative population containing both treatment-modified and treatment-naive individuals. However, it is important to understand that variations in disease outcome may also occur as a result of factors unrelated to therapeutic interventions, such as geographical location, ethnic background of the cohort and methodology.[22] There is also evidence that disability is accrued more slowly in cohorts where data has been recently collected.[7,16] This could relate to direct improvements in the management of MS or indirectly e.g. via improved management of cardiovascular morbidity.[23]

We have used prospectively acquired longitudinal data from the Cardiff MS registry in southeast Wales to analyse disability progression in a contemporary British MS cohort diagnosed between 1985 and 2021, including treatment-naive and treated people with MS at different stages of disease, reflecting modern caseloads for a regional MS service. This information will provide a resource for more effective patient counselling in a modern treatment era, baseline data to measure future dynamic changes in the overall health and disability outcomes of the MS population and contemporary outcome data to assess cost-effectiveness of future treatments.

Methods

Data collection

A cross-sectional epidemiological study of MS in Cardiff and Vale University Health Board was established in 1985,[24] with data updated periodically between 1985 and 1999.[25,26] Since 1999

prospectively acquired longitudinal clinical data has been collected on all people with MS on an annual basis where possible. This includes patients from Cardiff and surrounding areas as well as a proportion of patients from Cwm Taf Morgannwg University Health Board. In addition, the cohort includes patients from Aneurin Bevan, Swansea Bay and Hywel Dda University Health Boards who were originally resident in Cardiff and subsequently moved or who have undergone some degree of joint care. Patients are seen routinely on an annual basis, with additional urgent reviews for suspected relapse. In the UK, DMTs can only be prescribed by a specialist clinic and thus all DMT prescriptions in south Wales are provided or administered through the regional specialist MS service. The study was approved by the southeast Wales Research Ethics Committee (ref 05/WSE03/111). Informed written consent was obtained from all patients.

Inclusion criteria

Criteria for inclusion in the study were: definite diagnosis of MS made according to prevailing criteria at the time of diagnosis,[27–31] and availability of a minimum dataset including diagnosis, demographic data and a date of MS onset. Patients were followed up until death, until they moved out of south Wales, or until June 2021; whichever was earliest.

Disability measurement and defining disability progression

At all appointments EDSS score was documented by a specialist in neuroinflammatory disease. Current disease course was recorded, together with whether the patient was in relapse at the time of assessment and information on DMT prescriptions. EDSS scores measured at the time a patient was in relapse were not included in the analysis. Age profile and distribution of disease course at the time of EDSS measurement were calculated for all EDSS scores. SPMS was defined as an EDSS increase (if EDSS ≤5.5 an increase of 1 point was required; and if EDSS >5.5 an increase of 0.5 points was required), in the absence of a relapse, achieving a minimum EDSS score of 4, with confirmation of EDSS progression over ≥3 months.[32]

Time to EDSS milestones was calculated using EDSS 4.0 and 6.0 as endpoints, sustained and confirmed with a second measurement ≥6 months after the first instance.

Statistical analysis

Kaplan-Meier survival analysis was used to calculate time to and age at EDSS 6.0 and EDSS 4.0. In order to avoid immortal time bias, only patients who a) had disease onset after 1985 and b) had not reached the milestone prior to first assessment were included. Cox proportional hazards regression was used to estimate hazard of EDSS 6.0, with covariates of age at MS onset, sex, initial disease course (relapsing or progressive), polyfocal symptoms at onset, number of relapses in the first two years, and first EDSS scores included. We also examined hazard of EDSS 6.0 separately for men and women, with covariates of age at MS onset, initial disease course, polyfocal symptoms at onset, number of relapses in the first two years, and first EDSS score included. All three models were adjusted for calendar year of diagnosis and treatment with DMT as a time-dependent covariate. Models were checked to ensure that the proportional hazards assumption was not violated.

A continuous Markov model was also used to estimate transitional probabilities of EDSS scores. Patients were included in this analysis if they had two or more EDSS scores available. The continuous model was used as it allows EDSS scores to be measured at unevenly spaced time intervals, as occurs in routine clinical practice. Only integer EDSS scores were used, and fractional EDSS scores were rounded down (so that, for example, an EDSS score of 1.5 was included in the EDSS 1.0 scores).[33] In order to make the model computationally feasible, transitions of one EDSS integer up or down were permitted. In order to explore transitional EDSS probabilities by disease course, the Markov model was calculated firstly using all eligible patients, secondly using all eligible relapsing-onset patients, and thirdly using all eligible patients with a current secondary progressive disease course. All three models were adjusted for age at MS onset, sex, and DMT use at the time of EDSS

measurement. The continuous Markov model was used to calculate a transitional probability matrix for EDSS score at ten years, by starting EDSS score. Where patients had been treated with alemtuzumab or cladribine, they were considered to be continuously treated from the first day of treatment onwards for the purposes of statistical analysis. All statistical analysis was performed in R version 3.5.2.[34] The msm library was used to calculate the continuous Markov model.

Results

A total of 2,135 patients were included in the study, of which 1487 (70%) were female. Initial disease course was relapsing in 1,922 patients (90%) and progressive in 213 (10%). Mean age at MS onset was 33.1 years (standard deviation, SD, 11.1) and mean current age was 51.8 years (SD 13.4). Median disease duration was 18.8 years (interquartile range, IQR, 11.2–28.9). Median time from onset of MS to diagnosis was 2.4 years (IQR 0.7–6.7). Two hundred and twenty patients (10.3%) were included in the original 1985 prevalence study, 530 (24.8%) had onset before 1999 but were not included in the 1985 prevalence study, and 1385 (64.9%) were diagnosed since 1999. Demographics of the cohort are summarised in Table 1.

Eight hundred and sixty-five patients (41%) had been treated with DMT, and of these 359 were no longer on treatment. The most frequent first-line DMT was interferon-β (n=357), followed by alemtuzumab (n=132) and dimethyl fumarate (n=125). Three hundred and nineteen patients (37%) have used more than one DMT, and the maximum number of different DMTs in a single patient was five. Details of DMT treatment in our cohort are summarised in Supplementary Table 1.

Disability

In total 19,345 EDSS scores were available for analysis in 1,946 patients. At first assessment, median EDSS score was 4.0 (IQR 2.0–6.0). However, in those with MS onset after 2000, median first EDSS

score was 2.5 (IQR 1.5–4.0) (Figure 1). The time from onset to diagnosis was 3.7 years (IQR 0.9 – 9.0 years) for those diagnosed before 2005, while for those diagnosed after 2005 it was 1.4 years (IQR 0.6 – 3.3 years). Age at EDSS score was positively correlated with EDSS score ($R2=0.43$, $p<0.0001$, Figure 2).

Disease course varied by EDSS score; at EDSS scores of less than 4.0, most patients had a relapsing-remitting course. The proportion of patients with a progressive course increased gradually, and at scores of EDSS 5.0 or more represented the majority (Figure 3).

Time to EDSS milestones

Median time from symptom onset to EDSS 6.0 was 22.1 years (95% confidence interval [CI] 20.5–24.5), and to EDSS 4.0 was 18.2 years (95% CI 16.3–20.2) (Figure 4). Median age at EDSS 6.0 was 58.8 years (95% CI 57.2–60.6) and at EDSS 4.0 was 53.9 years (96% CI 52.5–56.4).

Older age at MS onset (hazard ratio [HR] 1.03, 95% CI 1.02–1.05), higher number of relapses in the first two years of MS (HR 1.14, 95% CI 1.05–1.25) and higher first EDSS score (HR 1.42, 95% CI 1.30–1.55) were associated with increased hazard of EDSS 6.0. Relapsing course at onset was associated with decreased hazard of EDSS 6.0 (HR 0.45, 95% CI 0.32–0.63). There was no association of polyfocal symptoms at onset or DMT treatment with hazard of EDSS 6.0. Findings were similar when analysed separately for men and women (Table 2). None of the models violated the proportional hazards assumptions.

Continuous Markov model of EDSS transitions

Of the total cohort, 1681 patients (79%) had at least two EDSS scores available and so were included in this analysis. Demographics of this group are detailed in Table 1. 18,613 EDSS scores were

available for analysis (Supplementary Table 2), of which 5063 (27%) were measured while the patient was on DMT.

For EDSS scores <6.0 the median time spent at each EDSS score was <1 year. However, at EDSS scores of ≥6.0, the median time spent at each EDSS score increased to >2 years, except for EDSS 7.0–7.5 where patients remained for a median of 0.87 years.

In general, the hazard of change in either direction was greater at EDSS scores <6.0, and at EDSS ≥6.0, there was a lower hazard of subsequent change in EDSS in either direction (Figure 5). Additionally, for most EDSS scores <6.0, the hazard of increasing EDSS score was greater than the hazard of decreasing EDSS, though there were some scores where the hazard of increasing or decreasing EDSS was similar. At EDSS scores ≥6.0, the hazard of increasing EDSS was similar to the hazard of decreasing EDSS. Time spent at each EDSS score and hazard of change in EDSS score is detailed in Figure 5.

The Markov model was used to estimate probabilities of each EDSS score at ten years, by starting EDSS score. For starting EDSS scores ≤7.5, the highest probability was of an EDSS score of 6.0–6.5 at ten years. For starting EDSS scores of >7.5, the highest probability was an EDSS score of 8.0–8.5 at ten years. The estimated probabilities from the Markov model are detailed in Table 3. The results of the Markov model were very similar when only relapsing-onset patients were included (Supplementary Table 3), and when only patients with a current secondary progressive disease course were included (Supplementary Table 4).

Discussion

In this study of disability progression in MS in a UK cohort, we have developed a contemporary model of disability trajectory. As expected, examining age and disease course profiles by EDSS score

showed increasing age and frequency of progressive disease course with increasing EDSS score. The median time to EDSS 6.0 was 26.9 years and median age at EDSS 6.0 was 59.9 years. In line with previous work, older age at MS onset, higher number of relapses in the first two years of MS and a progressive disease course at onset were associated with an increased hazard of EDSS 6.0. Our model adds value by demonstrating the hazard of transitioning at each EDSS grade. EDSS scores were more changeable at the lower end of the EDSS scale, but became more stable at EDSS 6, with a lower hazard of transitioning to different EDSS scores and a longer median time spent at each EDSS score.

Estimates of time to EDSS 6.0 in previous studies have consistently been around 20 years from MS onset[4,5,11,15,16] when data from all MS patients are analysed rather than focussing on a specific subgroup. Similarly, age at EDSS 6.0 has been reported as between 47 and 64 years. [11,13,16,35] Our study is at the upper end of the range of previous estimates but is consistent with a trend of longer times to EDSS milestones being reported in more recent studies. In 1989 the London, Ontario cohort was reported to have a time to EDSS 6.0 of 15.0 years,[4] compared to 23 years in a French cohort in 2009.[15] Recent data from the Danish national multiple sclerosis registry have shown a decline in the hazard of reaching EDSS 6.0 from 0.76 for those with MS onset 2001–2005 to 0.60 for those with MS onset 2006–2010. It is possible that this represents temporal improvements in disability accumulation, but also may be related to improved case ascertainment especially of those with milder disease, who may not have previously presented to tertiary centres, as well as more detailed monitoring and follow-up of patients once identified. The well-established MS database of British Columbia, Canada, has been used to examine temporal trends in proportion of people with MS reaching EDSS 6.0, and found no difference by year of MS onset,[22] suggesting that differences between earlier studies and more recent studies may be related to factors other than slowing of disability accumulation within a single geographical area.

Although widely utilised in both observational studies and clinical trials, the EDSS has limitations which should be acknowledged.[36,37] In particular, although it is apparently numerical, it is in fact an ordinal scale, so that an EDSS score of 6.0 does not represent twice as much disability as an EDSS score of 3.0. This may contribute to the variable amount of time spent at EDSS scores that we observed in our study. Furthermore, EDSS scores below 4.0 are dependent on neurological examination and therefore subject to inter-rater variability as well as subjective interpretation of classification of findings as mild/moderate/severe. However, it is also likely that disability does not exhibit a linear progression over time, and many factors may contribute to variation in disability over time in an individual. One of the most striking findings in our data was the increased length of time spent at EDSS 6.0 – 6.5 compared to lower EDSS scores, probably reflecting insensitivity of measuring non-motor aspects of disease. However, it also supports the use of EDSS 6.0 as a useful disability endpoint in survival analysis, particularly if taken together with the results of alternative statistical approaches.

Earlier studies analysing data collected before the era of wide-spread DMT usage may be considered to represent true natural history data, whereas more contemporary studies, including our current study, need to account for the possible effects of DMTs on disability progression, and could be considered treatment-modified history studies. As DMTs become more widely used, and particularly as treatments for progressive forms of MS are developed,[20,21] contemporary datasets incorporating data from treated patients will become more important. In Sweden DMTs have been estimated to delay EDSS 6.0 by 1.6 years[16] and risk of reaching EDSS 3.0, 4.0 and 6.0 has been shown to have reduced over the last decade in people with relapsing-onset but not PPMS,[38] suggesting a possible effect of DMT on disability accumulation in this population. In the UK, data from the Risk Sharing Scheme has been analysed in detail, using several different statistical techniques including continuous Markov models, and these studies have found that EDSS scores in the cohort of patients treated with interferon-β or glatiramer acetate were lower than predicted

from natural history data.[39,40] In our cohort, we have also previously identified improved prognosis in patients started on high efficacy DMTs compared to moderate efficacy DMTs.[41] In the current study we have adjusted all models for DMT exposure, so that our findings represent the evolution of disability in a contemporary cohort of MS patients, a significant proportion of whom are on DMTs, together with others who may have had MS for longer, have never been treated, and are in the progressive phase of the disease. This complex mix of patients is more representative of today's clinical practice than the older natural history cohorts with no treatment exposure. However, it is important to note that this study is not designed or powered to detect effects of DMTs on disability trajectory over time, rather it is a description of disability progression in a wide mix of patients with varying exposure to DMTs. As new interventions continue to be developed in MS, it is important that cost-effectiveness can be appropriately assessed, and large population-based cohorts providing comprehensive data on whole disease trajectory are essential in this regard. Furthermore, as focus turns to developing more effective interventions for progressive disease, including at higher levels of disability (such as the CHARIOT-MS trial[42]), the value of high quality data in the disease trajectory above EDSS 6.0 becomes is likely to become more apparent.

While there remains an overall trend towards slowly increasing disability levels over time in MS, disability may not always remain fixed, and in real world patient management it is recognised that there may be a reduction in EDSS score as well as an increase. Traditional methods of analysing disability in MS utilising survival analysis methods do not allow for the possibility of improvement. We have shown that even at an EDSS score of 6.0, a commonly used endpoint in disability survival models in MS,[4,5,11,15,16] there is a measurable probability of future improvement in EDSS score. Improvements in disability are more likely at lower EDSS scores, and at EDSS scores below 4.0 the hazard of improvement in EDSS score is similar to that of worsening EDSS score. This is also reflected in the relatively short time spent at lower EDSS scores. This raises questions over the validity of sustained accumulation of disability, defined as an increase of at least 1.5 points for patients with a

baseline score of 0, of at least 1.0 point for a baseline score of 1.0 or more, or an increase of at least 0.5 points for a baseline score of 5.5 or more, confirmed after a three or six-month period.[2,21] Our results suggest that this may not be an appropriate measure of long-term disability progression, particularly when baseline EDSS scores are low and at their most changeable.

Our study has several strengths. We have been able to analyse EDSS data collected prospectively over two decades, allowing detailed analysis of disability over time. This is the first UK study of longitudinal disability in all people with MS in a single population-based cohort, although we have previously examined disability in selected subgroups in our cohort.[43–45] We have shown a detailed profile of age and disease course at different EDSS scores, and this together with the use of different statistical approaches including survival analysis and continuous Markov modelling provides a more comprehensive picture of disability in MS, complementing previous data from other northern European countries[11–17] as well as north America.[7–10] Limitations of the study include the fact that a small minority of patients did not have any EDSS scores available, and that the constraints of the continuous Markov model meant that only the 79% of our patients who had at least two EDSS scores could be included in that analysis. However, the baseline characteristics of those patients included in the disability models was similar to those of the total cohort, suggesting that they are a representative sample of our total cohort. This finding reflects the challenge of collecting detailed longitudinal clinical data over the many decades that people are affected by MS.

In conclusion, we provide a contemporary model of MS outcome, including the hazard of transitioning to a different disability level at each EDSS stage. While EDSS 6.0 remains a useful disability endpoint, other methods of analysing disability provide a more rounded understanding of progression in MS. This data has value for counselling MS patients, for planning services, and as a useful comparison of the effects and cost-effectiveness of novel interventions.

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Tables

Table 1. Demographics of the whole cohort, by era of diagnosis, and of the patients included in the continuous Markov model.

Characteristic	Total cohort	1985 prevalence study	Diagnosed between 1985 and 1999	Diagnosed since 1999	Cohort included in the continuous Markov model
Total	2135	220 (10.3%)	530 (24.8%)	1385 (64.9%)	1681 (78.7%)
Female	1487 (69.6%)	156 (70.1%)	355 (67.0%)	976 (70.0%) 1170 (69.6%)	
Mean age at MS onset (SD)	33.1 yr (11.1)	31.9 yr (11.1)	30.1 yr (9.5)	34.4 yr (11.4)	32.8 (11.0)
Initial disease course: Relapsing Progressive	 1922 (90.0%) 213 (10.0%)	 216 (98.0%) 4 (2%)	 476 (89.8%) 54 (10.2%)	 1230 (88.8%) 155 (11.2%)	 1498 (89.1%) 183 (10.9%)
Mean number of events in the first two years of disease (SD)	1.7 (1.1)	1.2 (0.5)	1.3 (0.9)	1.8 (1.2)	1.8 (1.2)
Mean current age (SD)	51.8 years (13.4)	71.4 (11.5)	60.7 (9.4)	48.2 (12.2)	53.2 years (12.7)
Median disease duration (IQR)	18.8 yr (11.1 - - 28.9)	36.4 yr (22.8 - - 44.1)	29.8 (24.0 - 37.1)	14.0 (11.5 - 20.0)	19.1 years (12.4 - 28.7)
Ever treated with DMT	865 (40.5%)	9 (4.0%)	96 (18.1%)	760 (54.9%)	787 (46.8%)
Currently treated with DMT	457 (21.4%)	0 (0%)	30 (5.7%)	304 (21.9%)	485 (28.8%)

MS: multiple sclerosis; SD: standard deviation; IQR: interquartile range; DMT: disease-modifying treatment

Table 2. Cox proportional hazards regression for clinical variables associated with hazard of EDSS 6.0

Variable	All patients		Females		Males	
	Hazard ratio (95% CI)	**p**	**Hazard ratio (95% CI)**	**P**	**Hazard ratio (95% CI)**	**p**
Sex: Female	Reference	-	-	-	-	-
Male	1.16 (0.93 - 1.47)	0.19	-	-	-	-
Age at MS onset *	1.03 (1.02 - 1.05)	<0.0001	1.03 (1.02 - 1.04)	<0.0001	1.04 (1.02 - 1.06)	<0.0001
Onset type: Progressive onset	Reference	-	-	-	-	-
Relapsing onset	0.45 (0.32 - 0.63)	<0.0001	0.38 (0.25 - 0.56)	<0.0001	0.51 (0.30 - 0.87)	0.01
Number of events in the first 2 years*	1.14 (1.05 - 1.25)	<0.0001	1.15 (1.04 - 1.26)		1.17 (0.98 - 1.40)	0.09
EDSS at first presentation *	1.42 (1.30 - 1.55)	<0.0001	1.52 (1.36 - 1.70)	<0.0001	1.26 (1.10 - 1.43)	0.0005
Onset symptoms: Monofocal onset symptoms	Reference	-	-	-	-	-
Polyfocal onset symptoms	1.25 (0.97 - 1.61)	0.09	1.24 (0.90 - 1.70)	0.19	1.26 (0.81 - 1.97)	0.31
Disease-modifying treatment: Never treated	Reference	-	-	-	-	-
Treated	0.96 (0.84 - 1.10)	0.56	0.99 (0.84 - 1.16)	0.89	0.89 (0.71 - 1.11)	0.30

* Hazard ratio for continuous independent variables indicates the hazard per unit increase in the variable

Table 3: Transitional probability matrix, showing the estimated probabilities for each EDSS score at 10 years, for all MS patients in the Cardiff registry included in the continuous Markov model.

Starting EDSS	**To EDSS**									
	0	**1.0 – 1.5**	**2.0 – 2.5**	**3.0 – 3.5**	**4.0 – 4.5**	**5.0 – 5.5**	**6.0 – 6.5**	**7.0 – 7.5**	**8.0 – 8.5**	**9.0 – 9.5**
EDSS 0	0.033	0.087	0.116	0.095	0.128	0.080	0.324	0.056	0.071	0.010
EDSS 1.0–1.5	0.029	0.077	0.104	0.087	0.121	0.079	0.342	0.062	0.085	0.013
EDSS 2.0–2.5	0.025	0.069	0.093	0.080	0.114	0.077	0.357	0.068	0.100	0.017
EDSS 3.0–3.5	0.021	0.057	0.078	0.069	0.104	0.073	0.376	0.077	0.123	0.023
EDSS 4.0–4.5	0.014	0.041	0.058	0.054	0.089	0.068	0.397	0.088	0.159	0.033
EDSS 5.0–5.5	0.010	0.030	0.044	0.043	0.078	0.064	0.404	0.096	0.189	0.042
EDSS 6.0–6.5	0.006	0.019	0.029	0.031	0.064	0.058	0.405	0.105	0.227	0.056
EDSS 7.0–7.5	0.003	0.011	0.018	0.020	0.046	0.044	0.336	0.113	0.310	0.099
EDSS 8.0–8.5	0.002	0.006	0.010	0.013	0.031	0.033	0.275	0.117	0.377	0.138
EDSS 9.0–9.5	0.001	0.003	0.005	0.007	0.019	0.022	0.204	0.113	0.416	0.211

Figures

Figure 1: Scatterplot with line of best fit and 95% confidence interval, showing first recorded EDSS score by year of multiple sclerosis onset for all patients in the study (top) and by initial disease course (bottom).

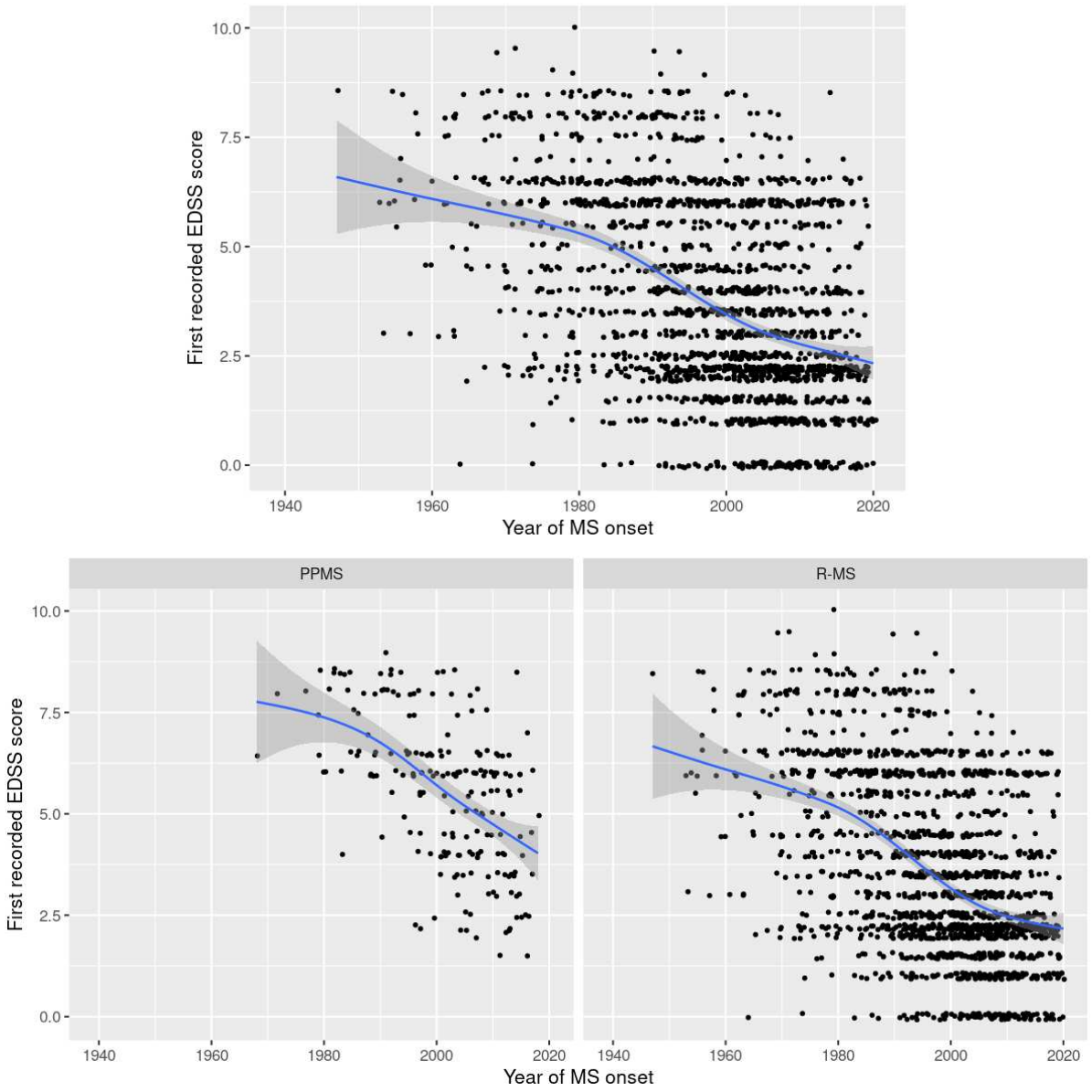

Figure 2: Boxplot showing age at each EDSS score, by EDSS score, for the whole cohort.

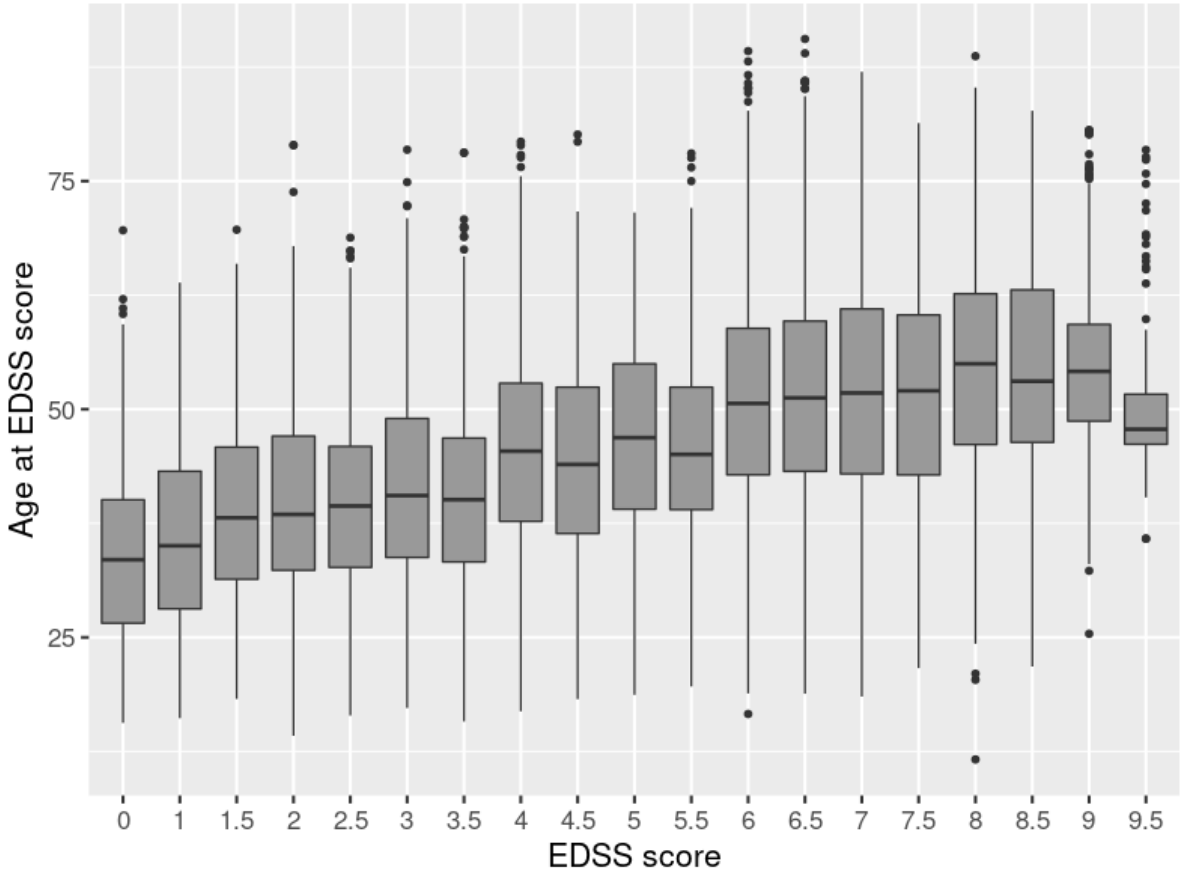

Figure 3: Bar chart showing the percentage of patients at each EDSS score with relapsing-remitting (RRMS), secondary progressive (SPMS) or primary progressive (PPMS) disease course.

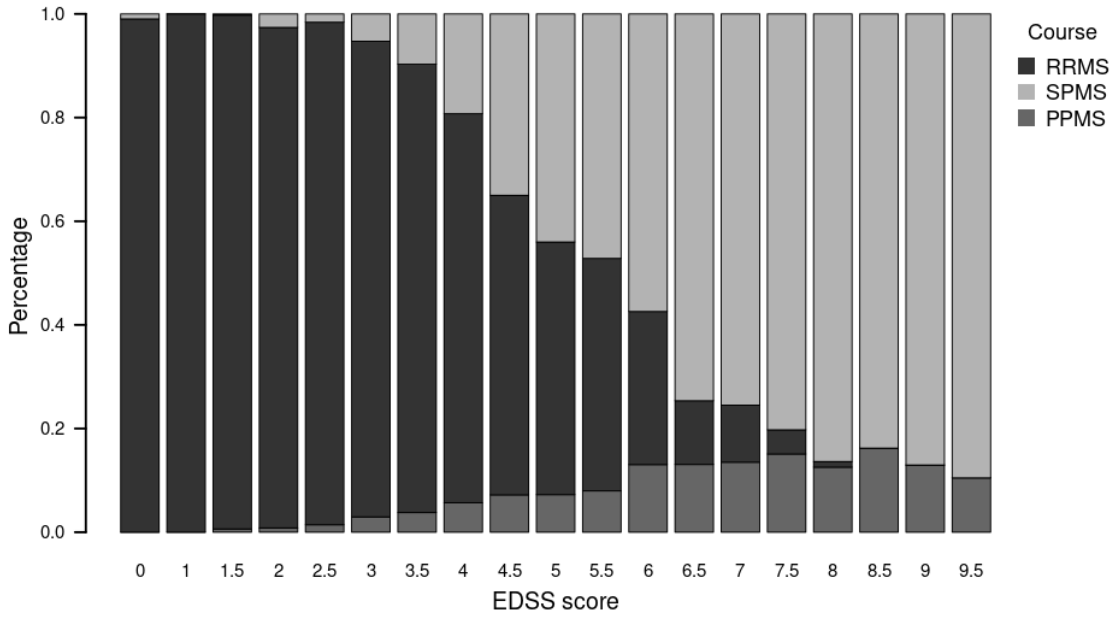

Figure 4: Kaplan-Meier curves showing time to EDSS 4.0 and 6.0 for all patients included in the study.

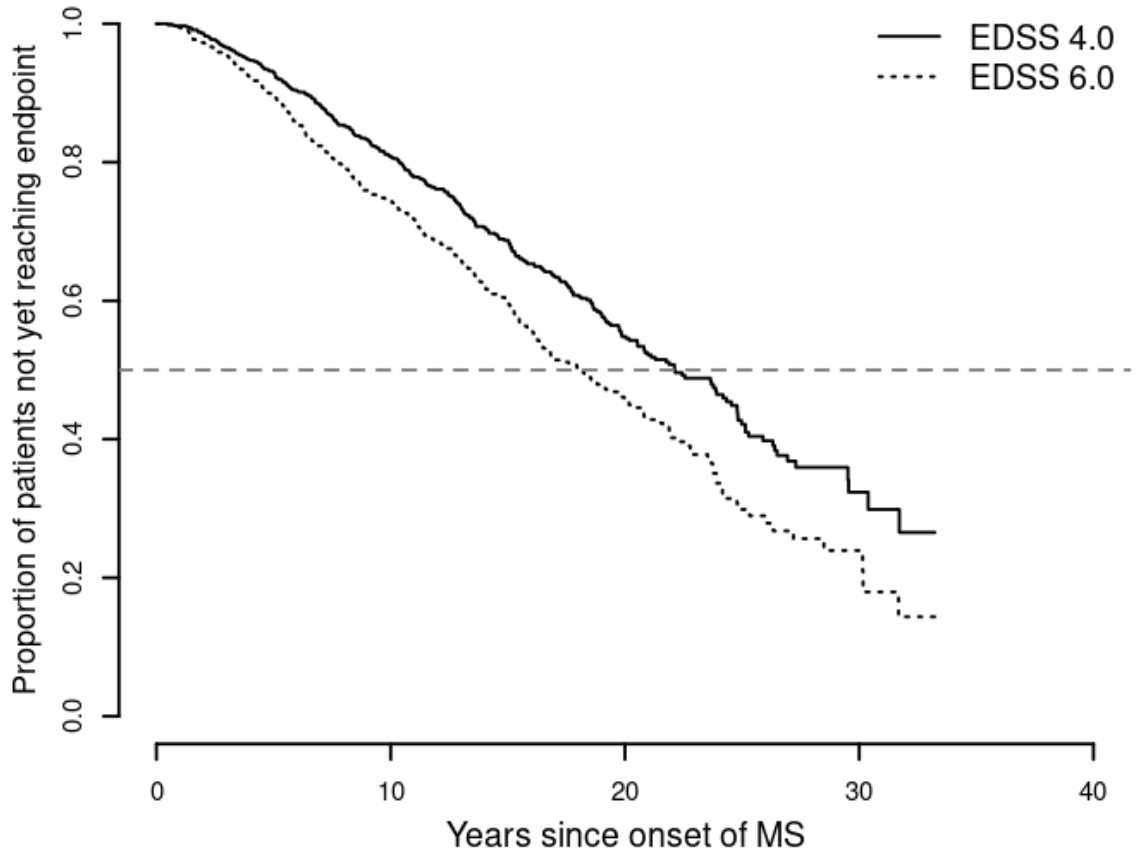

Figure 5: Output of Markov model, with median time spent at each EDSS score, and hazard ratio (HR) and 95% confidence intervals for change in EDSS score in either direction. The model is adjusted for age at MS onset, sex, and DMT treatment.