PharmacoEconomics
https://doi.org/10.1007/s40273-024-01417-4

ORIGINAL RESEARCH ARTICLE

Estimation of Transition Probabilities from a Large Cohort (> 6000) of Australians Living with Multiple Sclerosis (MS) for Changing Disability Severity Classifications, MS Phenotype, and Disease-Modifying Therapy Classifications

Julie A. Campbell[1] · Glen J. Henson[1] · Valery Fuh Ngwa[1] · Hasnat Ahmad[1] · Bruce V. Taylor[1] · Ingrid van der Mei[1] · MS Base Australian Researchers[2] · Andrew J. Palmer[1]

Accepted: 9 July 2024

Abstract

Background Multiple sclerosis (MS) is a chronic autoimmune/neurodegenerative disease associated with progressing disability affecting mostly women. We aim to estimate transition probabilities describing MS-related disability progression from no disability to severe disability. Transition probabilities are a vital input for health economics models. In MS, this is particularly relevant for pharmaceutical agency reimbursement decisions for disease-modifying therapies (DMTs).

Methods Data were obtained from Australian participants of the MSBase registry. We used a four-state continuous-time Markov model to describe how people with MS transition between disability milestones defined by the Expanded Disability Status Scale (scale 0–10): no disability (EDSS of 0.0), mild (EDSS of 1.0–3.5), moderate (EDSS of 4.0–6.0), and severe (EDSS of 6.5–9.5). Model covariates included sex, DMT usage, MS-phenotype, and disease duration, and analysis of covariate groups were also conducted. All data were recorded by the treating neurologist.

Results A total of $N = 6369$ participants (mean age 42.5 years, 75.00% female) with 38,837 person-years of follow-up and 54,570 clinical reviews were identified for the study. Annual transition probabilities included: remaining in the no, mild, moderate, and severe states (54.24%, 82.02%, 69.86%, 77.83% respectively) and transitioning from no to mild (42.31%), mild to moderate (11.38%), and moderate to severe (9.41%). Secondary-progressive MS was associated with a 150.9% increase in the hazard of disability progression versus relapsing–remitting MS.

Conclusions People with MS have an approximately 45% probability of transitioning from the no disability state after one year, with people with progressive MS transitioning from this health state at a much higher rate. These transition probabilities will be applied in a publicly available health economics simulation model for Australia and similar populations, intended to support reimbursement of a plethora of existing and upcoming interventions including medications to reduce progression of MS.

1 Introduction

1.1 Multiple Sclerosis

Multiple sclerosis (MS) is an inflammatory/neurodegenerative disease of the central nervous system (brain, optic nerves, and spinal cord) that manifests in an individual and diverse array of symptoms including visual, sensory, cognitive and sexual dysfunction, motor dysfunction and weakness, bowel or bladder continence issues, fatigue, and anxiety and depression [1]. Symptoms can appear individually or in concert and can result in marked declines in both physical and psychosocial health-related quality of life (HRQoL) and

Julie A. Campbell and Glen J. Henson joint first authorship and equal contribution.

✉ Julie A. Campbell
Julie.Campbell@utas.edu.au

✉ Andrew J. Palmer
Andrew.Palmer@utas.edu.au

[1] Medical Sciences Precinct, Menzies Institute for Medical Research, University of Tasmania, 17 Liverpool Street, Hobart, TAS 7000, Australia

[2] MS Base Central Clinical School at The Alfred Centre, 99 Commercial Road, Melbourne, VIC 3004, Australia

Published online: 02 August 2024

Key Points for Decision Makers

Using a large, validated, and neurologist-driven database of people living with MS, this study estimated transition probabilities for use in health economics models.

Transition probabilities were estimated for four health states, classified using the Expanded Disability Status Scale as no, mild, moderate, and severe disability, with adjustment for covariates including MS phenotype (relapsing–remitting and progressive) and disease-modifying therapy usage.

Our robust transition probabilities, estimated using methods that address several common issues when generating transition probabilities, can be used in health economics models for reimbursement for MS-related interventions, particularly disease-modifying therapies.

substantially increased costs as disability severity progresses from no to severe disability [1, 2]. Moreover, MS generally presents in younger people (with three in four being female) between the ages of 20 and 40 years when they are starting families and building careers, a time of escalating productivity [3].

The Atlas of MS estimated that the global prevalence of MS increased by 500,000 people to 2.8 million people from 2013 to 2020 [4]. Work by our group has also established that in Australia, MS prevalence increased by 20% over 2010–2017 to 25,607 people [5] and then to 33,335 people in 2021 [6, 7]. In addition, the societal cost of MS in Australia is increasing. Our group found that the annual societal costs of MS for Australia increased from $1.24 billion (Australian dollars) to $1.75 billion from 2010 to 2017, and to $2.45 billion in 2021. Additionally in 2021, as disability severity increases the average annual per person costs increased from $32,829 for people with MS with no disability to $123,333 for people with MS with severe disability. Therefore, the health economic impact of MS in Australia is substantial and the resource allocation decisions based on robust health economic modelling (especially full economic evaluation such as cost-effectiveness of cost-utility analysis) are crucial, particularly for resource allocation decisions such as medication reimbursement decisions [8, 9].

1.2 Generation of Health Economics Evidence Using Transition Probabilities

Transition probabilities are an important input metric for many health economics models that are used to provide advice to decision makers about the allocation of scarce healthcare resources [10]. Such healthcare resources include disease modifying therapies (DMTs) for the treatment of MS. A transition probability is the probability of transition from one health state (or level of disability) to another in a multistate Markov model [11]. Markov models often support full health economic evaluations, such as cost-utility or cost-effectiveness analyses [10], to assist healthcare resource decision makers in resource allocation [8, 12]. Notably, a recent systematic review that examined various issues regarding state transition models, concluded that common issues in transition probability estimation include: missing transitions, multiple sources of data, data on subgroups unavailable, need for extrapolation, long intervals between health assessments, and data incongruence [13].

Previously published work by our group estimated transition probabilities for Australians living with relapsing–remitting MS for an earlier health economics model [14, 15]. This multistate Markov model used the health states of no/mild (one combined health state), moderate, and severe MS-related disability and used data collected from a small cohort (n = 330) [14]. Death probabilities for this study were extracted from the Australian Life Tables and then adjusted by applying disability level-specific multipliers [14]. Another study, which used registry data, investigated annual transition probabilities for progressive forms of MS only (and a subset of Expanded Disability Status Scores of 3–7) using a cohort of 758 people living with progressive forms of MS in Northern Italy [16]. Other studies have used the MSBase registry international transition probabilities [9] or other databases such as the London Ontario database [17] or the British Columbia Multiple Sclerosis database [18]. Notably these studies are either older or encompass all MSBase registry data from all countries, which means that differing health systems and their heterogeneous healthcare and reimbursement policies are subsumed within these transition probabilities.

The rationale of our current study was to update and substantially expand on our previous work by utilizing a large cohort of > 6000 Australians with both relapsing–remitting and progressive MS phenotypes from the comprehensive neurologist driven MSBase registry database [9, 19, 20].

1.3 Aims of this Study

We aim to estimate transition probabilities for all MS phenotypes (including relapsing–remitting and progressive forms of MS) across four health states of, no, mild, moderate, and severe disability. Our second aim is to estimate transition probabilities for people with MS using differently classified DMTs, including people living with MS not on a DMT. A third aim is to estimate transition probabilities for people living with either relapsing–remitting MS or a progressive form of MS. These more robust and expanded transition

probabilities will be used to populate our publicly available MS health economics model (http: https://msresearchflagship.org.au/researchers/health-economics-simulation-model).

2 Materials and Methods

2.1 Validated Guidelines

This study was performed and reported in accordance with: (1) The International Society of Pharmacoeconomics and Outcomes Research (ISPOR) guidelines regarding good modelling practice [21] and (2) a systematic review that identified various issues commonly associated with transition probability estimation [13].

2.2 Data Acquisition and Patient Selection from MSBase

We acquired data from MSBase, the largest international MS registry [19]. The MSBase registry collects observational data for people living with MS as part of routine clinical care. The use of MSBase as a research platform was approved by the Melbourne Health Human Research Ethics Committee and by the local ethics committees in all participating centers (or exemptions were granted according to local laws and regulations). If required, written informed consent was obtained from enrolled patients.

Regarding data collection for MSBase's minimum data set, the usual practice at most centers was real-time or near real-time data entry. MSBase data entry was achieved through either the iMed patient record system or the MSBase online data entry system. Quality assurance procedures were applied as described elsewhere [19]. In addition, the MSBase protocol stipulates minimum annual updates of the minimum data set; nevertheless, people with MS with less-frequent MSBase updates were not excluded from our analysis if our inclusion criteria were fulfilled (2.3 below).

For the purposes of our study, we acquired all data for all MSBase patients contained within the minimum dataset that included: date of birth, sex, MS center, information regarding disease course, dates of disease onset, clinic visits, relapses, dates at the beginning and end of treatments, and disability quantified with the Expanded Disability Status Scale (EDSS) at baseline (i.e., first clinic review) and follow up visits. We also requested data for separate analysis of MS phenotypes including diagnosis for clinically isolated syndrome, relapsing–remitting MS, and forms of progressive MS phenotypes (i.e., primary progressive MS and secondary progressive MS), times (expressed as the date) for conversion from relapsing–remitting MS to secondary-progressive MS, DMTs including DMT type, and date of disease onset.

2.3 Inclusion Criteria

To permit our estimation of transition probabilities and adjust for important covariates (Sect. 2.4) MSBase study participants were screened using the following two inclusion criteria: (1) a resident of Australia and (2) a complete case defined as at least two clinic visits (e.g., baseline and at least one follow-up) and complete sociodemographic and clinical data for analysis. Participants were excluded if they had missing covariate data and not more than one EDSS observation. Importantly, where data were available, we compared sociodemographic data including age, sex, and disability severity of no, mild, moderate, and severe disability (Sect. 2.4) and MS phenotype (relapsing–remitting, secondary progressive, and progressive onset) between included and excluded participants.

2.4 Outcomes Measures and Covariates

For disability severity, the outcome variable was disease state, measured by the neurologist assessed EDSS, which is the most widely used scale to quantify and classify disability in MS [22]. We followed our previously published work regarding societal costs and quality of life [23, 24] and categorized disability as: no disability (EDSS of 0), mild disability (EDSS of 1.0–3.5), moderate disability (EDSS of 4.0–6.0), and severe disability (EDSS of 6.5–9.5) with all recorded by the treating neurologist.

For the covariates, unless otherwise stated, all covariates were set to their mean values when estimating transition probabilities. For categorical variables (such as DMT category), individual indicators were specified for each non-base category. For each indicator variable that could take the values of one or zero, the average score was equivalent to the percentage of observations to which a value of one applied. Covariates were controlled for in the analyses including: sex (male as the reference), disease duration (in years, continuous variable starting at zero), MS phenotype [three categories: relapsing–remitting MS (reference), secondary progressive MS, and progressive onset MS (including progressive-relapsing and primary progressive MS)], current DMT usage (as at the most recent observation for each participant), and type [four categories: no DMT (reference), category one DMT, category two DMT, category three DMT]; see Table 1 for DMT classifications and usage.

Given the nature of the analysis, there was no specific exposure of interest. Additionally, restrictions were placed on some covariate coefficient estimates. Specifically, hazard ratios were constrained to be equal for all forward transitions and all backward transitions for MS phenotype and DMT categorical indicators. This reduced the numerical complexity of modeling (reducing the number of coefficients to be

estimated by 80, which greatly facilitated the convergence of the final model).

2.5 Statistical Analysis

2.5.1 Descriptive Analysis

Sociodemographic and clinical characteristics were generally described using means and standard deviations (SD), with medians and interquartile ranges utilized for continuous variables. Frequencies and proportions were reported for categorical variables.

2.5.2 Markov Model

Our previous study fitted a three-state model for a relatively small cohort ($n = 330$) [14]. Our current study expanded on this work with a much larger cohort using a single registry dataset where we fitted a four-state homogenous, continuous-time, multistate Markov model to describe how people with MS transitioned between health states defined by MS-related disability severity [11, 25–30]. The analysis was performed using the well-validated "msm" package for R [29]. Also, multistate Markov models have been applied and their use validated in several previous studies [9, 31]. Importantly, the tractability of multistate Markov models is not dependent on regular follow-up times, which permitted the use of observational MSBase data [29]. State-to-state transitions were defined as a transition from an EDSS level (as recorded by the treating neurologist) within one EDSS category (namely, no, mild, moderate, or severe disability) to the same or another EDSS level within the same or another category. Necessarily, transitions were defined in adjacent observations. Importantly, transitions could result in no change in disability state. No time restrictions were imposed on transitions, although observation time for each individual (starting from the initial observation relating to that individual) was taken into account; this is standard in continuous-time multistate Markov models. Death (or the absorbing state) was not included in this model. Available death data was insufficient ($n = 102$ individuals with all-cause mortality) and provided spurious results for life expectancy when used with our full economic evaluation model. The implication of not including death in the model is that the presented annual transition probabilities are conditional on no patient mortality. This assumption is reasonable given that the mean age of our cohort is substantially below the average life expectancy of a person living with MS.

In our model, we captured the potential effects of relapses through the inclusion of the three major MS phenotypes as covariates. Therefore, these effects, when sufficiently large, were represented by instantaneous transitions between the health states defined in our model. The transient effects of relapse may not be included within the constraints of our model, which is concerned with generating annualized transition probabilities. Accordingly, the persistent impacts of relapse were represented though annual changes in disability severity.

Figure 1 describes the allowable transitions between health states for the multistate Markov model. Specifically, we modeled transitions through MS-related disability states as a time-homogeneous, continuous-time Markov process. This yielded a transition intensity matrix Q. Upon taking the exponential of this matrix, a transition probability matrix P was obtained. This matrix described the likelihood of a transition in health state (contingent on permissibility as dictated by a matrix of transition restrictions), between any two states over an interval of 1 year. The rows of P list the probabilities of moving from one state to another (or remaining in the existing state) and summed to 1.0.

More specifically regarding our model specification, we first estimated a restricted model where transitions were restricted to adjacent disease states for both health improvement and health deterioration (for example, constrained to

Table 1 Categories of MS-related disease modifying therapies (DMTs) for Australia's Pharmaceutical Benefits Scheme and the numbers of people living with MS using the specific DMTs for our study during the timeframe ($n = 4359$) and the relative proportions

Disease modifying therapy category		
Category 1 ($n = 539$; 12.36%)	Category 2 ($n = 514$; 11.79%)	Category 3 ($n = 3306$; 75.84%)
Interferon β-1b (betaferon) ($n = 96$)	Teriflunomide (aubagio) ($n = 213$)	Fingolimod (gilenya) ($n = 1083$)
Interferon β-1a (rebif) ($n = 71$)	Dimethyl fumerate (tecfidera) ($n = 301$)	Alemtuzumab (lemtrada) ($n = 163$)
Interferon β-1a (avonex) ($n = 59$)		Natalizumab (tysabri) ($n = 745$)
Pegylated interferon β-1a (plegridy) ($n = 65$)		Novantrone (mitoxantrone)* ($n = 4$)
Glatiramer acetate (copaxone) ($n = 248$)		Cladribine ($n = 281$) Ofatumumab ($n = 1$) Ocreluzimab ($n = 1012$) Siponimod ($n = 17$)

*Removed from the Australian Pharmaceutical Benefits Scheme over the study timeframe. Rounding error for percentages. 68.4% of the entire cohort is using a DMT

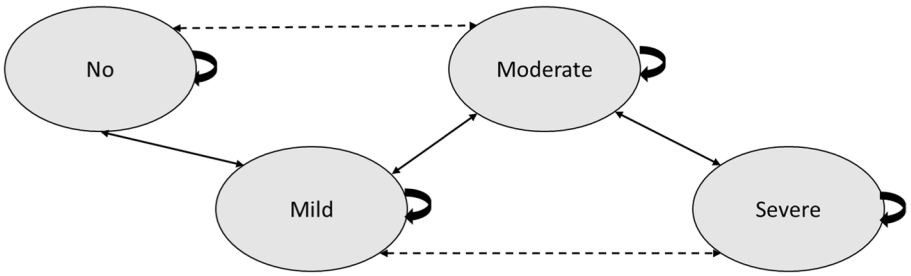

Fig. 1 Conceptual diagram of the allowable transitions between states for the multistate Markov model. The arrows illustrate the possible transitions between states. Transitions could occur into the immediate next state, previous state, or back to itself. Bidirectional transitions were allowed. Two-step movements were allowed; however, the subject may pass through the immediate adjacent state first. Participants can be in only one state at a time. For example, movement from no disability to moderate disability and vice versa are shown in the dashed lines to show that these movements are possible; however, the individual had to first pass through the mild disability state first. The same applied for mild to severe (pass through the moderate disability state first), where the adjacent state must be passed through first

no to mild, mild to moderate, moderate to severe, moderate to mild, mild to no, and so on) and were based on state table analysis which identified few transitions beyond adjacent transitions. This was followed by the estimation of a more robust model which allowed transitions between states one state removed from adjacency (Fig. 1). A matrix illustrating these restrictions is presented below, where $\beta_{2,3}$ represents the probability of transitioning from state 2 (mild disability) to state 3 (moderate disability):

$$\begin{Bmatrix} \beta_{1,1} & \beta_{1,2} & \beta_{1,3} & 0 \\ \beta_{2,1} & \beta_{2,2} & \beta_{2,3} & \beta_{3,4} \\ \beta_{3,1} & \beta_{3,2} & \beta_{3,3} & \beta_{3,4} \\ 0 & \beta_{4,2} & \beta_{4,3} & \beta_{4,4} \end{Bmatrix}$$

The above restrictions implied that transition could not occur directly between the two states for which the transition had been restricted.

For this final model, the minimal restrictions that were only applied to transitions between no to severe and severe to no disability, were necessary as data were insufficient for the estimation of some transitions. As a result of the restrictions, the annual transition probability from state 1 (no disability) to state 4 (severe disability) represents the chance of going from state 1 to 4 through at least one intervening state (that is, state 2 or 3). This is the implication of the Q-matrix restrictions for the transition probabilities. Implicit in the restriction is the assumption that the restricted transitions cannot occur directly. Although the restrictions were a practical decision to aid in estimation, they were also reasonable, given that our state-to-state transition data revealed that the restricted transitions between states 1–4 and 4–1 were rare and that other states were likely to be passed through as individuals traversed between no and severe disability.

After specifying the restrictions, crude initial estimates for the *Q*-matrix were generated using the assumption that the data represent exact times of transition in the multistate Markov process [11, 29]. These were used as starting values for maximum likelihood estimation using the Broyden–Fletcher–Goldfarb–Shanno (BFGS) algorithm [32]. We then fitted our model. Using our multivariable transition intensity estimates (obtained from the final—unrestricted and adjusted—model), mean covariate values, and a time interval of 1 year, a transition probability matrix was then obtained. The results of this are denoted as the "final model" the unrestricted and adjusted model. We also estimated sojourn times (expected length of stay in a health state before transitioning to any other state) using estimates from the final model.

Hazard ratios pertaining to model covariates were also estimated. These ratios indicate the relative likelihood of a person transitioning from one health state to another, dependent on covariate values [11]. Hazard ratios greater than one imply a covariate is associated with a greater probability of a specific transition and vice versa. Estimate significance was evaluated at an $\alpha = 0.05$ level and confidence intervals represented a range of parameter estimates $\pm$ 2 standard errors from the mean. Given this study's large sample size and the implications of the central limit theorem, statistical inferences assumed normality [33]. Additionally, as noted in the R "msm" package, the confidence intervals were calculated based on drawing a random sample (with a default size 1000) from the assumed multivariate normal distribution of the maximum likelihood estimates and covariance matrix [29].

2.5.3 Investigation of Covariate Groups

Following the generation of transition probabilities from our final model, we also conducted separate analysis of some of the model covariates (which we have termed hereafter as subgroups). For use in full economic evaluations, we

investigated transition probabilities for the "no DMT" and "category three DMT" subgroups, including for people with relapsing–remitting MS. We also investigated the clinical experience of people with relapsing–remitting and progressive forms of MS to understand the relative speed of disease progression in these groups [34, 35]. Notably, only one DMT for the treatment of progressive MS was approved in 2021 in Australia—this DMT was not funded through the Australian reimbursement agency (Pharmaceutical Benefits Advisory Committee).

Therefore, we conducted six analyses of subgroups, which involved examination of transition probabilities for: (1) all people with MS using no DMTs, (2) people with relapsing–remitting MS using no DMTs, (3) all people with MS using category three DMTs, (4) people with relapsing–remitting MS using category three DMTs, (5) males with progressive onset MS who were not using a DMT, and (6) females with relapsing–remitting MS using a category three DMT. A disease duration of 5 years was assumed for subgroups 5 and 6.

2.5.4 Model Validity

Regarding model validation, we undertook a goodness of fit test to compare predicted to observed disease state prevalences. The analyses of subgroups outlined in 2.5.3 were also conducted to evaluate validity of the model.

3 Results

3.1 Participant Characteristics

Figure 2 provides the flow of participants into the study. *N* = 6369 people with MS in Australia who were participants in the large MSBase database met our inclusion criteria and entered the study for complete case analysis. Reasons for exclusion included participants having less than two reviews and missing covariate data, such as DMT use or MS phenotype. Importantly, excluded and included participants were similar in terms of age, sex, and EDSS and MS phenotype distributions. To illustrate, there was only a 2.4 year difference in the mean ages of the two groups and the female proportion was 75.00% in both. Additionally, EDSS and MS phenotype distributions were similar (Supplementary Table 1).

Table 2 (supported by Fig. 3A, B) shows the distribution of the observation time and the number of clinical reviews per person. Noting a time horizon of 49 years from January 1973 to December 2021, our data contained 38,837 person years of follow up with a mean (SD) of 6.10 (4.47) years of observation time per person and 54,570 clinical reviews with a of mean (SD) 8.57 (6.66) reviews per person.

Table 3 describes sociodemographic and clinical characteristics of the study sample at baseline (index date). The mean age of the study cohort was 42.51 years and 75.00% of the cohort was female, typical of MS cohorts. Regarding MS phenotype, 87.39% of the cohort had relapsing-remitting MS, with the remaining cohort having a progressive form

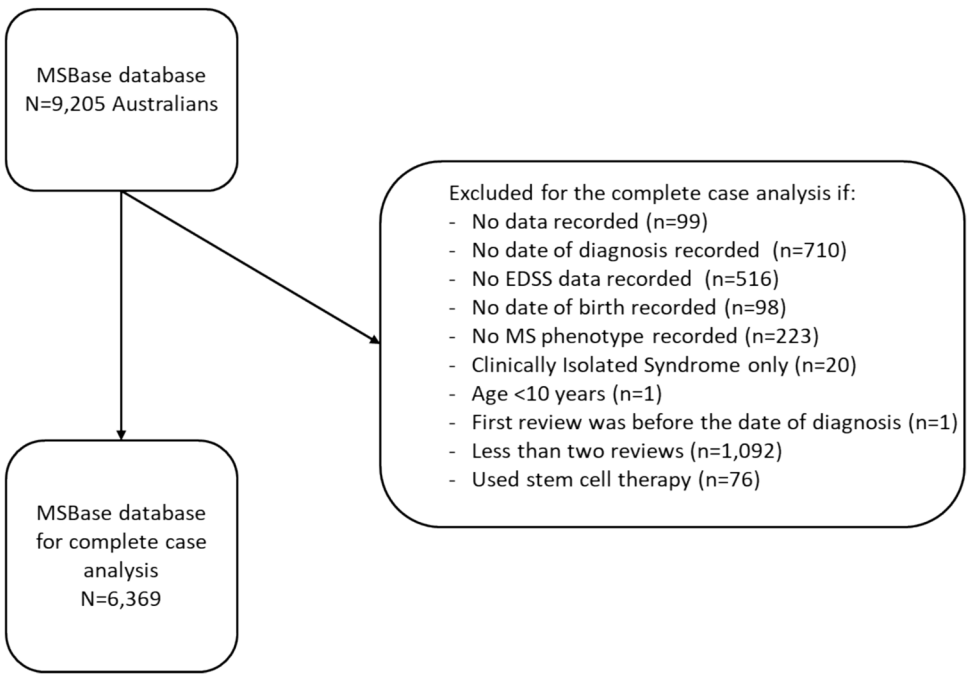

Fig. 2 Flow of MSBase Australian participants into the study. *EDSS* expanded status disability scale as assessed by a clinical neurologist

Table 2 Summary statistics for the observation time and clinical reviews for the included participants

$N = 6369$	Observation time in years	Number of reviews
Summary statistic		
Mean (standard deviation)	6.10 (4.47)	
Interquartile range		
0%	0.00	2
25%	2.41	4
50%	5.37	7
75%	8.85	11
100%	26.62	48
Mean (standard deviation)		8.57 (6.66)
Total	38,837.27 Person years	54,570 Clinical reviews

of MS, typical of MS cohorts and clinical presentation. As noted in Table 1, overall, 68.44% of the entire cohort were using DMTs and of these only 12.39% ($n = 539$) of that proportion of the cohort using DMTs ($n = 4359$) were using category one DMTs (namely interferons and glatiramer acetate), which reflects the "legacy" nature of the category one DMTs (Table 1). Usage of category 2 was $n = 514$ (11.79%) and category 3 was $n = 3306$ (75.84%). EDSS classifications revealed that there were sufficient people with MS in each health state for analysis (including for our analyses of subgroups). Supplementary Table 2 reveals that use of more granular EDSS categories of 0.0 and 1.0 and 2.0 through to 10.0 would have necessitated greatly restricting possible transitions due to small sample sizes (for example, only four people move from EDSS 4.0 to EDSS 7.0) making our model substantially less robust.

3.2 Number of State-to-State Transitions

Table 4 shows the frequency of transition between the four health states of no, mild, moderate, and severe disability. We observed 1815 transitions from no disability to mild disability, with 41 and 10 transitions occurring from no disability to moderate disability and severe disability, respectively. Regarding the severe disability health state, we observed 5, 26, and 526 transitions backward to the no, mild, and moderate disability states, respectively.

3.3 Transition Probabilities

Table 5 presents both the unadjusted transition probabilities as well as the covariate adjusted transition probabilities (the final model being the adjusted model). The final model revealed that there was a 54.24% probability of a person living with MS remaining in the no disability state over a time interval of 1 year, assuming mean covariate values (assumed from now on unless otherwise stated). It also revealed that there was a 42.31% probability of transitioning from the no disability state to the mild disability state and only a 3.29% probability of transition from the no disability to the moderate disability state (that is EDSS of 0.0 to EDSS of 4.0–6.0). It also revealed that the probability to transition from the severe disability state to the mild disability state was 2.78%.

The transition probability of greatest magnitude was the probability of remaining in the mild disability state (82.02%). The transition probability of second greatest magnitude was remaining in the severe disability state (77.83%). Interestingly, the probability of transitioning from moderate to severe disability was a relatively low 9.41%, with the probability of remaining in the moderate disability state being 69.86%.

Results presented in Table 5 are also supported by Supplementary Table 3, which displays transition probabilities generated using the restricted model. In this, restricted model transitions were allowed only to occur between adjacent health states. The estimation of this model constituted a sensitivity analysis which established that the results of the restricted model were similar to the final model. To illustrate, remaining in the no disability health state for the restricted and adjusted model was 54.08% and remaining in the mild disability state was 81.88%. Additionally, moving from moderate to severe disability for the restricted and adjusted model was 9.66%

Table 6 presents the transition probabilities for our analyses of subgroups and the sample sizes for these subgroups. We found that people not using a DMT were: more likely to leave the no disability health state after 1 year compared with those who used a DMT (51.02% remaining in the no disability health state compared to 54.24% remaining in the no disability health state), more likely to remain in the moderate disability health state (73.05% compared with 69.86%), and more likely to remain in the severe disability state after one year (82.52% compared with 77.83%). For these last two examples, they were less likely to experience an improvement in their disability severity (Tables 5 and 6). We also found that there were mostly health state improvements for people with relapsing–remitting MS using the category three DMT. For these people, remaining in the no disability health state yielded the highest annual transition probability of 58.95%.

The final two subgroups presented in Table 6 were males with progressive onset MS and no DMT usage and females with relapsing–remitting MS using a category three DMT, both with a 5 year disease duration. Aligning with our final model hazard ratio estimates, we see that the males with progressive MS and no DMT were less likely to experience a backward transition. For example, the probability of a mild to no disability transition is 1.27%, compared with 12.11%

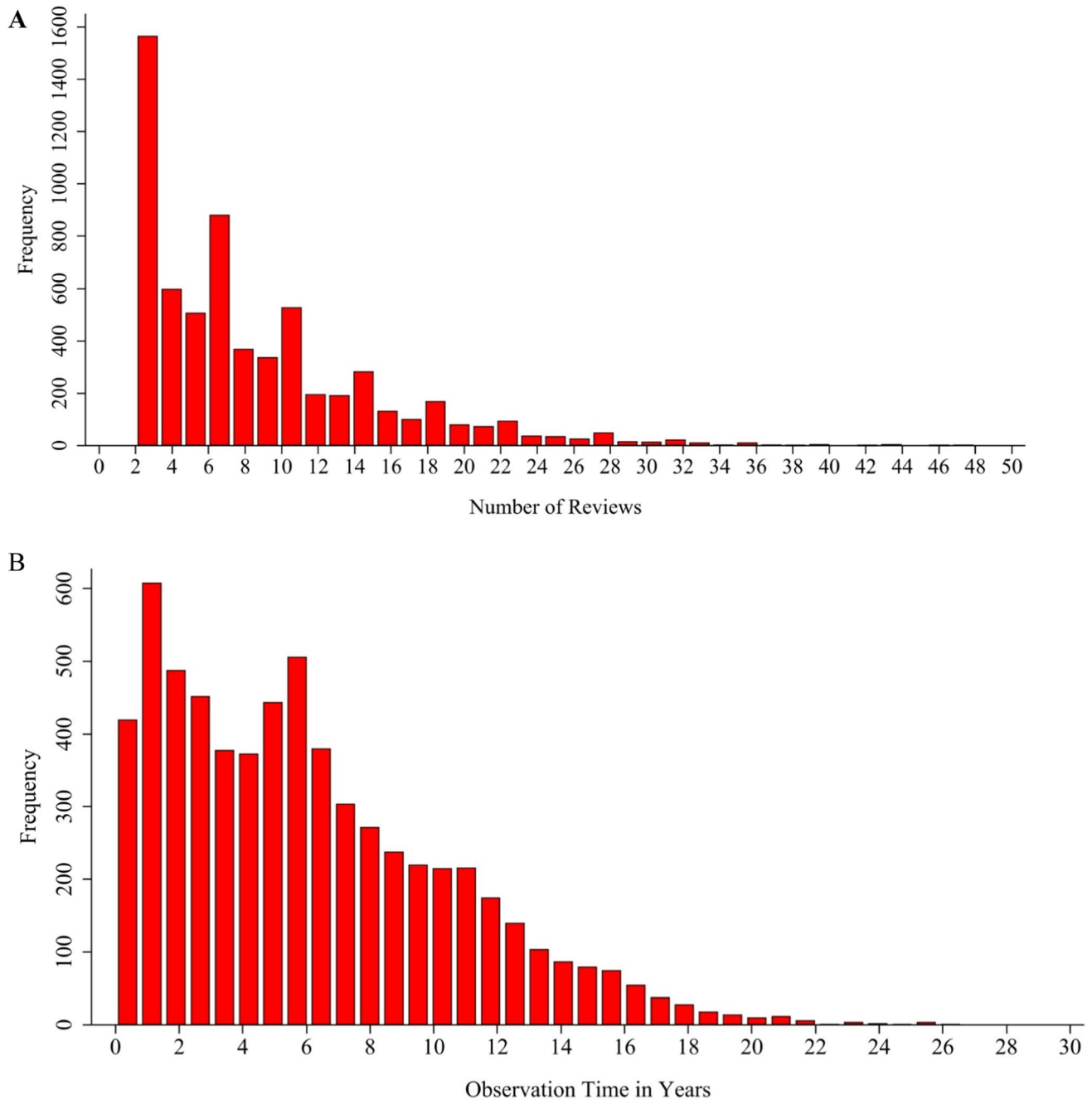

Fig. 3 **A** Distribution of the number of reviews conducted with the $n = 6369$ Australians living with MS who participated in the study. **B** Frequency of observation times per person in years

for the females with relapsing–remitting MS using a category three DMT. Conversely, we see that the males are more likely to transition forward. For example, there is a 22.40% chance of them transitioning from moderate to severe disability, compared with 6.93% for the females. Finally, for the males with progressive MS, the probability of remaining in the no disability state over a period of one year was only 25.55% and progressing from the no disability to the mild or moderate disability state was 61.93% and 11.23% for 1 year, respectively. These results also align with the clinical nature of progressive MS and the efficacy of DMTs, providing validation for our model.

Table 7 provides hazard ratios which describe the relative hazard of transition associated with model covariates. The results from our final model revealed that people living with MS with progressive MS phenotypes had a higher hazard of forward transition than persons with the relapsing–remitting MS phenotype and a lower hazard of backwards transition.

Table 3 Participant characteristics of the MSBase Australian cohort

Characteristic	Value
Number of included participants: *n*	6369
Age: mean (SD)	42.51 (12.37)
Sex: *n* (% female)	4777 (75.00)
Disability severity* *n* (%)	
No disability	959 (15.06)
Mild disability	3554 (55.80)
Moderate disability	1273 (19.99)
Severe disability	583 (9.15)
Number of deaths during the timeframe of clinical reviews	102 (1.60)
Disease duration: mean (SD)	5.69 (7.40)
Multiple sclerosis phenotype: *n* (%)	
Relapsing-remitting	5566 (87.39)
Secondary-progressive	460 (7.22)
Progressive-onset	343 (5.39)
Disease-modifying therapy usage: *n* (%)	
None	2010 (31.57)
Category 1	539 (8.46)
Category 2	514 (8.07)
Category 3	3306 (51.91)

*Disability severity calculated using the Expanded Disability Status Scale (EDSS): no disability, EDSS of 0.0; mild disability, EDSS of 1.0–3.5; moderate disability EDSS of 4.0–6.0; severe disability EDSS of 6.5–9.5

Table 4 Total number of transitions between health states of no, mild, moderate, and severe disability during the study period of clinical reviews

Disability severity*	No	Mild	Moderate	Severe
No	4071	1815	41	10
Mild	1736	21,820	1807	82
Moderate	36	1380	8288	1003
Severe	5	26	526	5553

Rows are the "from" states and columns are the "to" states. Disability severity classified with the Expanded Disability Status Scale (EDSS) where no EDSS is 0, mild EDSS is 1.03.5, moderate EDSS is 4.0–6.0, and severe EDSS is 6.5–9.5

Conversely, people with MS using DMTs had a lower hazard of disability progression and an increased hazard of disability improvement. Table 7 also illustrates that the probability of backward transition was higher among females than males (this relationship was more pronounced in backward transitions between less severe disability states) and the hazard of disability progression was similar between males and females. Table 7 also presents that increased disease duration was associated with a lower probability of backwards transition. We note that the hazard of a backward transition associated with the category two and three DMTs was similar and significant. These results, as well as the relative strength of the hazards of forward transition associated with category-specific DMT usage, are likely due to people with faster disability progression being treated with category three (or, more generally, higher efficacy) DMTs and therefore a consequence of indication bias. As MS-specific DMT treatments are not randomly assigned, this bias is unavoidable in observational studies of MS.

Sojourn times are the expected length of time in years in a particular health state, before a participant transitions to another health state. From the estimated transition probabilities (obtained from the final model using mean covariate values), the mean sojourn times [95% confidence interview (CI)] for the no disability state was 1.55 years (95% CI 1.27–1.66) of remaining in that health state. For the mild, moderate, and severe disability states the mean sojourn times were 4.13 (95% CI 2.10–4.28), 2.51 (95% CI 2.27–2.62), and 3.74 (95% CI 3.37–4.10) years, respectively for remaining in those health states.

Figure 4, supported by Supplementary Table 4, provides the results of a test of predictive capacity for the final model. Specifically, it presents a comparison of predicted and observed health state prevalence, suggesting that the final model was effective in predicting health state transitions. To illustrate, the expected number of participants in the no disability state in year 2 was 709 versus an observed 768 and 518 versus 553 in year 4. Similarly, the expected number of participants in the moderate disability state in year 2 was 1084 versus an observed 1021 and 884 versus 837 in year 4.

4 Discussion

This is the first study to use a large cohort of exclusively Australians living with MS and registered on the MSBase database to estimate transition probabilities for MS-related disability progression. Substantially expanding on earlier work by our group, we generated estimates relevant to people with either progressive or relapsing–remitting MS phenotypes and included separate no disability and mild disability health states that enabled us to capture changes from EDSS 0 to EDSS 1–3.5. We also estimated how DMT usage affects the hazard of health state transition and the probability of disability progression for three categories of DMTs. Importantly, this current study used a large longitudinal sample of $n = 6369$ people living with MS yielding almost 39,000 person years of follow up (mean 6.1 years) and 54,000 reviews (on average 8.6 reviews per person) compared with our previous study which involved 1297 person years of follow up and 660 reviews (on average two per person). A key finding of this study was that people living with MS during a period of one year were more likely to remain in their current health state and that there was

Table 5 Annual transition probability matrix of: (1) the unrestricted and unadjusted model and (2) the covariate adjusted final model

	No	Mild	Moderate	Severe
Annual transition probability matrix for unrestricted and unadjusted model				
No	0.5885 (0.5737, 0.6023)	0.3851 (0.3711, 0.3982)	0.0249 (0.0232, 0.0289)	0.0016 (0.0014, 0.0021)
Mild	0.0964 (0.0924, 0.1007)	0.8041 (0.7983, 0.8090)	0.0915 (0.0877, 0.0960)	0.0081 (0.0074, 0.0096)
Moderate	0.0118 (0.0109, 0.0141)	0.1707 (0.1630, 0.1786)	0.6963 (0.6848, 0.7059)	0.1212 (0.1142, 0.1282)
Severe	0.0006 (0.0005, 0.0009)	0.0127 (0.0113, 0.0157)	0.0984 (0.0906, 0.1064)	(0.8791, 0.8965)
Annual transition probability matrix for unrestricted and adjusted (final) model				
No	0.5424 (0.4361, 0.5618)	0.4231 (0.3441, 0.4414)	0.0329 (0.0308, 0.1558)	0.0016 (0.0014, 0.0669)
Mild	0.0582 (0.0459, 0.0627)	0.8202 (0.6037, 0.8257)	0.1138 (0.1083, 0.1304)	0.0078 (0.0071, 0.2204)
Moderate	0.0081 (0.0069, 0.0272)	0.1992 (0.1690, 0.2093)	0.6986 (0.6763, 0.7101)	0.0941 (0.0871, 0.1164)
Severe	0.0008 (0.0007, 0.0036)	0.0278 (0.0241, 0.0367)	0.1931 (0.1769, 0.2109)	0.7783 (0.7565, 0.7961)

The adjusted model controlled for sex, disease duration, multiple sclerosis phenotype, and disease-modifying therapy usage. Values in parentheses represent the 95% confidence interval.

Table 6 Annual transition probability matrix subgroup analysis for: (1) people with multiple sclerosis (MS) using no disease modifying therapies (DMT); (2) people with MS with relapsing–remitting MS and using no DMT; (3) people with MS using a category 3 DMT; (4) people with relapsing–remitting MS and using a category 3 DMT; (5) males with progressive MS not using a DMT and 5 years disease duration; and (6) females with relapsing–remitting MS using a category 3 DMT and 5 years disease duration

	No	Mild	Moderate	Severe
1. People with MS using no DMT ($n = 2010$)				
No	0.5102 (0.4314, 0.5367)	0.4484 (0.3121, 0.4708)	0.0394 (0.0355, 0.1284)	0.0021 (0.0018, 0.0969)
Mild	0.0428 (0.0303, 0.0473)	0.8192 (0.5205, 0.8276)	0.1283 (0.1203, 0.0960)	0.0097 (0.0086, 0.3159)
Moderate	0.0047 (0.0037, 0.0292)	0.1561 (0.1232, 0.1694)	0.7305 (0.7016, 0.7438)	0.1087 (0.1012, 0.1410)
Severe	0.0003 (0.0003, 0.0031)	0.0172 (0.0142, 0.0250)	(0.1428, 0.1731)	0.8252 (0.8034, 0.8407)
2. Relapsing–remitting MS and using no DMT ($n = 1453$)				
No	0.5631 (0.4964, 0.5892)	0.4056 (0.3233, 0.4276)	0.0299 (0.0270, 0.1093)	0.0014 (0.0011, 0.0916)
Mild	0.0546 (0.0420, 0.0602)	0.8287 (0.5198, 0.8356)	0.1096 (0.1029, 0.1255)	0.0071 (0.0061, 0.3120)
Moderate	0.0071 (0.0057, 0.0336)	0.1879 (0.1505, 0.2034)	0.7146 (0.6835, 0.7287)	0.0904 (0.0821, 0.1278)
Severe	0.0007 (0.0005, 0.0043)	0.0245 (0.0200, 0.0332)	0.1842 (0.1657, 0.2027)	0.7907 (0.7664, 0.8112)
3. People with MS using a category 3 DMT ($n = 3306$)				
No	0.5373 (0.4479, 0.5592)	0.4269 (0.3012, 0.4457)	0.0341 (0.0314, 0.1385)	0.0017 (0.0015, 0.1194)
Mild	0.0616 (0.0395, 0.0663)	0.8148 (0.4568, 0.8208)	0.1156 (0.1099, 0.1409)	0.0081 (0.0073, 0.3580)
Moderate	0.0092 (0.0078, 0.0293)	0.2125 (0.1580, 0.2249)	0.6840 (0.6558, 0.6960)	0.0943 (0.0871, 0.1438)
Severe	0.0010 (0.0008, 0.0044)	0.0321 (0.0256, 0.0446)	0.2062 (0.1872, 0.2252)	0.7607 (0.7373, 0.7835)
4. Relapsing–remitting MS and using a category 3 DMT ($n = 3132$)				
No	0.5895 (0.5321, 0.6084)	0.3838 (0.3209, 0.4009)	0.0257 (0.0238, 0.0889)	0.0011 (0.0009, 0.0607)
Mild	0.0781 (0.0625, 0.0837)	0.8187 (0.5823, 0.8244)	0.0975 (0.0925, 0.1201)	0.0058 (0.0052, 0.2363)
Moderate	0.0137 (0.0120, 0.0548)	0.2526 (0.2112, 0.2657)	0.6567 (0.6146, 0.6698)	0.0770 (0.0704, 0.1143)
Severe	0.0017 (0.0014, 0.0094)	0.0453 (0.0383, 0.0569)	0.2371 (0.2153, 0.2604)	0.7159 (0.6865, 0.7410)
5. Males with progressive-onset MS using no DMT and 5 years disease ($n = 108$)				
No	0.2555 (0.0000, 0.3144)	0.6193 (0.0519, 0.6463)	0.1123 (0.0884, 0.7301)	0.0129 (0.0095, 0.2440)
Mild	0.0127 (0.0000, 0.0158)	0.7291 (0.5485, 0.7604)	0.2229 (0.1886, 0.2587)	0.0350 (0.0291, 0.2271)
Moderate	0.0006 (0.0000, 0.0024)	0.0550 (0.0432, 0.0684)	0.7209 (0.6869, 0.7508)	0.2235 (0.1947, 0.2553)
Severe	0.0000 (0.0000, 0.0002)	0.0052 (0.0027, 0.0124)	0.0574 (0.0457, 0.0721)	0.9374 (0.9196, 0.9503)
6. Females with relapsing–remitting MS using a DMT and 5 years disease ($n = 2355$)				
No	0.5704 (0.5444, 0.5876)	0.4044 (0.3873, 0.4213)	0.0241 (0.0216, 0.0443)	0.0012 (0.0009, 0.0050)
Mild	0.1209 (0.1143, 0.1335)	0.7909 (0.7796, 0.7981)	0.0829 (0.0692, 0.0886)	0.0054 (0.0044, 0.0142)
Moderate	0.0278 (0.0256, 0.2198)	0.3175 (0.2998, 0.3410)	0.5857 (0.3949, 0.6039)	0.0690 (0.0538, 0.0766)
Severe	0.0044 (0.0037, 0.0502)	0.0708 (0.0615, 0.0921)	0.2570 (0.2034, 0.2875)	0.6679 (0.6250, 0.7000)

The model controlled for sex, disease duration, multiple sclerosis (MS) phenotype, and disease-modifying therapy (DMT) usage

Table 7 Hazard ratios for the final model for multiple sclerosis (MS) phenotypes (relapsing remitting, secondary progressive, and progressive onset) and disease-modifying therapy (DMT) usage including no DMT and category 1, category 2, category 3 DMTs

Variable	Transitions	
	Forward	Backward
MS phenotype		
Relapsing remitting	(Reference)	(Reference)
Secondary progressive	**2.5092 (2.2188, 2.8377)**	**0.3298 (0.2845, 0.3823)**
Progressive onset	**2.2985 (1.9748, 2.6753)**	**0.3083 (0.2528, 0.3760)**
Disease-modifying therapy		
No DMT	(Reference)	(Reference)
Category 1 DMT	**0.6838 (0.5987, 0.7809)**	**1.1879 (1.0255, 1.3761)**
Category 2 DMT	**0.7220 (0.6399, 0.8145)**	**1.5737 (1.3711, 1.8061)**
Category 3 DMT	0.9377 (0.8732, 1.0069)	**1.4177 (1.3008, 1.5451)**
Transition	Variable	
	Sex (Female)	Duration (Years)
No—Mild	1.1003 (0.9735, 1.2437)	**0.9815 (0.9711, 0.9921)**
No—Moderate	0.8852 (0.0000, 1.0982×10^8)[A]	1.3370 (0.9971, 1.7928)
Mild—No	**1.4269 (1.2551, 1.6223)**	**0.9108 (0.9007, 0.9210)**
Mild—Moderate	0.9853 (0.8802, 1.1030)	1.0185 (1.0120, 1.0250)
Mild—Severe	1.1432 (0.1018, 12.8377)	0.7802 (0.3145, 1.9356)
Moderate—No	3.9444 (0.0353, 4.4246×10^2)[A]	1.1184 (0.8004, 1.5628)
Moderate—Mild	**1.3681 (1.1993, 1.5608)**	**0.9474 (0.9397, 0.9553)**
Moderate—Severe	1.0077 (0.8756, 1.1597)	1.0041 (0.9962, 1.0121)
Severe—Mild	0.4102 (0.0689, 2.4420)	**0.6924 (0.5064, 0.9468)**
Severe—Moderate	**1.3071 (1.0692, 1.5979)**	**0.9748 (0.9639, 0.9861)**

Bolded results are significant at an $\alpha = 0.05$ level

[A]These large confidence intervals resulted from transitions between no and moderate disability being dominated by one sex, which was exacerbated by relatively small numbers of relevant observations

the highest probability of remaining in the mild disability state. We found that the probability of remaining in the no disability state (EDSS of 0.0) over a period of one year was almost 55%. In other words, there was an approximately 45% probability of a person with MS moving out of the no disability health state within the same timeframe.

We also examined MS-related phenotypes of relapsing-remitting (all using and not using a DMT, and females using a DMT) and a progressive form of MS (males not using a DMT) and found that the chance of remaining in the no disability state for the progressive form of MS was substantially reduced to 25.55%, whereas for the relapsing-remitting form it was 30% higher at 57.04%. We also found that people with MS using DMTs had a lower hazard of disability progression. We further established that people with relapsing–remitting MS using a category three DMT were the most likely group to remain in the no disability health state after 1 year. Conversely, people with MS not using a DMT mostly did worse in terms of disability progression than those using a DMT, including for relapsing–remitting MS.

4.1 Model Validity and Use in Our Publicly Available Health Economics Model

The validity of our results was supported by the predictive capacity of our model and analyses of subgroups that represented constrained covariate values. Regarding model fit, our test of predictive capacity for the final model compared observed versus expected health state prevalence and we found that prevalence was similar for the no, mild, moderate, and severe health states for all years of observation. This sound predictive capacity indicates that the final model was able to accurately predict health state transitions. The investigation of the subgroups also supported our model. To illustrate, the largest difference was between people with MS not using a DMT and people with relapsing-remitting MS using a category three DMT. Our results revealed that for people living with relapsing–remitting MS using the high efficacy category three DMT there as an almost 8% increased probability of remaining in the no disability health state after one year. Additionally, there was an almost 8% greater probability of remaining in the severe disability health state for

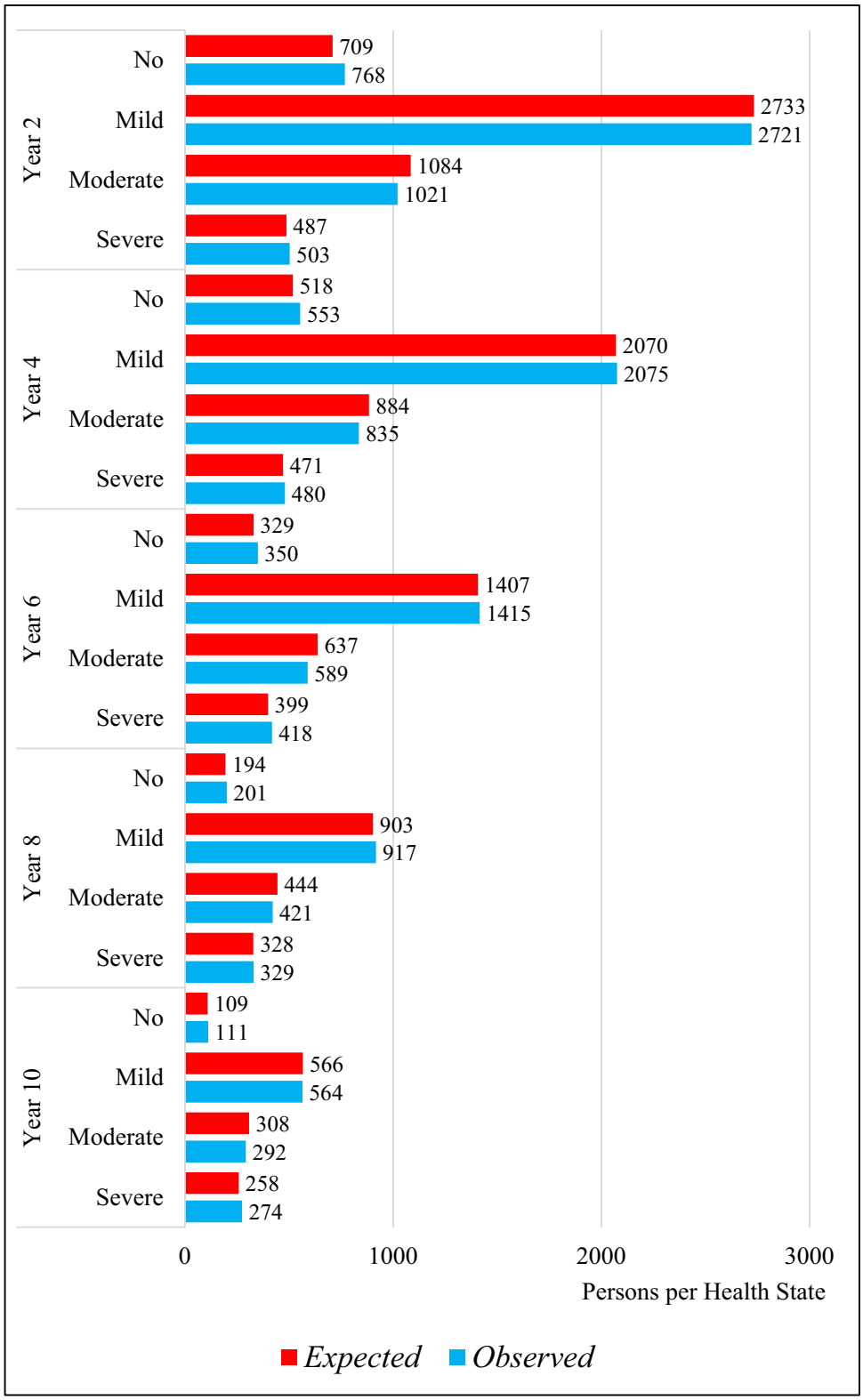

Fig. 4 Predictive capacity of the final model with the comparison of expected and observed results for years 2, 4, 6, 8, and 10 for the health states of no, mild, moderate, and severe disability. Disability severity measured with the Expanded Disability Status Scale (EDSS; scale 0–10), where no disability is EDSS of 0, mild EDSS is 1.0–3.5, moderate EDSS is 4.0–6.0, and severe disability EDSS ≥ 6.5

people using no DMT than for people with relapsing–remitting MS using the category three DMT after 1 year.

The model also revealed clinically expected results between males with progressive MS and females with relapsing–remitting MS. More specifically, males with primary progressive MS and no DMT usage experienced faster disease progression than females with relapsing–remitting MS using a category three DMT. This

finding is reflected in clinical literature [36] including for the mortality rates of people with progressive onset MS where the survival gap was significantly reduced from people with relapsing–remitting MS phenotypes [35]. These results also align with the findings of a study that investigated the annual transition probabilities of progressive forms of MS only [16]. This study only estimated transition probabilities from EDSS of 3.0 onwards and found that for Italians living with progressive forms of MS, remaining in an EDSS of 3.0 (aligning with the upper values of our mild disability health state) was 76.25% for primary progressive MS and 56.48% for secondary progressive MS. Our study revealed that the probability of remaining in the mild health state for males with a progressive form of MS was 72.91%. Importantly, our study also highlighted that remaining in the no disability health state within 1 year for males with a progressive form of MS was only 25.55%. Importantly, our study not only aligns with, but also adds to the Italian study given that we also investigated a no disability health state and severe disability heath state beyond EDSS of 7.0.

Hazard ratios were also estimated for the final model of our study and these estimates demonstrated two key clinical aspects of MS. First, these results showed that persons with progressive MS (as opposed to relapsing–remitting MS) have a higher probability of forward transition and a lower probability of backward transition. This was not investigated in the Italian study [16]. Second, these results illustrated that DMTs have a protective effect against MS-disability progression, in the context of our Australian study [37].

4.2 Exclusion of an Absorbing Death State

Our MSBase cohort had 6369 patients and 39,000 years of patient follow up (1973 to 2021) with only 102 (1.6%) recorded deaths over the follow-up period. Estimates produced using this data provided spurious results in our health economics model (e.g., life expectancy of 135 years). Furthermore, two recent and large studies informed by administrative data from British Columbia and New Zealand recorded much higher mortality rates over similar study periods. To illustrate, the British Columbian study sourced rich provincial administrative data, involving 6629 MS patients with 104,236 patient-years of follow-up (1986–2013), of whom 1416 died [38]. The New Zealand study found that at the end of the 15-year study period, 844 (29%) of the MS cohort were deceased [35]. Therefore, given the relatively low quality of recording of deaths in the MSBase database (which is updated after each clinical review in real time), we did not include the death state in our final Markov model to avoid underestimation of death probabilities.

4.3 Adherence with the Recommendations of a Recent Systematic Review

Notably, this extension on our previously published work avoids issues outlined in a recent systematic review regarding the estimation of transition probabilities using state-transition models [13]. To illustrate, we included a distinct "no disability" health state (and related transitions) unlike our previous work, thereby not omitting a key health state and transitions. Another avoided issue was the use of several datasets or datasets not relevant to our desired study population. Rather, we utilized data from one apt source: the large and representative MSBase repository. Additionally, though we conducted a complete case analysis, we determined that there were no material, demographic, or clinical differences between participants included and excluded from the study (Supplementary Table 1). Given this, it is unlikely that bias arose from missing data. Notably, we were also able to conduct analyses of subgroups given the completeness and richness of our data. Lastly, and as can be observed in Supplementary Fig. 1, disease duration varies greatly over our dataset's observations. This limits reliance on extrapolation when study transition probabilities are applied in health economics models.

4.4 Contextualization with Other Studies that have Generated Transition Probabilities for MS

Many studies have generated transition probabilities using registry data from the older databases, such as the London Ontario database [9]. A systematic review published in 2014 that investigated modeling approaches for cost-effectiveness analysis regarding MS, discussed the generation of transition probabilities, and noted that most studies in the review used data from the London Ontario database. The review noted that these data were collected years ago and do not reflect the current rate of disability progression for people living with MS due to changes in DMT usage [17]. There has been a revolution in DMT treatments since this time, including in Australia [39].

Moreover, a recent study using more granular EDSS categories (EDSS of 0 to 9 in 1-point increments) in the estimation of transition probabilities for international MSBase data has some limitations [9]. The most important of these limitations involves the aggregating of international data when generating transition probabilities—these heterogeneous data contain information sourced from multiple disparate worldwide healthcare systems (including public, private, and mixed systems), with differing subsidy and prescribing policies (particularly those pertaining to DMTs) relevant to the treatment and management of MS. In view of this, we

suggest that our homogeneous Australia specific transition probabilities are especially useful for Australian reimbursement decisions and those of other comparable countries with similar health systems.

4.5 Use of these Transition Probabilities in Our Publicly Available Health Economics Model

Our current study separated the no and mild disability health states, and we found that there was the highest probability of remaining in the mild disability state (82.02%) and that the probability of remaining in the no disability state was 54.24% over a period of 1 year. Our previously published less granular model found that the probability of remaining in the combined no/mild disability state was 93.4% [14]. Our current results found that the probability of remaining in the moderate disability state was 69.86%, compared with our previously published results of 90.4%. Furthermore, with the inclusion of the progressive MS phenotypes our analyses of subgroups found that for people with progressive forms of MS (not taking a DMT) transitioning to an increased disability severity from the no disability state was more rapid over a period of 1 year. We found that there was an almost 30% lower probability of remaining in the no disability state after 1 year for males with a progressive form of MS and not taking a DMT compared with a female with relapsing–remitting MS taking a DMT. We suggest that these differences compared with our earlier preliminary results highlight the increased granularity and robustness of our current results with the larger cohort and that these new results should now be used in future health economics models, particularly regarding DMT reimbursement decisions for MS. Therefore, these new transition probability results have been used for a health economics model that will be made publicly available particularly for DMT reimbursement decisions to continue to support the DMT evolution in MS treatments. This model will be continuously updated in real time and create a community of interest to encourage robust health economics decision making [40] (https://msresearchflagship.org.au/researchers/health-economics-simulation-model).

Regarding clinical trials of DMTs (or other interventions aimed to halt or ameliorate disability severity), our separation of the no and mild disability states is particularly important. This separation allows our transition probabilities to describe small EDSS changes, which may be especially relevant to trials examining induction treatment or other early disease-course interventions. In the context of clinical trials, our transition probabilities would be compared with the disease progression of trial participants. Importantly, EDSS scores obtained in a trial would need to be used as inputs to another Markov model, the transition probabilities obtained from which would be applied in the aforementioned comparison.

Importantly, our input data for this model include: costs (total, direct, and indirect), health state utilities measured with the EQ-5D-5L-Psychosocial [23], disutilities for MS-specific relapse events [41] (where our previous model only used a simple average disutility value from a study published in 2006 using data from European countries only), and state-dependent relapse probabilities. Our transition probabilities align with this other detailed input data. Our updated health economics model improves our previous health economics model by incorporating more granular disease states, improving the accuracy of input data based on a large MS cohort and by including contemporary cost and health state utility inputs that match the more detailed health states.

4.6 Strengths and Limitations

Our study is supported by a number of strengths. First, our study is informed by a large and representative sample of people living with MS. The large and enduring MSBase database, contained in one central repository, is informed by the clinic reviews of neurologists and has been validated in many clinical and health economics studies [9, 19, 42, 43]. The second strength is the method underpinning our model. Our study benefits from using a multistate Markov model to estimate the transition probabilities for four MS-related health states and differing phenotypes [14]. The Markov modeling technique takes into account irregular follow-up times and also EDSS changes that are not sustained, especially for relapsing–remitting MS [29]. Our study also addresses common problems raised in a recent systematic review regarding the generation of transition probabilities [13]. Another strength is that we also conducted six variations of our analyses of subgroups and these additional analyses also supported what we would expect clinically from these transition probabilities. We have used our transition probabilities to populate our new health economics model for Australia, and this model has provided robust and expected results and is the subject of a further study. A final strength of the paper is the multidisciplinary team on this study that includes a MS-specialist clinical neurologist and specialists in MS epidemiology and health economics. The combined nature of the team has enabled broad discussion regarding the clinical relevance (as well as the health economics relevance) of the transition probabilities and the generation of overall expected transition probabilities within the limitations of the paper.

Our study also has some limitations. The main limitation was the dearth of mortality data available and therefore the inability to generate useful transition probabilities pertaining to an absorbing death state. However, we note that in our subsequent full economic evaluation model, we assumed that people with MS with no disability had the

same mortality rate as the Australian general population. To estimate mortality rates following the development of a MS-related disability, relative mortality risks were applied to the Australian general population mortality rate by multiplying it with 1.60, 1.84, and 4.44 for people with mild, moderate, and severe MS-related disability (as noted in an earlier survival study) [44]. Another limitation is the potential for indication bias for the three categories of DMTs that may have affected the hazard ratios pertaining to DMT usage. Importantly, when providing DMT treatment options, the assignment of DMTs is not a random process. It is likely that people with increased disability severity (and more severe MS-related disease progression) will be commenced on higher efficacy category three DMTs, and therefore, there is potential indication bias for category two and three DMTs. On this point, it is also noted that people with MS on category one DMTs are the legacy group (12.39%) where these people were likely to remain on their category one DMT before the advent and approvals of the higher efficacy categories, given that this is the current DMT.

A further limitation of our final model was the relaxation of restrictions where jumps of more than two health states were excluded from our model to enable model convergence. Nevertheless, this only meant that no disability to severe disability, and severe disability to no disability were excluded—these restrictions were key in achieving model convergence. Our choice of restrictions also reflects the modelling practices of other complex and chronic disease such as pulmonary hypertension [45] where the final model was also similarly restricted. Another limitation is the inclusion of data for complete case analysis. We acknowledge that this selection can introduce bias as outlined by Drummond et al. (2015) [10] and Allison (2009) [46]. However, where possible, we compared the included and excluded MSBase participants at baseline, and this comparison revealed no material differences between age, sex, proportions of EDSS classifications for health states, and MS phenotypes. On this point, we further acknowledge that not including people with MS in the MSBase database that have more than one EDSS score could mean that those people may be too unwell to visit their neurologist at that time. However, it could also mean that their EDSS is stable and that these people have chosen to visit a neurologist when there is a change in their MS-related disability health status.

A further potential limitation of our study is the use of the four health states of no, mild, moderate, and severe disability; however, there were two reasons for the selection of these health states: first, the availability of our homogeneous Australian-specific MSBase data to generate robust estimates and second, to align with our new and updated health economics model that has produced robust and validated estimates of life expectancy, QALYs, and lifetime costs for people living with MS. Our model input data from large Australian cohorts including MSBase and the Australian MS Longitudinal Study aligned with costs (total, direct, and indirect), health state utilities, disutilities for relapse events, and state-dependent relapse probabilities. Our current health states are more granular and robust than our previous model [14] and also capture changes between people with no disability and people with mild disability. Additionally, we did not have data regarding whether particular EDSS records were influenced by relapses. Importantly, our transition probabilities associated with different phenotypes correspond with what was expected based on their relapse profiles; for example, people with relapsing forms of MS were substantially more likely to experience remission compared to persons with progression forms of MS. As such, there is no clear indication that this data limitation affected our results.

Finally, we acknowledge that DMT data related to the DMTs most currently used by participants (as of their most recent MSBase entry) is a potential limitation. Despite this, indication bias notwithstanding, effects on transition probabilities regarding DMT usage were universally in the expected directions. Furthermore, once a DMT is selected by a neurologist for treatment of MS (possibly following attempts with first and second line DMTs), usage of that DMT is generally persistent, suggesting that current DMT is an effective proxy for DMT usage generally.

5 Conclusions

For people living with MS, there is just under a 50% probability of progressing from the no disability health state after 1 year, with people with progressive forms of MS progressing at a higher rate than people with relapsing–remitting MS. These estimated transition probabilities can now be applied in a health economics simulation model for Australia, intended to support reimbursement of interventions including medications to reduce progression of MS. Specifically, our transition probability results will be used for our robust and well-validated health economics model that will be made publicly available, particularly for DMT reimbursement decisions to continue to support the evolution of DMTs in MS treatments.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40273-024-01417-4.

Acknowledgements We acknowledge and thank Dr Ting Zhao, Menzies Institute for Medical Research, University of Tasmania for her assistance with our revisions to this paper.

Declarations

Funding Open Access funding enabled and organized by CAUL and its Member Institutions. This study was supported by Dr Julie Campbell's MS Australia Research Fellowship number 19-0702 and the Australian Government, Medical Research Future Fund, emerging priorities in consumer driven research, EPCD000008. The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Conflicts of interest All authors declare that they have no conflict of interest

Author contributions Concept and Design: Campbell, Henson, Fuh Ngw, Ahmad, Palmer; acquisition of data: Campbell, Fuh Ngwa, Palmer, Taylor, Ahmad; analysis and interpretation of data: Campbell, Henson, Fuh Ngwa, Taylor, van der Mei, Palmer; drafting of the manuscript: Campbell and Henson; critical revision of the paper for important intellectual content: all authors; provision of study materials or patients: Taylor and MS Base Australian Researchers; obtaining funding: Campbell, Taylor, van der Mei, Palmer; administrative, technical or logistical support: Fuh Ngwa; supervision: Campbell, Taylor, van der Mei, Palmer.

Ethics approvals The use of MSBase as a research platform was approved by the Melbourne Health Human Research Ethics Committee and by the local ethics committees in all participating centres (or exemptions were granted according to local laws and regulations).

Data availability This study used MSBase registry data. Data approvals for access to the data used for this study can be sought through the corresponding authors who will then liaise with MSBase.

References

1. Campbell JA, Jelinek GA, Weiland TJ, et al. SF-6D health state utilities for lifestyle, sociodemographic and clinical characteristics of a large international cohort of people with multiple sclerosis. Qual Life Res. 2020;29(9):2509–27.
2. Kuspinar A, Mayo NE. A review of the psychometric properties of generic utility measures in multiple sclerosis. Pharmacoeconomics. 2014;32:759–73.
3. Ahmad H, Campbell JA, Taylor BV, van der Mei I, Palmer AJ. The health economic impact of multiple sclerosis in Australia in 2017. Commissioned Report for MS Australia. https://www.msaustralia.org.au/wp-content/uploads/2018/08/health-economic-impact-of-ms-in-australia-in-2017_ms-research-australia_web.pdf.
4. The Multiple Sclerosis International Federation, Atlas of MS, 3rd Edition (September 2020). https://www.msif.org/resource/atlas-of-ms-2020.
5. Campbell JA, Simpson S Jr, Ahmad H, Taylor BV, van der Mei I, Palmer AJ. Change in multiple sclerosis prevalence over time in Australia 2010–2017 utilising disease-modifying therapy prescription data. Mult Scler. 2020;26(11):1315–28.
6. Campbell JA, van der Mei, Taylor BV, Palmer AJ. Health economic impact of MS in 2021: an interim update of prevalance, costs and costs of illness from 2017 to 2021. Commissioned Report for MS Australia. 2023. https://www.msaustralia.org.au/wp-content/uploads/2023/02/health-economic-impact-of-multiple-sclerosis-in-australia-in-2021_final.pdf.
7. Campbell JA and Simpson-Yap S, Taylor BV, van der Mei I, Laslett L, Henson GJ, Zhao T, Palmer AJ. Significantly increasing multiple sclerosis prevalence in Australia from 2010 to 2021. Mult Scler, 2024; Accepted June 2024, In Press.
8. Kennedy-Martin M, Slaap B, Herdman M, et al. Which multi-attribute utility instruments are recommended for use in cost-utility analysis? A review of national health technology assessment (HTA) guidelines. Eur J Health Econ. 2020;21:1245–57.
9. Spelman T, Herring WL, Zhang Y, et al. Comparative effectiveness and cost-effectiveness of natalizumab and fingolimod in patients with inadequate response to disease-modifying therapies in relapsing-remitting multiple sclerosis in the United Kingdom. Pharmacoeconomics. 2022;40:323–39.
10. Drummond MF, Sculpher MJ, Claxton K, et al. Methods for the economic evaluation of health care programmes. Oxford: Oxford University Press; 2015.
11. Culyer AJ. The dictionary of health economics. London: Edward Elgar Publishing; 2010.
12. Claflin S, Campbell JA, Norman R, et al. Using the EQ-5D-5L to investigate quality-of-life impacts of disease-modifying therapy policies for people with multiple sclerosis (MS) in New Zealand. Eur J Health Econ. 2023;24:939–50.
13. Srivastava T, Latimer NR, Tappenden P. Estimation of transition probabilities for state-transition models: a review of NICE appraisals. Pharmacoeconomics. 2021;39:869–78.
14. Ahmad H, van der Mei I, Taylor BV, et al. Estimation of annual probabilities of changing disability levels in Australians with relapsing-remitting multiple sclerosis. Mult Scler. 2019;25:1800–8.
15. Palmer AJ, van der Mei I, Taylor BV, et al. Modelling the impact of multiple sclerosis on life expectancy, quality-adjusted life years and total lifetime costs: evidence from Australia. Mult Scler J. 2020;26:411–20.
16. Cortesi PA, Fornari C, Capra R, et al. Multiple sclerosis progressive courses: a clinical cohort long-term disability progression study. Value in Health. 2022;25:1489–98.
17. Guo S, Pelligra C, Saint-Laurent Thibault C, et al. Cost-effectiveness analyses in multiple sclerosis: a review of modelling approaches. Pharmacoeconomics. 2014;32:559–72.
18. Shirani A, Zhao Y, Kingwell E, et al. Temporal trends of disability progression in multiple sclerosis: findings from British Columbia, Canada (1975–2009). Mult Scler. 2012;18:442–50.
19. Butzkueven H, Chapman J, Cristiano E, et al. MSBase: an international, online registry and platform for collaborative outcomes research in multiple sclerosis. Mult Scler. 2006;12:769–74.
20. Auguste P, Colquitt J, Connock M, et al. Ocrelizumab for treating patients with primary progressive multiple sclerosis: an evidence review group perspective of a NICE single technology appraisal. Pharmacoeconomics. 2020;38:527–36.
21. Caro JJ, Briggs AH, Siebert U, et al. Modeling good research practices—overview: a report of the ISPOR-SMDM modeling good research practices task force–1. Med Decis Making. 2012;32:667–77.

22. Kobelt G, Berg J, Atherly D, et al. Costs and quality of life in multiple sclerosis: a cross-sectional study in the United States. Neurology. 2006;66:1696–702.
23. Campbell JA, Ahmad H, Chen G, et al. Validation of the EQ-5D-5L and psychosocial bolt-ons in a large cohort of people living with multiple sclerosis in Australia. Qual Life Res. 2023;32:553–68.
24. Ahmad H, Campbell JA, van der Mei I, et al. The increasing economic burden of multiple sclerosis by disability severity in Australia in 2017: results from updated and detailed data on types of costs. Mult Scler Relat Dis. 2020;2: 102247.
25. Culyer AJ. Encyclopedia of health economics. Elsevier, New York 2014.
26. Jalal H, Pechlivanoglou P, Krijkamp E, et al. An overview of R in health decision sciences. Med Decis Making. 2017;37:735–46.
27. Green N, Lamrock F, Naylor N, et al. Health economic evaluation using markov models in r for microsoft excel users: a tutorial. Pharmacoeconomics. 2023;41:5–19.
28. Briggs A, Sculpher M, Claxton K. Decision modelling for health economic evaluation. Oxford: Oxfor University Press; 2006.
29. Jackson C. Multi-state models for panel data: the msm package for R. J Stat Softw. 2011;38:1–28.
30. Gray AM, Clarke PM, Wolstenholme JL, et al. Applied methods of cost-effectiveness analysis in healthcare. Oxford: Oxford University Press; 2010.
31. Gani R, Giovannoni G, Bates D, et al. Cost-effectiveness analyses of natalizumab (tysabri®) compared with other disease-modifying therapies for people with highly active relapsing-remitting multiple sclerosis in the UK. Pharmacoeconomics. 2008;26:617–27.
32. Broyden CG. The convergence of a class of double-rank minimization algorithms. Appl Math. 1970;6(76–90):222–31.
33. Kirkwood BR, Sterne JA. Essential medical statistics. New York: John Wiley & Sons; 2010.
34. McKay KA, Kwan V, Duggan T, et al. Risk factors associated with the onset of relapsing-remitting and primary progressive multiple sclerosis: a systematic review. BioMed Res Int. 2015;20:15.
35. Leadbetter R, MacAskill M, Myall DJ, et al. Multiple sclerosis mortality in New Zealand: a nationwide prospective study. J Neurol Neurosurg Psychiatry. 2023;2:2.
36. Taylor BV. What causes multiple sclerosis? Getting closer to the answers. Med J Aust. 2022;217:180–2.
37. Filippi M, Amato MP, Centonze D, et al. Early use of high-efficacy disease-modifying therapies makes the difference in people with multiple sclerosis: an expert opinion. J Neurol. 2022;269:5382–94.
38. Kingwell E, Zhu F, Evans C, et al. Causes that contribute to the excess mortality risk in multiple sclerosis: a population-based study. Neuroepidemiology. 2020;54:131–9.
39. Zhao T, Taylor BV, Campbell JA, et al. The disease-modifying therapy utilisation and cost trend for multiple sclerosis in Australia between 2013 and 2022. Multi Scler. 2024;30:80–8.
40. Palmer AJ, Campbell JA, de Graaff B, et al. Population norms for quality adjusted life years for the United States of America, China, the United Kingdom and Australia. Health Econ. 2021;30:1950–77.
41. Ahmad H, Campbell JA, van der Mei I, et al. Estimating the disutility of relapse in relapsing–remitting and secondary progressive multiple sclerosis using the EQ-5D-5L, AQoL-8D, EQ-5D-5L-psychosocial, and SF-6D: implications for health economic evaluation models. Qual Life Res. 2023;32:3373–87.
42. Kenney R, Liu M, Patil S, et al. Long-term outcomes in patients presenting with optic neuritis: analyses of the MSBase registry. J Neurol Sci. 2021;430: 118067.
43. Jokubaitis VG, Spelman T, Lechner-Scott J, et al. The Australian Multiple Sclerosis (MS) immunotherapy study: a prospective, multicentre study of drug utilisation using the MSBase platform. PLoS ONE. 2013;8: e59694.
44. Pokorski RJ. Long-term survival experience of patients with multiple sclerosis. J Insur Med New York. 1997;29:101–6.
45. Boateng GO, Lartey ST, Baiden P, et al. Measuring hypertension progression with transition probabilities: estimates from the WHO SAGE longitudinal study. Front Public Health. 2021;9: 571110.
46. Allison PD (2009) Missing data. The SAGE handbook of quantitative methods in psychology. 23:72–89