Multiple Sclerosis and Related Disorders 69 (2023) 104456

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Original article

Trajectories of disease-modifying therapies and associated sickness absence and disability pension among 1923 people with multiple sclerosis in Sweden

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ARTICLE INFO

Keywords:
Disease modifying drugs
Sequence analysis
Sick leave
High-efficacy DMTs
Multiple sclerosis treatment

ABSTRACT

Background: There is limited information on the trajectories of disease-modifying therapy (DMT) use and their association with sickness absence and/or disability pension (SADP) among people with multiple sclerosis (PwMS). The objective of the study was to identify trajectories of DMT use over 10 years among PwMS, identify sociodemographic and clinical factors associated with the trajectories, and to assess the association between identified trajectories and SADP days.

Methods: A longitudinal register-based study was conducted, on a prospective data set linked across six nationwide registers, assessing treatment courses of PwMS with DMTs for the 10 years following multiple sclerosis (MS) onset. The study included 1923 PwMS with MS onset in 2007–2010, when aged 19–56 years. In each 6-month-period, their treatment was categorized as before treatment, high-efficacy, non-high-efficacy, or no DMT. Sequence analysis was performed to identify sequences of the treatment categories and cluster them into different DMT trajectories. Cluster belonging, in relation to demographic and clinical characteristics, was assessed through log-multinomial regression analysis. The association of trajectories/cluster-belonging with SADP net days was assessed using generalized estimating equation (GEE) models.

Results: Cluster analyses identified 4 trajectories of DMT use: *long-term non-high-efficacy DMTs* (38.6%), *escalation to high-efficacy DMTs* (31.2%), *delayed start and escalation to high-efficacy DMTs* (15.4%), and *discontinued/ no DMT* (14.2%). Age, MS type, expanded disability status scale (EDSS) score and the number of DMT switches were associated with cluster belonging. The youngest age group (18–25) were more likely to be in the *escalation to high-efficacy* cluster. People with primary progressive MS were more likely to be in the *delayed start* or *discontinued/ no DMT* cluster. Higher EDSS scores were associated to being in the other three clusters than in the *long-term non-high-efficacy DMTs* cluster. Higher number of DMT switches were associated with being in the *escalation to high-efficacy DMTs* cluster but less likely to be in the *delayed start* or *discontinued/ no DMT* clusters. Descriptive analyses showed a trend of fewer mean SADP days among PwMS using non-high-efficacy DMT than the other clusters about 9 years after onset. PwMS in the *escalation to high-efficacy* and *discontinued/no DMT* clusters had more SADP days. PwMS in the *delayed start and escalation to high-efficacy DMTs* cluster, started with fewer SADP days which increased over time. SADP days adjusted through GEE models showed trends comparable with the descriptive analysis.

Conclusion: This study described the long-term real-world trajectories of DMT use among PwMS in Sweden using sequence analysis and showed the association of the trajectories with SADP days as well as sociodemographic and clinical characteristics.

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https://doi.org/10.1016/j.msard.2022.104456
Received 29 August 2022; Received in revised form 7 November 2022; Accepted 3 December 2022
Available online 9 December 2022

Abbreviations

DMT	disease-modifying therapy
DP	disability pension
EDSS	expanded disability status scale
GEE	generalized estimating equations
HSCT	hematopoietic stem cell transplantation
LISA	Longitudinal Integrated Database for Health Insurance and Labor Market Studies
MiDAS	Micro-Data for Analysis of the Social Insurance System
MS	multiple sclerosis
PPMS	primary progressive multiple sclerosis
PwMS	people with multiple sclerosis
RRMS	relapsing-remitting multiple sclerosis
SADP	sickness absence and/or disability pension
SA	sickness absence
SD	standard deviation
SMSreg	Swedish Multiple Sclerosis Registry
SPMS	secondary progressive multiple sclerosis

1. Introduction

Multiple sclerosis (MS) is the most common non-traumatic disabling neurologic disease of working-aged people, often impacting work life (Pearson et al., 2017). A global survey of more than 12,000 people with MS (PwMS) showed that 43% and 70% of the PwMS stopped working 3 and 10 years after MS diagnosis, respectively (Jones et al., 2016). In Sweden, influence of MS on work life and productivity has been shown using sickness absence (SA) and disability pension (DP) data (Tinghög et al., 2013; Gyllensten et al., 2016), showing increasing proportions of PwMS granted DP over time (Wiberg et al., 2015). Higher levels of SA and DP were also noted for the years before MS diagnosis, compared to references without MS (Gyllensten et al., 2016).

In MS treatment, disease-modifying therapies (DMTs) aim to reduce disease activity, progression, and long-term disability (Robertson and Moreo, 2016; Filippi et al., 2018). Since the approval of interferon beta-1b in 1993, more than a dozen DMTs have been approved for MS, particularly in recent years (Fig. S1) (Robertson and Moreo, 2016; De Angelis et al., 2018; Läkemedelsfakta [online] 2021). Most have been used to treat relapsing-remitting multiple sclerosis (RRMS) with ocrelizumab becoming the first for primary progressive multiple sclerosis (PPMS) (De Angelis et al., 2018). Currently, treatment using DMTs involves alternative strategies of escalation therapy and induction therapy. In escalation therapy, historically a more traditional approach internationally, PwMS start treatment with non-high-efficacy DMTs, later changing to high-efficacy ones. In induction therapy PwMS receive more effective DMTs as early as possible to prevent accumulation of disability, with possible de-escalation if disease control is attained (Filippi et al., 2018). Early treatment using high-efficacy DMTs is reported to have better effectiveness than non-high-efficacy DMTs in reducing the probability of relapse and the worsening of disability (He et al., 2020; Spelman et al., 2021). However, higher efficacy DMTs have also been associated with serious adverse events (Sorensen, 2017).

Early use of DMTs was also shown to be associated with better outcome in earnings and with longer time before increased use of sickness absence and/or disability pension (SADP) benefits (Kavaliunas et al., 2020). Studies based on patient-reported data also showed that DMTs had a positive impact on work attendance and productivity (Chen et al., 2018), as well as improved work ability with decreased fulltime DP (Wickström et al., 2015). In Sweden PwMS using natalizumab, a high-efficacy DMT, showed a decrease in SA by a third and an increase in productivity after one year of treatment (Wickström et al., 2014).

There is limited information on how treatment of PwMS with different types of DMTs looks over long follow-up periods and their possible association with SADP. The entry of newer DMTs to clinical use also warrants studying their pattern of use over time and identifying associated sociodemographic and clinical factors. Furthermore, sequence analysis (Ritschard and Studer, 2018), a relatively new method in health research for longitudinal analysis of categorical states, provides an illustrative approach to characterize different trajectories of DMTs use over time revealing treatment sequencing and changes in treatments. Sequence analysis can be used to illustrate individual trajectories in a manner suitable for quantitative analysis and to compare trajectories among different groups. One of the important features of sequence analysis is that it has a holistic perspective providing information on an entire trajectory rather than specific transitions. It also provides easily interpretable illustration of sequences and trajectories (Ritschard and Studer, 2018). These and it being easier for computations have been among its advantages in comparison to similar methods such as event history analysis and latent class analysis (Roux et al., 2019; Mikolai and Lyons-Amos, 2017). Using the sequence analysis method, the aim of the present study was to identify trajectories of DMT use over 10 years among PwMS, identify sociodemographic and clinical factors associated with the trajectories, and to assess the association between identified trajectories and SADP days.

2. Materials and methods

A prospective register-based cohort study was conducted on PwMS, sampled from the Swedish Multiple Sclerosis Registry (SMSreg) (Hillert and Stawiarz, 2015), with disease onset in 2007–2010 when aged 19–56. The follow-up period for each individual was divided into 6-month time windows starting from onset date. The follow-up covered a total of 10.5 years of the DMT use trajectories for each of the PwMS during the period from 2007 to the first half of 2021. The follow-up of SA/DP days covered 11.5 years for each of the PwMS within the period from 2006 to the first half of 2021.

2.1. Study population

Of a total of 2373 PwMS with onset in 2007–2010, exclusions were made for missing information (onset, diagnosis, and treatment start dates), PwMS with pediatric onset MS, and those not in working ages (<18 and >55 years at baseline (Y_{-1})) (to ensure PwMS remain in working-age throughout the follow-up). In addition, individuals not living in Sweden at baseline (Y_{-1}), and those who died ($n = 18$) or emigrated during the follow-up were excluded. This resulted in a cohort of 1923 PwMS.

2.2. Data sources

Linked microdata on the included PwMS were obtained from 6 Swedish nationwide registers: SMSreg (Hillert and Stawiarz, 2015), the Longitudinal Integrated Database for Health Insurance and Labor Market Studies (LISA) (Ludvigsson et al., 2019), the Cause of Death Register (Brooke et al., 2017), the Swedish Prescribed Drug Register (The Swedish Prescribed Drug Register [online] 2020), the Swedish Cancer Register (The Swedish Cancer Register [online] 2019), and the Micro-Data for Analysis of the Social Insurance System (MiDAS) (MiDAS, 2011).

A modified Rx-Risk comorbidity index, which uses records of dispensed drugs to estimate comorbidity, was used. The validity of this method has been compared with other approaches of identifying comorbidity and has been used previously to assess comorbidity in PwMS (Lu et al., 2011; Pratt et al., 2018; Murley et al., 2020).

Data regarding SA and DP were obtained from MiDAS. We used information on all SA spells >14 days and net SADP days (hereafter SADP days) were calculated by using gross days and the extent/percentage of SADP.

2.3. Sickness absence and disability pension in Sweden

In Sweden, all individuals 16 years or older with income from work,

unemployment or parental leave benefits can apply for SA benefits from the social insurance agency in case of reduced work capacity due to disease or injury. SA and DP cover about 80% and 64% of lost income, respectively, up to a certain level. Both SA and DP can be provided on a part- or fulltime basis.

2.4. DMT states

DMT states were defined for each 6-month time period from MS onset date for a total of 10.5 years. DMT states were assigned to one of 4 categories: (1) a *before treatment* state, the time between MS onset and the first registered information/decision regarding treatment/no treatment; (2) a *high-efficacy DMT* state, a period with high-efficacy DMTs; (3) a *non-high-efficacy DMT* state, treatment with moderate to low-efficacy DMTs; and (4) a *no DMT* state indicates one of the following: a period with no DMTs since the time of registered treatment information (i.e., registered information of no treatment or treatment with non-DMTs), using no DMTs throughout the follow-up, or discontinuing a DMT. In cases of more than one state in the 6-month time period, the state with the longest duration was used.

The 16 DMTs in the present study were categorized as high-efficacy and non-high-efficacy DMTs based on classifications employed in recent literature reviews (Giovannoni, 2018; Hauser and Cree, 2020), systematic reviews (Li et al., 2020; Samjoo et al., 2021), empirical studies (Samjoo et al., 2021; Kalincik et al., 2017), guidelines, (Scolding et al., 2015) and expert opinions from neurologists. Accordingly, alemtuzumab, daclizumab, hematopoietic stem cell transplantation (HSCT), mitoxantrone, natalizumab, ocrelizumab, ofatumumab, and rituximab were categorized as high-efficacy. The non-high-efficacy DMTs were cladribine, dimethyl fumarate, fingolimod, glatiramer acetate, interferons (interferon beta-1a, interferon beta-1b, and peginterferon beta-1a), and teriflunomide.

2.5. Statistical analyses

Descriptive analyses of demographic and clinical characteristics were performed, through proportions, means, and chi-square tests to assess the distribution of PwMS by year of onset and by clusters resulting from the sequence analysis. In comparing demographic and clinical characteristics of PwMS by onset year, beside chi square tests, one-way analysis of variance (for continuous variable version of age) and Kruskal Wallis (as a non-parametric test to compare SADP days across the onset years) tests were also performed.

Sequence analysis was performed to determine trajectories of DMTs during the follow-up. This provided an approach to assess longitudinal sequences of categorical states, revealing different trajectories based on the dissimilarities among a set of sequences (Ritschard and Studer, 2018). Two to 10 clusters of trajectories were assessed for their quality to choose the best solution. The choice of the number of clusters was based on cluster quality assessment and on whether the clusters reflected meaningful real-world DMT use trajectories (Table S1). After selection, the clusters were named to depict their overall trend.

A log-multinomial regression analysis was performed to assess the association of different demographic (age and sex) and clinical (type of MS, comorbidity, first available expanded disability status scale (EDSS) score, frequency of DMT switch and MS onset year) variables with belonging to a cluster.

Mean SADP days in each cluster over the follow-up period were calculated and generalized estimating equations (GEE) with a negative binomial distribution was used to assess mean SADP days over time in the clusters. Unadjusted models and those adjusted for sex, age, type of MS, comorbidity, EDSS score, frequency of DMT switches and MS onset year were assessed. These demographic (age and sex) and clinical variables were selected for adjustment as they were considered crucial factors in multiple sclerosis in the progression and prognosis and were found to have association with SADP among PwMS. The analyses were performed using R version 4.1.1 (R foundation for statistical computing, Vienna, Austria), SAS software version 9.4 (SAS Institute Inc, Cary NC, USA) and Stata software version 17.0 (Stata Corp, College Station, Texas 77845, USA).

The sMethods section of the Supplement provides more details on the categorization of DMTs, on the steps followed in the sequence analysis including selection of the number of clusters as well as more information on the GEE models.

2.6. Ethics

The project was approved by the Regional Ethics Review Board in Stockholm, Sweden. In this type of study based on pseudonymized register data, patient consents are not applicable.

3. Results

Of the 1923 PwMS, 70.4% were female (Table 1). At baseline, 64.8% were aged 26–45 years, 49.1% were single with no children at home, and 86.9% had at least some high school education. PwMS with RRMS or secondary progressive multiple sclerosis (SPMS) constituted 91.1% while 6.6% had PPMS. The first available EDSS score was between 0 and 2.5 in 73.2% of the PwMS. All the demographic and clinical variables were distributed evenly among PwMS across MS onset years from 2007 to 2010, based on chi-square tests. Mean SADP days in the year before onset showed some variation by onset year.

3.1. DMT trajectories

A total of 916 unique sequences of treatments were identified among the 1923 PwMS. The 10 most frequent sequences were observed in 20.4% of the PwMS (Fig. S2). On average PwMS spent 4.5 years on treatment with non-high-efficacy DMTs, 3.2 years on no treatment (before treatment (1.8 years) and no DMT states (1.4 years)) and 2.8 years on high-efficacy DMTs. Cluster analysis of the sequences of DMT states showed that 4 clusters performed best (Table S1, Table S2, Fig. 1). These were *long-term non-high-efficacy DMTs; escalation to high-efficacy DMTs; delayed start and escalation to high-efficacy DMTs* and *discontinued/no DMT* clusters termed hereafter as *non-high-efficacy, escalation to high-efficacy, delayed start and discontinuation* clusters, respectively. The main features of each cluster are described briefly in Table 2.

3.2. Association of demographic and clinical characteristics with cluster belonging

The log-multinomial regression analysis showed no statistically significant sex differences regarding cluster-belonging. However, among females those who had a pregnancy during the follow-up represented a higher proportion in the *escalation* cluster (nearly 10%) than the others (about 4% each). Age, type of MS, EDSS score, and number of DMT switches were associated with cluster-belonging. Specifically, the 18–25 age group was more likely to belong to the *escalation* and the *delayed start* clusters than to the *non-high-efficacy* cluster group (Table 3).

People with PPMS showed a higher risk of belonging to the *delayed start* and the *discontinuation* clusters than people with RRMS. PwMS with higher EDSS scores were at a higher risk of being in the 3 other clusters than the *non-high-efficacy* cluster. PwMS who had one or more DMT switches were at higher risk to be in the *escalation* than in the *non-high-efficacy* cluster. In contrast, these PwMS were less likely to be in the *delayed start* or the *discontinuation* clusters. PwMS with onset in 2009 and 2010 were more likely to be in the *escalation* cluster than the *non-high-efficacy* cluster compared to those with onset in 2007 (Table 3).

Table 1
Descriptive statistics and chi-square tests on distribution of sociodemographic and clinical characteristics of people with multiple sclerosis by onset year ($n = 1923$).

Variable	MS onset year				Total	P-value
	2007 $n = 459$ % (n)	2008 $n = 475$ % (n)	2009 $n = 486$ % (n)	2010 $n = 503$ % (n)	$n = 1923$ % (n)	
Sex						0.3624
Female	71.7 (329)	72.6 (345)	67.9 (330)	69.4 (349)	70.4 (1353)	
Male	28.3 (130)	27.4 (130)	32.1 (156)	30.6 (154)	29.6 (570)	
Age groups						0.7779
18–25 years	19.6 (90)	20.4 (97)	23.5 (114)	23.3 (117)	21.7 (418)	
26–35 years	35.7 (164)	37.3 (177)	34.4 (167)	33.4 (168)	35.2 (676)	
36–45 years	32.0 (147)	28.6 (136)	29.0 (141)	28.8 (145)	29.6 (569)	
46–55 years	12.6 (58)	13.7 (65)	13.2 (64)	14.5 (73)	13.5 (260)	
Age (mean (SD))	34.3 (8.88)	34.3 (9.29)	33.9 (9.41)	34.4 (9.79)	34.2 (9.35)	0.986[a]
Birth country						0.8925
Sweden	87.1 (400)	88.4 (420)	87.9 (427)	88.7 (446)	88.0 (1693)	
Other	12.9 (59)	11.6 (55)	12.1 (59)	11.3 (57)	12.0 (230)	
Family composition						0.2556
Married/cohabitant without children <18 years	8.1 (37)	6.1 (29)	7.6 (37)	9.7 (49)	7.9 (152)	
Married/cohabitant with children	37.5 (172)	35.4 (168)	36.4 (177)	36.4 (183)	36.4 (700)	
Single without children	46.6 (214)	53.1 (252)	48.1 (234)	48.7 (245)	49.1 (945)	
Single with children	7.8 (36)	5.5 (26)	7.8 (38)	5.2 (26)	6.6 (126)	
Type of living area						0.3543
Big cities	39.7 (182)	42.1 (200)	45.5 (221)	38.8 (195)	41.5 (798)	
Medium-sized cities	34.4 (158)	33.3 (158)	31.9 (155)	37.4 (188)	34.3 (659)	
Rural areas	25.9 (119)	24.6 (117)	22.6 (110)	23.9 (120)	24.2 (466)	
Educational level						0.1858
Elementary school (0–9 years)	12.9 (59)	13.9 (66)	12.1 (59)	13.3 (67)	13.1 (251)	
High school (10–12 years)	51.9 (238)	42.9 (204)	47.9 (233)	45.5 (229)	47.0 (904)	
University/ college (>12 years)	35.3 (162)	43.2 (205)	39.9 (194)	41.2 (207)	39.9 (768)	
Type of multiple sclerosis[b]						0.6528
Relapsing-remitting/ secondary progressive	90.6 (416)	91.6 (435)	90.1 (438)	91.8 (462)	91.1 (1751)	
Primary progressive	7.0 (32)	5.9 (28)	8.0 (39)	5.4 (27)	6.6 (126)	
Missing	2.4 (11)	2.5 (12)	1.9 (9)	2.8 (14)	2.4 (46)	
EDSS score (earliest)						0.1948
0 to 2.5	70.4 (323)	72.4 (344)	75.3 (366)	74.6 (375)	73.2 (1408)	
3 to 5.5	22.2 (102)	18.9 (90)	15.2 (74)	18.5 (93)	18.7 (359)	
6 to 9	3.1 (14)	3.4 (16)	3.3 (16)	1.6 (8)	2.8 (54)	
Missing	4.4 (20)	5.3 (25)	6.2 (30)	5.4 (27)	5.3 (102)	
Comorbidity index						0.6852
0	9.8 (45)	9.9 (47)	11.5 (56)	9.3 (47)	10.1 (195)	
1 to 2	48.8 (224)	51.6 (245)	53.7 (261)	54.1 (272)	52.1 (1002)	
3 to 4	28.3 (130)	26.7 (127)	24.7 (120)	26.2 (132)	26.5 (509)	
5+	13.1 (60)	11.8 (56)	10.1 (49)	10.3 (52)	11.3 (217)	
Frequency of DMT switch during follow-up						0.4364
0	24.6 (113)	25.3 (120)	24.9 (121)	26.6 (134)	25.4 (488)	
1	32.7 (150)	31.8 (151)	38.7 (188)	36.4 (183)	34.9 (672)	
2	26.4 (121)	25.3 (120)	20.0 (97)	22.3 (112)	23.4 (450)	
3+	13.1 (60)	14.1 (67)	13.0 (63)	10.9 (55)	12.7 (245)	
No DMT	3.3 (15)	3.6 (17)	3.5 (17)	3.8 (19)	3.5 (68)	
Sickness absence/ disability pension days [mean (SD)][c]						
Y_{-1} (6 to 12 months prior to onset date)	17.9 (49.1)	13.9 (43.7)	10.6 (37.7)	10.7 (38.6)	13.3 (42.4)	**0.0114**
$Y_{-0.5}$ (6 months prior to onset date)	20.1 (52.3)	14.7 (43.9)	10.5 (35.7)	10.7 (37.5)	13.9 (42.8)	**0.0278**
Y_0 (6 months from onset date)	41.0 (64.3)	30.4 (55.4)	29.8 (53.8)	26.7 (51.1)	31.8 (56.4)	**0.0054**

DMT: disease modifying therapy; **EDSS**: Expanded disability status scale; **MS**: multiple sclerosis; **PwMS**: people with multiple sclerosis; **SD**: standard deviation. Statistically significant results are shown in bold.

[a] one-way analysis of variance.

[b] relapsing-remitting and secondary progressive multiple sclerosis are grouped together.

[c] P-values are based on Kruskal Wallis test.

3.3. Trends of sickness absence and disability pension in the four clusters

Of the 1923 PwMS, 74.6%, 29.6%, and 79.3% had at least one occurrence of SA, DP, and SA or DP throughout the follow-up, respectively. Table 2 provides brief descriptions of the SADP trend in the clusters shown in Fig. 2. Similar trends were shown in the proportion of PwMS with at least 90 SADP days across the clusters (Fig. S3).

The final adjusted GEE model (Table 4) and the models from the unadjusted to those sequentially adjusted for sex, age, type of MS, comorbidity, EDSS score, frequency of DMT switches and MS onset year (Table S3), showed trends in SADP days across clusters which are comparable in their relative trajectories to the observed mean SADP days. Examples of the similarity are the relatively lower SADP days in the follow-up in the *non-high-efficacy* trajectory and the SADP days which start low and increase over time in the *delayed start* cluster which are generally comparable in the observed and the adjusted models (Fig. 2).

Looking into the final adjusted model, PwMS in the *delayed start cluster* had lower SADP days than the others up to the second year from onset. Towards the end of the follow-up (from the 8th year onwards) PwMS in the *non-high-efficacy* trajectory had lower SADP days than those in the *escalation* and *discontinuation* trajectories.

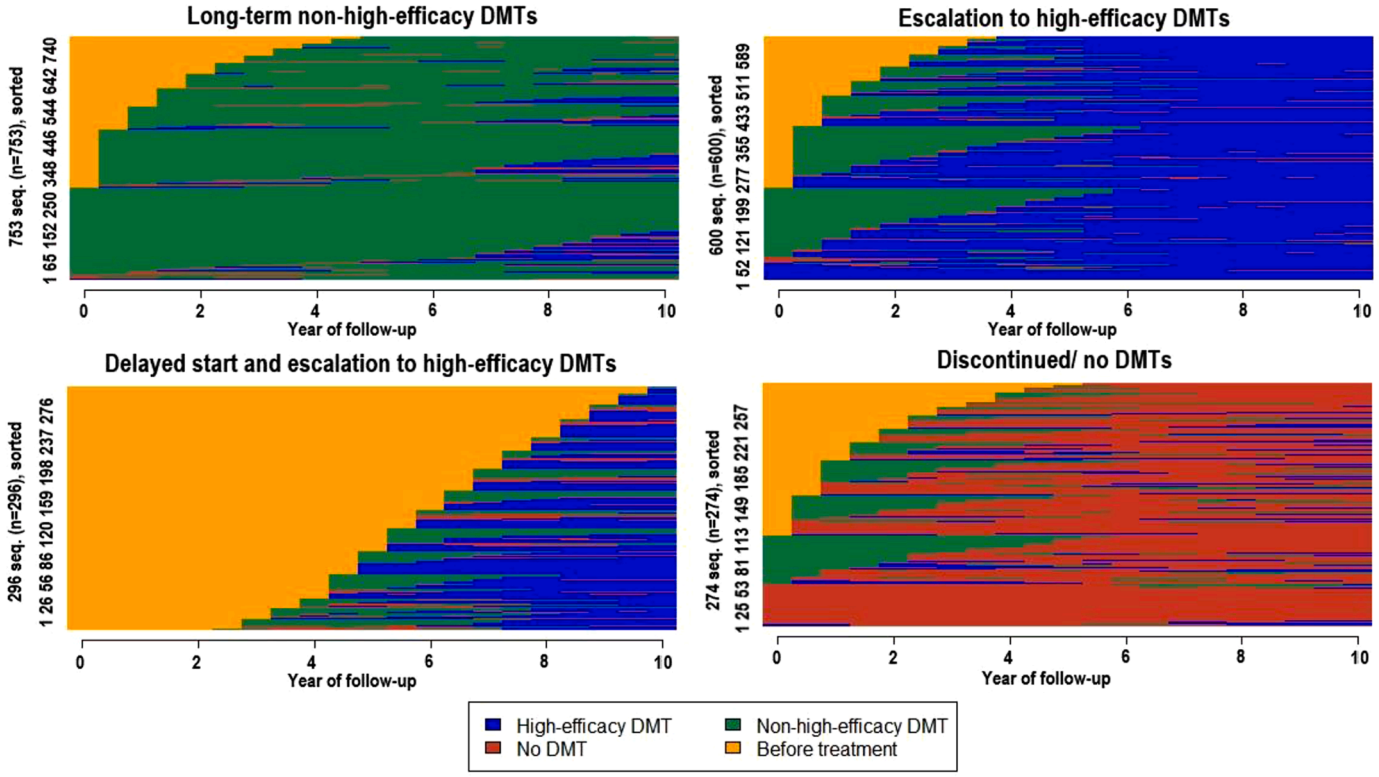

Fig. 1. Sequence index plots of the four clusters of DMT trajectories among people with multiple sclerosis [DMT: disease-modifying therapy] [The figure presents the DMT use trajectory of each of the PwMS in each cluster, sorted by the DMT category at the start of the follow-up.].

Table 2
Main features of the four clusters of DMT use and respective sickness absence and disability pension days.

Feature	Long-term non-high-efficacy DMTs	Escalation to high-efficacy DMTs	Delayed start and escalation to high-efficacy DMTs	Discontinued/ no DMTs
PwMS per cluster,% (n)	39.2% (753)	31.2% (600)	15.4% (296)	14.2% (274)
Description	PwMS mainly taking non-high-efficacy DMTs throughout the over 10 years follow-up	Shorter time to initial treatment with non-HE DMTs then escalation to high-efficacy DMTs	Longer time to initial treatment, then using non-high-efficacy DMTs followed by escalation to high-efficacy DMTs	Discontinuation occurred after some time on non-high-efficacy DMTs or no DMTs were taken throughout
Differences by demographic and clinical variables				
Age compared to overall sample	Comparable	Younger	Comparable	Older
Proportion of people with PPMS compared to overall sample	Lower	Lower	Higher	Higher
Proportion of PwMS with EDSS score of 6+	Lower	Comparable	Higher	Slightly higher
Proportion of PwMS across onset years compared to the overall sample	Comparable	Higher in 2010 (last/most recent cohort)	Comparable across 2007, 2009 and 2010 onset; higher in 2008 onset	Comparable
Mean sickness absence and disability pension days	The trend showed a steep increase during the 6 months since onset, followed by a relatively stable trend towards the end of the follow-up It showed a statistically significantly lower SA/DP days than the others towards the final two years of the follow-up	PwMS showed higher number of SA/DP days than in long-term non-high-efficacy DMTs cluster for most of the follow-up	PwMS showed fewer mean SA/DP days from around onset up to midway through follow-up. From there it showed a relatively larger increase towards the end of the follow-up	PwMS showed higher number of SA/DP days than in the *long-term non-high-efficacy DMTs* cluster for most of the follow-up

DMT: disease modifying therapy; **EDSS**: Expanded disability status scale; **PPMS:** primary progressive multiple sclerosis; **PwMS**: people with multiple sclerosis; **SA/DP**: sickness absence/ disability pension.

Table 3
Distribution of PwMS by cluster and a mutually adjusted log-multinomial regression analysis on the association of demographic and clinical characteristics with belonging to the four clusters of DMT use trajectories.

Variable	Distribution of PwMS by DMT use cluster ($n = 1923$)				Adjusted relative risk ratio (95% CI) of belonging to a DMT use cluster ($n = 1725$)			
	Long-term non-high-efficacy DMTs ($n = 753$) % (n)	Escalation to high-efficacy DMTs ($n = 600$) % (n)	Delayed start and escalation to high-efficacy DMTs ($n = 296$) % (n)	Discontinued/ no DMT ($n = 274$) % (n)	Long-term non-high-efficacy DMTs ($n = 696$) RRR	Escalation to high-efficacy DMTs ($n = 582$) RRR	Delayed start and escalation to high-efficacy DMTs ($n = 255$) RRR	Discontinued/ no DMT ($n = 192$) RRR
Sex								
Female	69.9 (526)	71.2 (427)	69.9 (207)	70.4 (193)	1.00	1.00	1.00	1.00
Male	30.1 (227)	28.8 (173)	30.1 (89)	29.6 (81)	1.00	0.91 [0.70–1.18]	0.80 [0.56–1.13]	0.81 [0.55–1.18]
Age group								
18–25 years	16.5 (124)	32.0 (192)	20.3 (60)	15.3 (42)	1.00	**2.01 [1.48–2.73]**	**1.82 [1.19–2.78]**	1.26 [0.77–2.06]
26–35 years	37.6 (283)	37.5 (225)	32.1 (95)	26.6 (73)	1.00	1.00	1.00	1.00
36–45 years	33.1 (249)	24.2 (145)	32.4 (96)	28.8 (79)	1.00	**0.71 [0.53–0.95]**	0.78 [0.53–1.14]	0.80 [0.53–1.23]
46–55 years	12.9 (97)	6.3 (38)	15.2 (45)	29.2 (80)	1.00	**0.44 [0.28–0.69]**	**0.55 [0.32–0.93]**	1.14 [0.69–1.89]
Type of multiple sclerosis								
Relapsing-remitting/ secondary progressive	95.2 (717)	95.3 (572)	83.1 (246)	78.8 (216)	1.00	1.00	1.00	1.00
Primary progressive	2.3 (17)	2.7 (16)	16.2 (48)	16.4 (45)	1.00	1.36 [0.65–2.86]	**3.28 [1.63–6.60]**	**2.71 [1.29–5.66]**
Missing	2.5 (19)	2.0 (12)	0.7 (2)	4.7 (13)	–	–	–	–
Comorbidity								
0	10.5 (79)	9.0 (54)	8.8 (26)	13.1 (36)	1.00	1.00	1.00	1.00
1 to 2	54.2 (408)	54.3 (326)	48.6 (144)	45.3 (124)	1.00	0.99 [0.66–1.49]	1.11 [0.65–1.91]	0.67 [0.39–1.14]
3 to 4	25.5 (192)	26.2 (157)	28.7 (85)	27.4 (75)	1.00	1.06 [0.68–1.65]	1.21 [0.68–2.17]	0.73 [0.41–1.31]
5+	9.8 (74)	10.5 (63)	13.9 (41)	14.2 (39)	1.00	1.04 [0.61–1.77]	1.25 [0.63–2.46]	0.76 [0.38–1.50]
EDSS score								
Mean (SD)	1.43 (1.33)	2.08 (1.63)	1.92 (1.45)	2.31 (1.74)	1.00	**1.37 [1.25–1.50]**	**1.42 [1.27–1.58]**	**1.28 [1.14–1.45]**
Number of DMT switch								
0	21.5 (162)	9.3 (56)	51.7 (153)	42.7 (117)	1.00	1.00	1.00	1.00
1	42.9 (323)	36.7 (220)	27.0 (80)	17.9 (49)	1.00	**1.91 [1.31–2.78]**	**0.28 [0.19–0.40]**	**0.24 [0.16–0.36]**
2	25.6 (193)	31.7 (190)	10.8 (32)	12.8 (35)	1.00	**2.61 [1.76–3.87]**	**0.17 [0.10–0.26]**	**0.28 [0.17–0.44]**
3+	10.0 (75)	22.3 (134)	5.7 (17)	6.9 (19)	1.00	**4.42 [2.83–6.91]**	**0.24 [0.13–0.43]**	**0.37 [0.20–0.68]**
No DMT	0.0 (0)	0.0 (0)	4.7 (14)	19.7 (54)	–	–	–	–
MS onset year								
2007	25.8 (194)	25.5 (70)	20.5 (123)	24.3 (72)	1.00	1.00	1.00	1.00
2008	24.8 (187)	24.8 (68)	21.5 (129)	30.7 (91)	1.00	1.07 [0.76–1.51]	1.45 [0.96–2.19]	0.98 [0.62–1.56]
2009	25.4 (191)	25.9 (71)	25.8 (155)	23.3 (69)	1.00	**1.42 [1.01–1.98]**	0.98 [0.63–1.52]	1.01 [0.64–1.61]
2010	24.0 (181)	23.7 (65)	32.2 (193)	21.6 (64)	1.00	**1.87 [1.35–2.60]**	0.80 [0.51–1.26]	0.89 [0.56–1.44]

References: female; 26–35; relapsing remitting/secondary progressive multiple sclerosis, 0 comorbidity, 0–2.5 EDSS score, 0 DMT switch.
RRR: relative risk ratio; **CI**: confidence interval; **DMT**: disease-modifying therapies; **EDSS**: expanded disability status scale; statistically significant results are shown in **bold**.

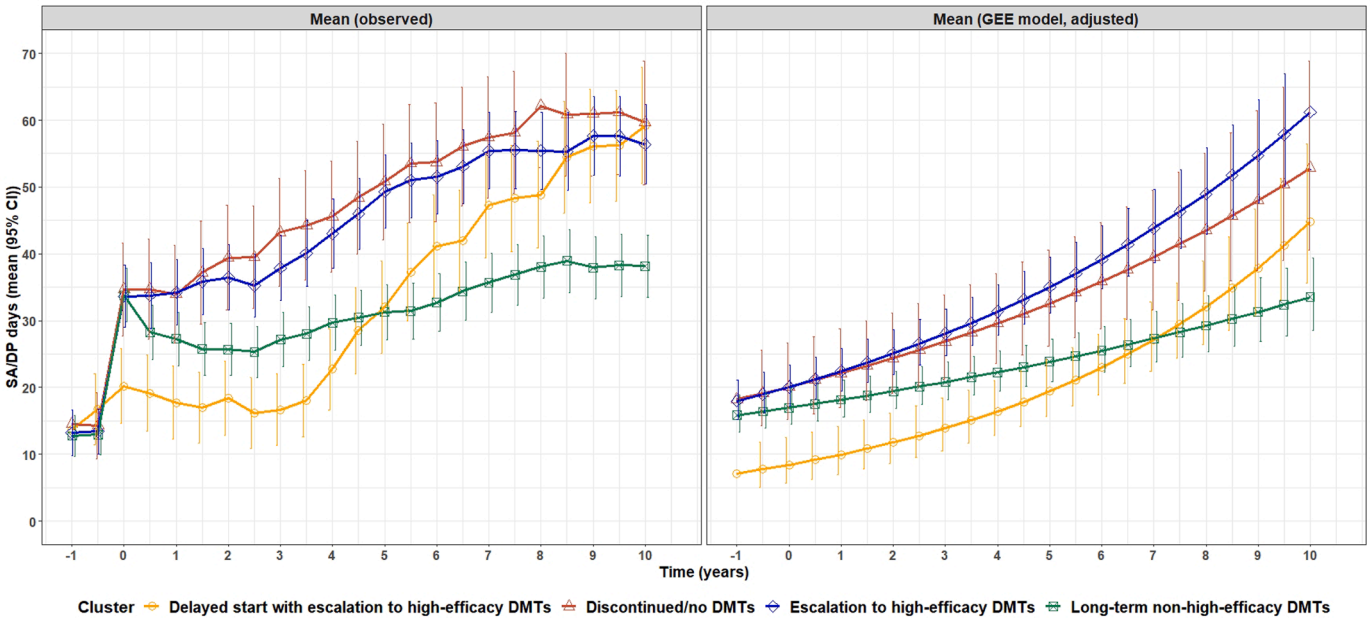

Fig. 2. Sickness absence and disability pension days per 6-month period (observed mean and adjusted mean through generalized estimating equations (GEE)) across clusters over the 10-year follow-up [DMT: disease-modifying therapy; SA/DP: sickness absence and/or disability pension; triangular shapes: observed means; circular shapes: adjusted means; the GEE models are adjusted for sex, age, multiple sclerosis (MS) type, comorbidity, expanded disability status scale score, frequency of DMT switches and MS onset year.].

Table 4
Generalized estimating equations outputs of sickness absence and disability pension by DMT clusters overtime adjusted for demographic and clinical variables.

Parameter	Adjusted (sex, age group, type of MS, comorbidity, EDSS score, number of DMT switch, MS onset year)		
	Estimate	Standard error	P-value
Intercept	2.05	0.244	**<0.0001**
Time	0.07	0.009	**<0.0001**
Cluster (Escalation to high-efficacy DMTs)	0.17	0.112	0.1331
Cluster (Delayed start with escalation to high-efficacy DMTs)	−0.70	0.220	**0.0014**
Cluster (Discontinued/no DMTs)	0.17	0.165	0.3067
Time*cluster (Escalation to high-efficacy DMTs)	0.04	0.013	**0.0012**
Time*cluster (Delayed start with escalation to high-efficacy DMTs)	0.10	0.026	**0.0002**
Time*cluster (Discontinued/no DMTs)	0.03	0.019	0.1300
Sex (Male)	−0.21	0.095	**0.0278**
Age group (18–25)	−0.37	0.118	**0.0018**
Age group (36–45)	0.32	0.095	**0.0008**
Age group (46–55)	0.62	0.127	**<0.0001**
Type of MS (primary progressive MS)	0.05	0.172	0.7495
Comorbidity index (1 to 2)	0.20	0.172	0.2342
Comorbidity index (3 to 4)	0.88	0.177	**<0.0001**
Comorbidity index (5+)	1.28	0.181	**<0.0001**
EDSS score	0.27	0.025	**<0.0001**
Frequency of DMT switch (1)	0.02	0.128	0.8534
Frequency of DMT switch (2)	0.20	0.128	0.1217
Frequency of DMT switch (3+)	0.23	0.136	0.0892
MS onset year (2008)	−0.47	0.106	**<0.0001**
MS onset year (2009)	−0.42	0.110	**0.0002**
MS onset year (2010)	−0.31	0.121	**0.0101**

DMT: disease-modifying therapy; **EDSS**: expanded disability status; **MS**: multiple sclerosis.
References: Long-term non-high-efficacy DMTs; Female; age: 26–35; relapsing-remitting + secondary progressive MS; Comorbidity index: 0; frequency of DMT switch:0; MS onset year: 2007.

3.4. Sensitivity analysis

In the sensitivity analysis performed by re-categorizing DMTs into 3 groups, adding a modest- efficacy group, 5 clusters were chosen with an added trajectory of *escalation from low to modest-efficacy DMTs* (368, 19.1%) coming mainly from *non-high-efficacy* and *escalation* clusters (Fig. S4). Cluster quality metrics showed relatively weaker cluster structures. Results of the log-multinomial regression analysis were comparable to the two-group DMT categorization (Table S4). Mean SADP days in the clusters showed similar trends to the main analysis, with an added trend among PwMS who switched to modest-efficacy DMTs which was close to those on long-term low-efficacy DMTs (Fig. S5).

An additional sensitivity analysis, excluding people with SPMS, showed similar results to the main analysis in the number of clusters identified, association of demographic and clinical characteristics to

cluster-belonging and the trends of SA/DP days in the clusters.

4. Discussion

This 10-year prospective cohort study of working-aged PwMS, with onset in 2007–2010, on average spent 4.5 years using non-high-efficacy and 2.8 years using high-efficacy DMTs. Four clusters of trajectories of DMTs were identified. Age was associated with cluster belonging. People with PPMS were more likely to be in the *delayed start* and the *discontinuation* clusters. PwMS with higher EDSS score were also less likely to be in the *non-high-efficacy* cluster. More stable trends in SADP days, with a relatively lower increase over time, were found in the *non-high-efficacy* cluster, with fewer days than other clusters about 9 years after onset. The trends in the observed mean SA/DP days across the clusters were comparable to those of the findings from the GEE models which were adjusted for demographic and clinical variables.

We used sequence analysis to identify trajectories of treatment with DMTs. Sequence analysis has become an important method in social science studies and more recently employed in life-course studies, analysis of career pathways, and health trajectories (Ritschard and Studer, 2018). It has also recently been employed in MS studies which looked into care consumption patterns in France and Canada (Roux et al., 2019; Roux et al., 2022) and the usage of DMTs in France (Leblanc et al., 2021). Our findings were similar to the study from France (Leblanc et al., 2021) despite a slightly different design (treatment initiation was a starting point in the French study while onset date in our study). Three of the groups (first and second line DMTs, and no treatment) identified in the French study were roughly comparable with our *non-high efficacy* (39.2% of the PWMS), *escalation* (31.2% of the PwMS) and *discontinuation* (15.4% of the PwMS) clusters, respectively. They had no comparable findings for the *delayed start* (14.2% of the PwMS) cluster due to the different start points in the 2 studies.

The predominant use of *non-high-efficacy DMTs* (39.2%) among PwMS could partly be attributed to the onset time 2007–2010 and that entry of most high-efficacy DMTs into market and their use in Sweden increased in the latter half of the past decade (De Angelis et al., 2018; Berntsson et al., 2018). This may also explain why early use of high-efficacy DMT was not the most prevalent cluster. A similar increase in the use of mostly high-efficacy DMTs with time has been shown by a study in Australia (Hillen et al., 2022). In relation to the substantial duration without treatment, assessment of the trajectories from MS onset rather than diagnosis time and possible treatment delay or not taking DMTs after diagnosis could have contributed. Considerable delay in MS diagnosis had been previously reported (Cárdenas-Robledo et al., 2021). However, such delays are reduced with more recent changes to the diagnostic criteria (Schwenkenbecher et al., 2019) and access to MRI. Another possible reason could be related to PwMS staying longer without or with only mild symptoms.

Older PwMS were less likely to be in the *escalation* and the *delayed start* clusters in comparison to *non-high-efficacy* cluster which was similar to the study from France (Leblanc et al., 2021). A meta-analysis of 38 randomized clinical trials showed the comparatively better efficacy of high-efficacy DMTs over non-high-efficacy ones decreased with age (Weideman et al., 2017). In addition, the increased risk of adverse events among older PwMS in relation to high-efficacy DMTs, particularly immune cell depleting agents (alemtuzumab, cladribine, ocrelizumab) was also identified (Prosperini et al., 2021; Schweitzer et al., 2019). Also, as the disease becomes less inflammatory with age (Vaughn et al., 2019), immuno-modulating effects of DMTs are not expected.

People with PPMS, compared to RRMS/SPMS, were more likely to be in the *discontinuation* and *delayed start* clusters. These 2 clusters seem to reflect the features of PPMS where there is limited options for treatment (Ciotti and Cross, 2018). Ocrelizumab, the DMT used in the treatment of PPMS entered the market only as recently as 2017 (Ciotti and Cross, 2018). Studies showed siponimod (Gaber, 2021) and cladribine (Patti et al., 2020) have very recently been used for SPMS with disease activity. The unavailability of drugs aimed at PPMS until recently could partly explain the trajectory of taking no DMTs for a long time or not taking them at all.

PwMS with higher first EDSS scores were more likely to belong to the *escalation* cluster, as would be expected by indication. Escalation could also be associated with relatively recent availability of high-efficacy DMTs in the market (De Angelis et al., 2018). In a large Italian study, higher EDSS scores were also shown among PwMS before DMTs switch and at enrolment in the study (Patti et al., 2020). The higher initial EDSS score in the *delayed start* cluster could be related to delay in diagnosis and treatment. The higher EDSS scores in PwMS who discontinued or did not take DMTs was congruent with the studies from France and Italy (Leblanc et al., 2021; Patti et al., 2020).

The relatively fewer mean SADP days among PwMS in the *non-high-efficacy* cluster towards end of follow-up could partly be related to treatment effectiveness and tolerability among PwMS in that cluster. On the contrary, the higher number of SADP days with steeper increase over time noted in *escalation* and *discontinuation* clusters could have followed worsening in disease severity leading to escalation/discontinuation. As discussed above, PwMS in these clusters were also more likely to have higher EDSS scores, which might explain more SA/DP days (Gyllensten et al., 2018; Selmaj et al., 2017). Similarly, the SADP days trend in the *delayed start* cluster could indicate delayed diagnosis or worsening condition which may have necessitated treatment initiation and subsequent escalation. Also, the higher likelihood of PwMS in this cluster to have PPMS and higher EDSS scores could relate to more SADP days, as a previous study showed substantial SADP among persons with PPMS (Gyllensten et al., 2018). In the GEE models adjusted stepwise for demographic and clinical characteristics, trends of adjusted mean SADP days were generally comparable to the trajectories shown in observed mean SADP days. PwMS in the *non-high-efficacy* cluster showed fewer mean SADP days than *escalation* cluster over the second half of the follow-up. Overall, the DMT use trajectories and the SADP days seem to reflect the underlying disease progression, considering treatment choices are determined accordingly and that SADP days follow different symptoms and stages of the disease progression.

The strengths of this study include the long follow-up period, the use of sequence analysis method and the comprehensive data employed by linking several high-quality nationwide registers. As to the limitations, one concerns the consideration of individuals grouped in one cluster as the same, overlooking possible trajectory differences. The lack of baseline EDSS data for all PwMS necessitated using the first available score, which were taken after MS onset (median lag time=1.8 years). The focus on assessing long-term trajectories with earlier MS onset years prevented the possibility to observe recent cohorts more likely to initiate on high-efficacy DMTs. Another limitation could be related to not capturing time-varying covariates which may be associated to belonging to DMT use trajectory.

5. Conclusions

This Swedish 10-year prospective cohort study of identified 4 clusters of real world DMT use among PwMS, using sequence analysis, a relatively new method in health research. Age, type of MS, and EDSS score were important variables associated with the trajectories. The study also provides information on SA/DP trends in the different DMT trajectories showing fewer mean SA/DP days among PwMS on long-term non-high-efficacy DMTs than the others towards the end of the follow-up from onset to 10 years onwards. The study documented the trajectories of treatments among PwMS and how they relate to SA/DP. It also provides useful information for further studies of the individual trajectories, specific DMTs, and how they relate to work disability.

Funding/support

The project was supported by unrestricted research grants from

Biogen. We utilized data from the REWHARD consortium, supported by the Swedish Research Council (VR Grant No.: 201700624). The design of the study, data collection, analyses, interpretations of data, and manuscript drafting were performed without involvement of the funding bodies. Biogen was given the opportunity to comment on the manuscript before submission. Open access funding provided by Karolinska Institutet.

CRediT authorship contribution statement

Fitsum Sebsibe Teni: Conceptualization, Visualization, Formal analysis, Data curation, Methodology, Writing – original draft, Writing – review & editing. **Alejandra Machado:** Conceptualization, Visualization, Formal analysis, Supervision, Data curation, Methodology, Writing – original draft, Writing – review & editing. **Chantelle Murley:** Conceptualization, Formal analysis, Methodology, Resources, Writing – review & editing. **Anna He:** Conceptualization, Formal analysis, Methodology, Resources, Writing – review & editing. **Katharina Fink:** Conceptualization, Formal analysis, Supervision, Methodology, Writing – review & editing. **Hanna Gyllensten:** Conceptualization, Formal analysis, Supervision, Methodology, Writing – review & editing. **Anna Glaser:** Conceptualization, Formal analysis, Methodology, Writing – review & editing. **Kristina Alexanderson:** Conceptualization, Funding acquisition, Formal analysis, Project administration, Methodology, Writing – review & editing. **Jan Hillert:** Conceptualization, Funding acquisition, Formal analysis, Project administration, Methodology, Writing – review & editing. **Emilie Friberg:** Conceptualization, Funding acquisition, Formal analysis, Project administration, Methodology, Supervision, Writing – review & editing.

Declaration of Competing Interest

FST: funded partly by unrestricted research grant from Biogen and Celgene/Bristol-Myers Squibb. AM: funded partly by unrestricted research grant from Biogen. CM: funded partly by unrestricted research grant from Biogen AH: declares no conflicting interests. KF: received honoraria for serving on advisory boards for Biogen, Merck, Roche and speaker's fees from Merck. HG: was employed by IQVIA; a contract research organization that performs commissioned pharmacoepidemiological studies, and therefore was collaborating with several pharmaceutical companies; previously funded partly by an unrestricted research grant from Biogen. AG: has received research support from Novartis. KA: had unrestricted research grants from Biogen. JH: received honoraria for serving on advisory boards for Biogen and Novartis and speaker's fees from Biogen, Merck-Serono, Bayer-Schering, Teva, and Sanofi-Aventis. He has served as PI for projects sponsored by, or received unrestricted research support from, Biogen, Merck-Serono, TEVA, Novartis, and Bayer-Schering. JH's MS research is also funded by the Swedish Research Council. EF: funded partly by unrestricted research grant from Biogen, and has received unrestricted research grants from Celgene/Bristol-Myers Squibb.

Acknowledgments

The authors acknowledge Emma Pettersson, a statistician at the Division of Insurance Medicine, Karolinska Institutet, for her support in the statistical analyses.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2022.104456.

References

Berntsson, S.G., Kristoffersson, A., Boström, I., Feresiadou, A., Burman, J., Landtblom, A. M., 2018. Rapidly increasing off-label use of rituximab in multiple sclerosis in Sweden - outlier or predecessor? Acta Neurol. Scand. 138, 327–331.

Brooke, H.L., Talbäck, M., Hörnblad, J., et al., 2017. The Swedish cause of death register. Eur. J. Epidemiol. 32, 765–773.

Cárdenas-Robledo, S., Lopez-Reyes, L., Arenas-Vargas, L.E., Carvajal-Parra, M.S., Guío-Sánchez, C., 2021. Delayed diagnosis of multiple sclerosis in a low prevalence country. Neurol. Res. 43, 521–527.

Chen, J., Taylor, B.V., Blizzard, L., Simpson, S., Palmer, A.J., van der Mei, I.A.F., 2018. Effects of multiple sclerosis disease-modifying therapies on employment measures using patient-reported data. J. Neurol. Neurosurg. Psychiatry 89, 1200–1207.

Ciotti, J.R., Cross, A.H., 2018. Disease-modifying treatment in progressive multiple sclerosis. Curr. Treat. Options Neurol. 20, 12.

De Angelis, F., John, N.A., Brownlee, W.J., 2018. Disease-modifying therapies for multiple sclerosis. BMJ 363, k4674. British Medical Journal Publishing Group.

Filippi, M., Bar-Or, A., Piehl, F., et al., 2018. Multiple sclerosis. Nat. Rev. Dis. Prim. 4, 1–27.

Gaber, T., 2021. Siponimod for active secondary progressive multiple sclerosis. Prog. Neurol. Psychiatry 25, 4–5.

Giovannoni, G., 2018. Disease-modifying treatments for early and advanced multiple sclerosis: a new treatment paradigm. Curr. Opin. Neurol. 31, 233–243.

Gyllensten, H., Wiberg, M., Alexanderson, K., Hillert, J., Tinghög, P., 2016. How does work disability of patients with MS develop before and after diagnosis? A nationwide cohort study with a reference group. BMJ Open 6, e012731. British Medical Journal Publishing Group.

Gyllensten, H., Kavaliunas, A., Alexanderson, K., Hillert, J., Tinghög, P., Friberg, E., 2018. Costs and quality of life by disability among people with multiple sclerosis: a register-based study in Sweden. Mult. Scler. J. Exp. Transl. Clin. 4, 2055217318783352.

Hauser, S.L., Cree, B.A.C., 2020. Treatment of multiple sclerosis: a review. Am. J. Med. 133, 1380–1390 e2.

He, A., Merkel, B., Brown, J.W.L., et al., 2020. Timing of high-efficacy therapy for multiple sclerosis: a retrospective observational cohort study. Lancet Neurol. 19, 307–316.

Hillen, J., Ward, M., Slee, M., et al., 2022. Utilisation of disease modifying treatment and diversity of treatment pathways in relapsing remitting multiple sclerosis. Mult. Scler. Relat. Disord. 57, 103412.

Hillert, J., Stawiarz, L., 2015. The Swedish MS registry – clinical support tool and scientific resource. Acta Neurol. Scand. 132, 11–19.

Jones N., Napier C.A., Baneke P., Bastin G., Chandraratna D., Paterson S. Global M.S. Employment Report 2016 [online]. MS International Federation; 2016. Accessed at: https://www.msif.org/wp-content/uploads/2016/05/Global-MS-Employment-Report-2016.pdf.

Kalincik, T., Brown, J.W.L., Robertson, N., et al., 2017. Treatment effectiveness of alemtuzumab compared with natalizumab, fingolimod, and interferon beta in relapsing-remitting multiple sclerosis: a cohort study. Lancet Neurol. 16, 271–281.

Kavaliunas, A., Manouchehrinia, A., Gyllensten, H., Alexanderson, K., Hillert, J., 2020. Importance of early treatment decisions on future income of multiple sclerosis patients. Mult. Scler. J. Exp. Transl. Clin. 6, 2055217320959116. SAGE Publications Ltd.

Läkemedelsfakta [online]. Swedish medical products agency. Accessed at: https://www.lakemedelsverket.se/sv/sok-lakemedelsfakta?activeTab=1. Accessed December 14, 2021.

Leblanc, S., Roux, J., Tillaut, H., Le Page, E., Leray, E, 2021. Disease-modifying therapy usage in patients with multiple sclerosis in France: a 6-year population-based study. Rev. Neurol. 177, 1250–1261 (Paris).

Li, H., Hu, F., Zhang, Y., Li, K., 2020. Comparative efficacy and acceptability of disease-modifying therapies in patients with relapsing–remitting multiple sclerosis: a systematic review and network meta-analysis. J. Neurol. 267, 3489–3498.

Lu, C.Y., Barratt, J., Vitry, A., Roughead, E., 2011. Charlson and Rx-Risk comorbidity indices were predictive of mortality in the Australian health care setting. J. Clin. Epidemiol. 64, 223–228.

Ludvigsson, J.F., Svedberg, P., Olén, O., Bruze, G., Neovius, M., 2019. The longitudinal integrated database for health insurance and labour market studies (LISA) and its use in medical research. Eur. J. Epidemiol. 34, 423–437.

Österlund N. MiDAS, 2011. Sjukpenning och rehabiliteringspenning version 1.02 (in Swedish) [MiDAS: sickness benefit and rehabilitation allowance] [online]. Swedish Soc. Insur. Agency. Accessed at. https://www.forsakringskassan.se/wps/wcm/connect/f1e0dce5-e310-4d6d-8076-d4493534c10b/MiDAS_Sjukpenning_och_rehabiliteringspenning_Version_1_02.pdf?MOD=AJPERES. Accessed May 4, 2022.

Mikolai, J., Lyons-Amos, M., 2017. Longitudinal methods for life course research: a comparison of sequence analysis, latent class growth models, and multi-state event history models for studying partnership transitions. Longit. Life Course Stud. 8, 191–208.

Murley, C., Tinghög, P., Karampampa, K., Hillert, J., Alexanderson, K., Friberg, E., 2020. Types of working-life sequences among people recently diagnosed with multiple sclerosis in Sweden: a nationwide register-based cohort study. BMJ. Open 10, e039228. British Medical Journal Publishing Group.

Patti, F., Chisari, C.G., D'Amico, E., et al., 2020. Clinical and patient determinants of changing therapy in relapsing-remitting multiple sclerosis (SWITCH study). Mult. Scler. Relat. Disord. 42, 102124.

Pearson, J.F., Alla, S., Clarke, G., et al., 2017. Multiple sclerosis impact on employment and income in New Zealand. Acta Neurol. Scand. 136, 223–232.

Pratt, N.L., Kerr, M., Barratt, J.D., et al., 2018. The validity of the Rx-Risk comorbidity index using medicines mapped to the anatomical therapeutic chemical (ATC) classification system. BMJ. Open 8, e021122. British Medical Journal Publishing Group.

Prosperini, L., Haggiag, S., Tortorella, C., Galgani, S., Gasperini, C., 2021. Age-related adverse events of disease-modifying treatments for multiple sclerosis: a meta-regression. Mult. Scler. 27, 1391–1402. SAGE Publications Ltd STM.

Ritschard, G., Studer, M., Ritschard, G., Studer, M., 2018. Sequence analysis: where are we, where are we going? Sequence Analysis and Related Approaches: Innovative Methods and Applications. Springer International Publishing, Cham, pp. 1–11. https://doi.org/10.1007/978-3-319-95420-2_1 [online]Accessed atAccessed April 22, 2021.

Robertson, D., Moreo, N., 2016. Disease-modifying therapies in multiple sclerosis: overview and treatment considerations. Fed. Pract. 33, 28–34.

Roux, J., Grimaud, O., Leray, E., 2019. Use of state sequence analysis for care pathway analysis: the example of multiple sclerosis. Stat. Methods Med. Res. 28, 1651–1663. SAGE Publications Ltd STM.

Roux, J., Kingwell, E., Zhu, F., Tremlett, H., Leray, E., 2022. Care consumption of people with multiple sclerosis: a multichannel sequence analysis in a population-based setting in British Columbia, Canada. Mult. Scler. 28, 309–322. SAGE Publications Ltd STM.

Samjoo, I.A., Worthington, E., Drudge, C., et al., 2021. Efficacy classification of modern therapies in multiple sclerosis. J. Comp. Eff. Res. Futur. Med. 10, 495–507.

Schweitzer, F., Laurent, S., Fink, G.R., et al., 2019. Age and the risks of high-efficacy disease modifying drugs in multiple sclerosis. Curr. Opin. Neurol. 32, 305–312.

Schwenkenbecher, P., Wurster, U., Konen, F.F., et al., 2019. Impact of the McDonald criteria 2017 on early diagnosis of relapsing-remitting multiple sclerosis. Front. Neurol. 10, 1–10.

Scolding, N., Barnes, D., Cader, S., et al., 2015. Association of British neurologists: revised (2015) guidelines for prescribing disease-modifying treatments in multiple sclerosis. Pract. Neurol. 15, 273–279. BMJ Publishing Group Ltd.

Selmaj, K., Kobelt, G., Berg, J., Orlewska, E., Capsa, D., Dalén, J., 2017. New insights into the burden and costs of multiple sclerosis in Europe: results for Poland. Mult. Scler. 23, 130–142. SAGE Publications Ltd STM.

Sorensen, P.S., 2017. Safety concerns and risk management of multiple sclerosis therapies. Acta Neurol. Scand. 136, 168–186.

Spelman, T., Magyari, M., Piehl, F., et al., 2021. Treatment Escalation vs Immediate Initiation of highly effective treatment for patients with relapsing-remitting multiple sclerosis: data from 2 different national strategies. JAMA Neurol. 78, 1197–1204.

The Swedish Cancer Register [online]. Socialstyrelsen 2019. Accessed at: https://www.socialstyrelsen.se/en/statistics-and-data/registers/register-information/swedish-cancer-register/. Accessed October 28, 2021.

The Swedish Prescribed Drug Register [online]. Socialstyrelsen 2020. Accessed at: https://www.socialstyrelsen.se/en/statistics-and-data/registers/register-information/the-swedish-prescribed-drug-register/. Accessed October 28, 2021.

Tinghög, P., Hillert, J., Kjeldgård, L., Wiberg, M., Glaser, A., Alexanderson, K., 2013. High prevalence of sickness absence and disability pension among multiple sclerosis patients: a nationwide population-based study. Mult. Scler. 19, 1923–1930. SAGE Publications Ltd STM.

Vaughn, C.B., Jakimovski, D., Kavak, K.S., et al., 2019. Epidemiology and treatment of multiple sclerosis in elderly populations. Nat. Rev. Neurol. 15, 329–342.

Weideman, A.M., Tapia-Maltos, M.A., Johnson, K., Greenwood, M., Bielekova, B, 2017. Meta-analysis of the age-dependent efficacy of multiple sclerosis treatments. Front. Neurol. 8, 577.

Wiberg, M., Friberg, E., Stenbeck, M., et al., 2015. Sources and level of income among individuals with multiple sclerosis compared to the general population: a nationwide population-based study. Mult. Scler. 21, 1730–1741.

Wickström, A., Dahle, C., Vrethem, M., Svenningsson, A., 2014. Reduced sick leave in multiple sclerosis after one year of natalizumab treatment. A prospective ad hoc analysis of the TYNERGY trial. Mult. Scler. 20, 1095–1101. SAGE Publications Ltd STM.

Wickström, A., Sundström, P., Wickström, L., Dahle, C., Vrethem, M., Svenningsson, A., 2015. Improved working ability in a contemporary MS population compared with a historic non-treated MS population in the same geographic area of Sweden. Mult. Scler. J. Exp. Transl. Clin. 1, 2055217315608203.