THERAPEUTIC ADVANCES in
Neurological Disorders

Original Research

Disease-modifying therapy initiation patterns in multiple sclerosis in three large MS populations

Ther Adv Neurol Disord

2024, Vol. 17: 1–18

DOI: 10.1177/17562864241233044

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Abstract

Background: Treatment guidelines recommend early disease-modifying therapy (DMT) initiation after diagnosis of multiple sclerosis (MS). Multinational comparative studies that assess time to DMT initiation in MS may allow detection of barriers inherent to healthcare systems to explain potential adverse systematic delays in commencing DMTs.

Objectives: To investigate and compare the time to first DMT and its association with sociodemographic and clinical variables after MS diagnosis in three large MS registries.

Design: This observational study was conducted using data from the German MS Registry (GMSR), the North American Research Committee on MS Registry (NARCOMS, US data only), and the United Kingdom MS Registry (UKMSR, both self- and clinician-reported).

Methods: Data from relapsing people with MS (PwMS), with a diagnosis of MS between 2014 and 2019, and available DMT and disability status were pooled using a meta-analytic approach.

Results: A total of 5395 PwMS were included in the analysis (GMSR: $n = 2658$; NARCOMS: $n = 447$; UKMSR: $n = 2290$). Kaplan–Meier estimates for the time to first DMT [median months (95% CI)] were 2.0 (1.9–2.0), 3.0 (2–4), and 9.0 (7.7–10.6) for GMSR, NARCOMS, and UKMSR, respectively. Pooled multivariable Cox regression demonstrated shorter time to first DMT for PwMS diagnosed after 2017 [1.65 (1.42–1.92), $p < 0.01$], and longer time to DMT when a higher-efficacy DMT was selected (0.69 (0.54–0.90), $p < 0.0001$].

Conclusion: Time to DMT initiation differs across the populations studied, indicating that barriers may exist in early access to DMT, particularly in the United Kingdom. However, a consistent decrease in time to DMT initiation was noted since 2017 across all registries. Further studies are warranted comparing the effects of time to DMT and time to higher-efficacy DMT on long-term outcome.

Keywords: disease-modifying therapy, healthcare, multiple sclerosis, therapy initiation

Received: 15 May 2023; revised manuscript accepted: 29 January 2024.

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Introduction

Disease-modifying therapy (DMT) for multiple sclerosis (MS) aim to modulate or selectively suppress the immune system to slow down or stop injury to the central nervous system (CNS) driving relapses and disability progression.[1] The number of DMTs available has grown over time with a steep increase since 2013,[2,3] predominantly for people with MS (PwMS) with relapsing forms (RMS). Studies in PwMS following the first clinical episode suggestive of an inflammatory demyelinating event in the CNS, also termed clinically isolated syndrome, and retrospective real-world data suggest that early DMT initiation may have beneficial long-term effects.[2,4,5] Furthermore, early application of DMT with higher efficacy, for example, within the first 2 years of diagnosis, may result in positive effects on disability progression,

supporting a 'hit hard and early' concept favored by a growing number of MS clinicians.[6–8]

Consensus guidelines from the European Academy of Neurology (EAN) and the European Committee for Treatment and Research in MS (ECTRIMS)[9] recommend the early introduction of DMT. Additionally, the case definition for MS has been repeatedly revised resulting in shorter times from initial symptoms to clinical diagnosis, facilitating earlier DMT initiation.[10,11] However, in clinical practice, barriers (e.g. related to healthcare systems or with regard to dissemination of knowledge) might exist that hamper early DMT initiation, despite the recommendations and the evolution of MS diagnostic criteria described above.

Thus, we investigated and compared the time to first DMT and its association with sociodemographic and other clinical patient characteristics after MS diagnosis in three large MS registries.

Materials and methods

MS registries and healthcare systems

This observational study was conducted using data from voluntary MS registries spanning three different healthcare systems, including the German MS Registry (GMSR),[12] the North American Research Committee on MS Registry (NARCOMS),[13] and the United Kingdom MS Registry (UKMSR).[14]

The total number of PwMS in Germany is estimated to be at around 280,000.[15] Since its inception in 2001, the GMSR has collected data on more than 80,000 PwMS in Germany, thus covering around 29% of the total estimated patient population. Data for the GMSR, including data on diagnosis of MS according to the MS diagnostic criteria, are provided by clinical MS centers (members of the medical staff) *via* a web-based electronic data capture system.[12] The GMSR represents the German healthcare system and includes patients covered by statutory health insurance (SHI covers ~87% of the German general population), private health insurance, and other reimbursements. In insured people, the SHI reimburses the cost of all DMT approved for the respective indication. In eligible individual cases, the costs of drugs used as off-label therapy will also be reimbursed.[16]

In the United States, the number of PwMS has been estimated based on claims data at approximately 914,000.[15] The NARCOMS Registry has since 1996 captured data on more than 42,000 PwMS, covering around 5% of the total estimated patient population. The NARCOMS Registry is based on self-reports of PwMS and is heterogeneous with respect to demographic and clinical characteristics, location of MS care, and insurance coverage of DMT.[13] For this analysis, only data of NARCOMS-participants residing in the United States were included. The US health system is made up of multiple types of coverage including public, private, for profit and nonprofit insurers, and healthcare providers. The estimated uninsured rate is 8.5% of the population in the United States.[17] Within the study population less than 8% of participants were uninsured. A healthcare provider can prescribe DMT, but the cost of the DMT vary by insurance type and availability of patient assistance programs.

In the United Kingdom, the number of PwMS is estimated to be about 134,000.[15] The UKMSR since 2011 has captured data on more than 42,000 PwMS (web: 26,000; clinical: 16,000), thus covering around 31% of the total estimated patient population. Data have been collected directly from PwMS *via* web (portal data) and from treating clinicians in MS specialist treatment centers (clinical data). For this study, data were analyzed from the core dataset collected at both UKMSR-clinical (by clinical team) and UKMSR-web (patient-reported). In addition, there are data that are only collected at UKMSR-web but not at UKMSR-clinical, for example, EQ-5D or Fatigue Severity Scale. The comparison and validation (e.g. of MS diagnoses) of the two data sources is described in detail in the article by Middleton *et al.*[14] The UKMSR includes PwMS eligible for treatment through the National Health Service (NHS) approved by the National Institute of Clinical Excellence (NICE). Treatments are free at the point of delivery but can only be prescribed at specialist NHS treatment centers by Consultant Neurologists. Treatment audit guidelines are strict, with treatment only being dispensed in line with NICE guidance for particular disease forms with Expanded Disability Status Scale (EDSS) scores in a set range. If treatment is given outside of these parameters, then centrally funded drug costs are not refunded by NHS England to the treating center.

Further information on the technical infrastructure and data acquisition of the registries have been previously published in articles by Ohle *et al.* (GMSR),[12] Marrie *et al.* (NARCOMS),[13] Jones *et al* (UKMSR),[18] and Middleton *et al.* (UKMSR).[14]

Classification of DMTs

For this study, we divided DMTs into two groups. Higher-efficacy DMT included alemtuzumab, cladribine, daclizumab, fingolimod, mitoxantrone, natalizumab, ocrelizumab, and rituximab. Lower-efficacy DMT included azathioprine, dimethyl fumarate, glatiramer acetate, (peg-) interferon beta-1a/1b, and teriflunomide.

Data harmonization

Following the Maelstrom guidelines,[19] representatives from each registry formed a working group, who met virtually to develop a protocol. Data management and quality measures were conducted at registry level. Aggregated results based on the data elicited in the protocol were then shared and analyzed across registries. The feasibility of this type of data harmonization was demonstrated in a methodological article by Salter *et al.*[20]

For harmonization purposes, a fixed set of variables was selected following reviews of design, questionnaire format, and the data dictionary for each registry, ensuring all variables required for the analysis would be consistent across registries. Furthermore, the protocol included specific details regarding variable stratification, mapping variables between cohorts and statistical methods.

Because data collection started at different timepoints for the registries, we identified a common date for study inclusion (2014), partly due to data availability. NARCOMS began enrolling participants in 1996. However, the GMSR only included data from the new infrastructure launched in 2014 and the UKMSR from 2011.

Study population

Each registry selected participants with RMS diagnosed during 2014–2019 with available data on onset date, DMT use or treatment-naïve, and disability status. PwMS are required to be 18 years of age at time of informed consent although DMT could have been initiated before the age of 18 years. Each registry had additional specific inclusion criteria for the purpose of this study.

The GMSR included PwMS with a clinic visit between 2014 and 2019 and relapsing-remitting disease course (RRMS) during the corresponding visit. Patients with primary or secondary progressive MS as diagnosed by the treating physician were excluded from this analysis. Data on previous DMT can be captured. Data used for the analysis were captured through a standardized electronic case report form or *via* prespecified interfaces.[12]

NARCOMS included RMS patients, resident in the United States, who completed a semi-annual update survey after the enrollment. Patients with progressive MS were excluded. RMS was self-determined by the participant reporting relapses in their enrollment or semi-annual update surveys. In a large proportion of >98% of participants diagnoses were confirmed based on records review, physician survey, or telephone interview.[21]

UKMSR selected participants with RRMS diagnosis and at least one clinical visit between 2014 and 2019. The UKMSR collects patient-reported outcome data *via* a web portal (UKMSR-web) as well as clinical data from more than 45 NHS sites (UKMSR-clinical). Most sites use the UKMSR electronic case report form that is secure, accessible from within the NHS, and incorporates standard validation rules. RRMS was determined at the date of diagnosis by a neurologist and recorded by the clinical practitioner at the corresponding practice visit.

Time to first DMT use

We calculated time to first DMT by using date of diagnosis and start time of first recorded DMT. In both date cases, day, month, and year were considered. If day was missing, then the calculation was made from the 15th of the month. If no DMT use was reported for the available data (until the end of the follow-up), then the participant was censored at the date of the last update (either the last visit recorded or the last follow-up questionnaire).

Covariates

Across all registries, covariates were grouped as follows: age at diagnosis (17–30, 31–40, 41–50, 51–60, ⩾61 years), year of diagnosis (2014–2016, 2017–2019), time to diagnosis (0–5, 6–10, 11–15, >15 years), sex (males, females), type of DMT, and comorbidities (no comorbidity or at least one comorbidity) (Table 1). Within the GMSR, comorbidities are collected as ICD-10 codes entered by the treating centers participating in the pharmacovigilance module of the GMSR,[12] at the time of data export covering 18.7% of the GMSR population analyzed. NARCOMS-participants report their comorbidity status (presence/absence) using the following validated question format: 'Has a doctor ever told you that you have. . .?' and, if present, the year of diagnosis.[22] In the UKMSR, participants are given an explanation of other illnesses they may have and are asked if they have no other medical conditions but MS. If the UK patients report the presence of comorbidities, they are given help in specifying comorbidities, based on the work by Marrie *et al*.[23] For education, all categories were mapped to the international standard classification of education 2011, and levels were adopted as previously described.[20] Disability measures were recorded differently between registries. The GMSR uses the EDSS, NARCOMS uses Patient-Determined Disease Steps (PDDS), and UKMSR uses either EDSS (clinical sites) or a webEDSS.[24] The EDSS is an eight-domain, physician-scored assessment of disability.[25] Mobility milestones are linked with EDSS scores of at least 4. The PDDS and EDSS are strongly correlated.[26] We categorized disability as mild, moderate, or severe. Mild disability was defined as an EDSS score of 0.0–2.5, moderate disability as 3.0–5.5, and severe disability as ⩾6.0. The PDDS levels were mapped to mild (0–1), moderate (2–4), and severe (5–8) categories using PDDS levels that corresponded to specific EDSS levels.

Data processing and analysis

To adhere to the ethical and legal standards of each registry, a template was formed to combine summary level results separately; the individual-level data were not shared. Harmonization quality was evaluated by the comparison of descriptive statistics for each of the covariates listed above (see Table 1). Descriptive statistics included mean and standard deviation (SD)/median and quantiles when appropriate for the continuous variables and frequency/percentages for the categorical variables of the study population. The median (25%, 75% quantile) time to the first DMT use was estimated using the Kaplan–Meier method (Table 2). For univariable and multivariable analyses on covariates, Cox proportional hazards regression models with DMT initiation as event were performed. Hazard ratios (HRs) and 95% confidence intervals (CIs) are reported. Data regarding comorbidities at diagnosis were only available for NARCOMS and sparsely available in UKMSR-web and GMSR data. Therefore, this covariate was not considered in the multivariable models. As the education level was not captured in the UK clinical sites, this variable was also not considered in the multivariable model.

To account for potential differences within the higher-efficacy DMT group, we conducted a complementary analysis investigating the time to the first DMT for PwMS treated with higher-efficacy DMT without fingolimod and the fingolimod-treated PwMS as a separate group within the GMSR.

A meta-analytic approach was taken to produce pooled overall and factor-specific estimates since HRs and CIs were reported for each registry. Random effect models were utilized to compute pooled estimates using restricted maximum likelihood for estimating variances to account for data sources being possibly heterogeneous.[27] Heterogeneity of the pooled estimates was assessed using the I^2 quantity with values <30% considered as mild and >50% as substantial.[28]

Analysis for GMSR and UKMSR was conducted in R 4.0 (R Foundation for Statistical Computing, Vienna, Austria) including the packages 'survival 3.2-10' for time-to-event analyses and 'metafor v3.0-2' for meta-analyses. NARCOMS conducted analyses in SAS v9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Cohort comparability

Comparisons of the demographic and clinical characteristics of the participants in all three registries included in the analysis (GMSR $n=2658$, NARCOMS $n=447$, UKMSR-web $n=1143$, UKMSR-clinical $n=1147$) are presented in Table 1. Greater similarities were identified between the

Table 1. Characteristics of registry participants included in the analysis.

Variables	GMSR (*n* = 2658)		NARCOMS (*n* = 447)		UKMSR-clinical (*n* = 1147)		UKMSR-web (*n* = 1143)	
Female, *n* (%)	1909	71.8%	360	80.5%	846	73.8%	925	80.9%
Age at onset (years), mean (±SD)	33.7	±10.8	32.8	±11.4	35.5	±10.6	35.1	±9.9
Time from first MS symptom to diagnosis (months), mean (±SD)	24.5	±49.3	90.3	±93.2	48.4	±70.0	45.7	±68.0
Time from first MS symptom to diagnosis (months), median (Q25, 75)	3.0	(0.2, 24.0)	60.0	(24.0, 132.0)	19.0	(7.1, 60.0)	17.0	(6.1, 57.0)
Age at diagnosis (years), mean (±SD)	35.7	±11.1	40.3	±11.2	39.6	±11.1	38.9	±9.9
Year of diagnosis, mean (±SD)	Sep 2016	1.6	May 2015	1.6	Oct 2016	1.6	Sep 2016	1.7
Year of diagnosis, *n* (%)								
2014–2016	1536	57.8%	335	74.9%	599	52.2%	642	56.2%
2017–2019	1122	42.2%	112	25.1%	548	47.8%	501	43.8%
Time to registry enrollment (years), mean (±SD)	1.4	±1.4	1.6	±1.3	1.6	±1.3	1.6	±1.4
Disability status (closest to diagnosis), *n* (%)								
Mild	2453	92.3%	232	53.6%	419	72.0%	256	35.1%
Moderate	202	7.6%	171	39.5%	111	19.1%	327	44.9%
Severe	3	0.1%	30	6.9%	52	8.9%	146	20.0%
Missing	0	N/A	14	N/A	565	N/A	414	N/A
Comorbidity status, *n* (%)								
No comorbidity	234	46.9%	125	28.0%	N/A	N/A	85	14.0%
⩾1 comorbidity	265	53.1%	322	72.0%	N/A	N/A	520	86.0%
Missing	2159	N/A	0	N/A	1147	N/A	538	N/A
Education level								
Secondary or less	179	8.5%	84	25.5%	N/A	N/A	145	15.2%
Higher education (technical or associates)	1424	67.2%	63	19.1%	N/A	N/A	293	30.8%
Higher education (university)	514	24.3%	183	55.5%	N/A	N/A	515	54.0%
Missing	541	N/A	117	N/A	1147	N/A	190	N/A
Care setting, *n* (%)								
Academic center	405	15.2%	110	36.2%	373	32.5%	689	69.0%
Non-academic center	2253	84.8%	194	63.8%	774	67.5%	310	31.0%
Missing	0	N/A	143	N/A	0	N/A	144	N/A

(Continued)

Table 1. (Continued)

Variables	GMSR (*n* = 2658)		NARCOMS (*n* = 447)		UKMSR-clinical (*n* = 1147)		UKMSR-web (*n* = 1143)	
Started DMT, n (%)								
Yes	2318	87.2%	363	81.2%	682	59.5%	994	87.0%
No	340	12.8%	84	18.8%	465	40.5%	149	13.0%
Type of first DMT, *n* (%)								
Lower-efficacy therapies	1862	69.3%	286	79.4%	466	68.3%	670	67.4%
Azathioprine	1	0.0%	0	0.0%	0	0.0%	0	0.0%
Dimethyl fumarate	511	19.2%	88	19.7%	272	23.7%	387	33.9%
Glatiramer acetate	562	21.1%	125	28.0%	80	7.0%	147	12.9%
Interferon beta (-1a/-1b/peg-)	572	21.5%	50	11.2%	90	7.9%	112	9.8%
Teriflunomide	216	8.1%	23	5.2%	24	2.1%	24	2.1%
Higher-efficacy therapies	456	17.0%	74	20.6%	216	31.7%	324	32.6%
Alemtuzumab	45	1.7%	0	0.0%	79	6.9%	76	6.7%
Cladribine	27	1.0%	0	0.0%	10	0.9%	38	3.3%
Daclizumab	26	1.0%	0	0.0%	0	0.0%	0	0.0%
Fingolimod	130	4.9%	22	4.9%	8	0.7%	27	2.4%
Mitoxantrone	3	0.1%	0	0.0%	1	0.1%	0	0.0%
Natalizumab	125	4.7%	22	4.9%	83	7.2%	104	9.1%
Ocrelizumab	92	3.5%	21	4.7%	34	3.0%	79	6.9%
Rituximab	8	0.3%	9	2.0%	1	0.1%	0	0.0%
Other therapeutics (e.g. special situations)								
Multiple	0	N/A	3	0.7%	0	N/A	0	N/A

DMT, disease-modifying therapy; GMSR, German MS Registry; MS, multiple sclerosis; *n*, number of patients; N/A, not applicable; NARCOMS, North American Research Committee on MS; Q25, 75, 25% and 75% quantiles; SD, standard deviation; UK, United Kingdom; UKMSR, United Kingdom MS Registry; %, proportion of patients.

two patient-reported data sources (NARCOMS and UKMSR-web), and between the two clinical data sources (GMSR and UKMSR-clinical), especially with respect to the proportion of females and the age at MS symptom onset.

The mean time to registry enrollment, measured from the date of diagnosis, was comparable in all four data sources (range: 1.45–1.61 years). The mean year of diagnosis was comparable between the UKMSR (both data sources) and the GMSR (August 2016 *versus* October 2016) whereas in NARCOMS participants, the mean year of diagnosis was around 1 year earlier (March 2015). Median time to diagnosis differed between the data sources (GMSR: 3 months | UKMSR-clinical: 19 months | UKMSR-web: 17 months | NARCOMS: 60 months). Cohorts differed regarding the percentage of mild (GMSR 92.3% *versus* NARCOMS 53.6% *versus*

Table 2. (Kaplan–Meier) median (95% CI) time to first DMT use (in months), stratified by the data sources.

Variables	GMSR (*n* = 2658)		NARCOMS (*n* = 447)		UKMSR-clinical (*n* = 1147)		UKMSR-web (*n* = 1143)	
Overall	2.0	1.9–2.0	3	2–4	9.0	7.7–10.6	7.1	6.2–7.9
Sex								
Female	2.0	1.9–2.1	3	2–5	9.2	8.0–11.7	7.2	6.3–8.2
Male	2.0	1.7–2.3	2	2–4	7.7	6.0–10.2	6.1	5.0–9.0
Care setting								
Academic	2.5	2.0–3.0	4	2–8	10.2	7.0–12.0	8.1	7.2–9.7
Other	1.9	1.8–2.0	3	2–6	8.6	7.1–10.2	7.0	5.7–9.6
Missing	N/A	N/A	2	2–4	N/A	N/A	4.0	3.4–5.2
Age at diagnosis (years)								
17–30	1.8	1.6–2.0	2	1–3	6.5	5.4–9.0	6.0	5.0–7.6
31–40	2.0	1.8–2.6	3	2–6	8.4	6.7–12.0	7.0	5.8–8.9
41–50	2.0	1.9–2.6	3	2–6	8.2	6.3–11.0	7.2	5.9–9.2
51–60	2.5	2.0–3.6	5	2–12	18.7	9.5–N/A	10.2	7.1–15.3
⩾61	4.7	2.2–20.5	4	2–30	40.3	40.3–N/A	4.0	2.3–N/A
Time from first MS symptom to diagnosis (years)								
0–5	1.9	1.8–2.0	2	2–4	7.0	6.1–8.1	6.2	5.5–7.1
6–10	2.7	2.2–3.8	3	2–6	13.0	9.0–20.0	11.0	8.7–15.1
11–15	3.0	2.0–5.4	3	2–4	22.0	9.5–N/A	9.2	6.0–18.0
>15	3.0	1.9–8.4	5	2–15	N/A	N/A	12.1	6.0–29.0
Year of diagnosis								
2014–2016	2.0	1.9–2.5	3	3–5	11.3	9.2–13.7	8.2	7.2–10.0
2017–2019	1.9	1.8–2.0	2	2–3	6.5	5.9–8.1	5.7	5.0–7.0
Disability status (closest to diagnosis)								
Mild	2.0	1.8–2.0	2	2–3	6.1	5.4–7.7	6.0	5.3–8.3
Moderate	3.1	2.4–5.0	5	2–8	8.1	5.2–12.0	7.0	5.4–8.4
Severe	3.2	0.4–N/A	4	2–12	13.0	6.0–N/A	15.8	11.5–19.2
Missing	N/A	N/A	60	2–64	13.0	10.2–18.7	6.7	5.8–7.8
Comorbidity status								
No comorbidities	2.6	2.0–3.0	2	2–3	N/A	N/A	7.5	5.0–12.9

(Continued)

Table 2. (Continued)

Variables	GMSR (*n* = 2658)		NARCOMS (*n* = 447)		UKMSR-clinical (*n* = 1147)		UKMSR-web (*n* = 1143)	
⩾1 comorbidity	2.5	1.9–3.1	3	2–6	N/A	N/A	7.6	6.1–9.0
Missing	1.9	1.8–2.0	N/A	N/A	N/A	N/A	6.9	5.9–7.7
Education level								
Secondary or less	2.0	1.7–2.8	4	2–14	N/A	N/A	8.0	5.6–13.0
Higher education (technical or associates)	1.9	1.6–2.0	8	3–15	N/A	N/A	8.1	6.8–12.0
Higher education (university)	2.0	1.9–2.7	3	2–5	N/A	N/A	6.1	5.6–7.3
Missing	2.2	2.0–3.0	2	2–3	N/A	N/A	7.5	5.6–8.7
Type of DMT								
Lower-efficacy therapies	1.2	1.1–1.4	2	N/A	4.0	3.5–4.4	4.7	4.2–5.2
Higher-efficacy therapies	4.0	3.3–4.7	3	2–4	4.8	4.0–5.4	8.0	7.2–9.5
Other/special situations	N/A	N/A	6	1–9	N/A	N/A	N/A	N/A

CI, confidence interval; DMT, disease-modifying therapy; GMSR, German Multiple Sclerosis Registry; MS, multiple sclerosis; *n*, number of patients; N/A, not applicable (if there were no patients in the respective category); NARCOMS, North American Research Committee on MS; UK, United Kingdom; UKMSR, United Kingdom MS Registry.

UKMSR-clinical 72% *versus* UKMSR-web 35.1%; $p < 0.0001$), moderate (GMSR 7.6% *versus* NARCOMS 39.5% *versus* UKMSR-clinical 19.1% *versus* UKMSR-web 44.9%; $p < 0.0001$), and severely (GMSR 0.1% *versus* NARCOMS 6.9% *versus* UKMSR-clinical 8.9% *versus* UKMSR-web 20%; $p < 0.0001$) disabled PwMS at diagnosis.

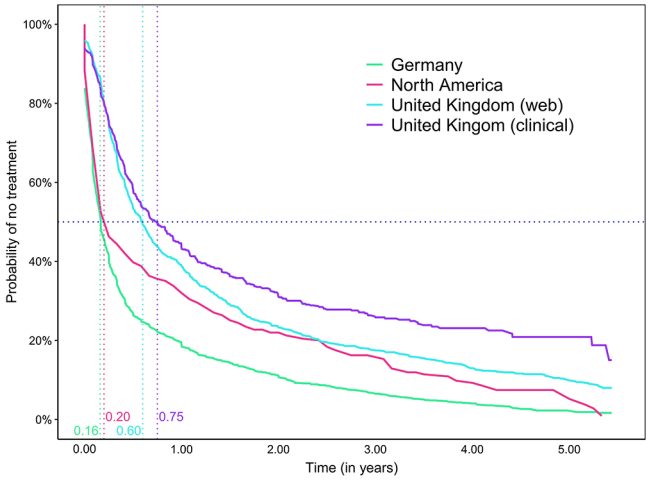
Time to DMT initiation

Figure 1 presents the Kaplan–Meier curves for time to DMT initiation in each data source. Within 9 months of diagnosis, more than 50% of the patients had initiated a DMT. However, there were differences between the cohorts: In GMSR, the median time for initiating a DMT was the shortest [2.0 (1.9–2.0) months], longer in the NARCOMS population [3 (2–4) months; $p = 0.02$ compared to GMSR] and was longest in the UK-clinical and UK-web populations [9.0 (7.7–10.6) and 7.1 (6.2–7.9) months (global p value <0.001), respectively, Table 2].

Association between the time to first DMT and patient characteristics

Findings from a Cox-regression model using a univariable approach for each data source are shown in Table 3. A shorter time to first DMT was associated with younger age (NARCOMS, UKMSR-clinical/web, GMSR), lower disability level (UKMSR-clinical/web, GMSR), shorter time to MS diagnosis (UKMSR-clinical/web, GMSR), diagnosis after 2017 (UKMSR-clinical/web, GMSR), lower-efficacy treatment as first DMT (UKMSR-web, GMSR), and treatment at clinical centers that were not academic centers (GMSR). The complementary analysis looking at fingolimod-treated PwMS separately in the GMSR did not result in significant changes (see Supplemental Figure S1).

The pooled results from the univariable models are shown in Figure 2 and Supplemental Table S1. Higher-efficacy treatment as first DMT [0.74 (0.55–1.00), $p < 0.0001$] as well as time to MS diagnosis of more than 15 years [0.58



Number at risk at respective year	1	2	3	4	5
United Kingom (clinical)	343	182	104	60	25
United Kingdom (web)	439	241	153	102	56
North America	132	60	35	18	10
Germany	413	207	103	46	12

Figure 1. Kaplan–Meier curves for time to DMT initiation in years for each data source. The median time is shown by vertical lines. Number of patients at risk after full years are given in the lower panel of the figure. About 50% of the patients initiated a DMT within 9 months of diagnosis. German patients showed the shortest time to first DMT initiation of the majority of PwMS [2.0 (1.9–2.0) months], followed by the US patients [3 (2–4) months] and the UK-clinical as well as UK-web populations [9.0 (7.7–10.6) and 7.1 (6.2–7.9) months].
DMT, disease-modifying therapy; PwMS, patients with multiple sclerosis.

(0.39–0.87), $p < 0.01$; reference: 0–5 years] were associated with longer times to first DMT. There were nonsignificant trends for a shorter time to first DMT with younger age at diagnosis [17–30 years – HR (95% CI): 1.14 (1.00–1.29), $p = 0.11$; reference: 41–50 years], male sex [1.06 (0.99–1.13), $p = 0.76$], visit of non-academic centers [1.08 (1.00–1.16), $p = 0.53$], and higher educational level [university: 1.02 (0.90–1.17), $p = 0.38$; reference: secondary or less education].

In multivariable Cox-regression models, MS diagnosis after 2017 (NARCOMS, UKMSR-web, GMSR), shorter time to diagnosis (UKMSR-web), age ⩾61 years (UKMSR-web), and a lower-efficacy treatment as first DMT (UKMSR-web, GMSR) were predictors of shorter time to first DMT (Table 3). The pooled multivariable analysis indicated that MS diagnosis after 2017 [1.65 (1.42–1.92), $p < 0.01$] was associated with a shorter time to the first DMT, whereas treatment initiation with a higher-efficacy DMT had a higher hazard for a longer time to first DMT [0.69 (0.54–0.90), $p < 0.0001$], see Figure 3 and Supplemental Table S2.

Discussion

In this study we built upon our prior successful application of the Maelstrom framework.[20] We found that the median time to initiate a DMT was the shortest in the German registry population, followed by the United States, and the UK registries population. Factors associated with a shorter time to initiating a DMT were a MS diagnosis after 2017 while treatment with a higher-efficacy DMT was associated with a longer time to initiating the first DMT. These factors were generally consistent across health systems. A matter of discussion is the attribution of DMTs into the two groups, as for example, in Germany the 2021 revision of the national MS guideline divided the DMT spectrum into three groups. Resulting in an additional group including sphingosine-1-phosphate receptor modulators (S1Ps) and cladribine seen as a category of medium efficacy between traditional baseline therapies (interferons, glatiramer acetate, dimethyl fumarate/diroximel fumarate, and teriflunomide) and high efficacy (alemtuzumab, anti-CD20 monoclonal antibodies, natalizumab). While creating the protocol for this analysis, this separation in three categories was not

Table 3. Results of the uni-/multivariable Cox-regression regarding the association between the time to first DMT and patient characteristics per data source, hazard ratio (95% CI).

Variable	Categories	GMSR ($n = 2658$)		NARCOMS ($n = 447$)		UKMSR-clinical ($n = 1147$)		UKMSR-web ($n = 1143$)	
		Univariable	Multivariable	Univariable	Multivariable	Univariable	Multivariable	Univariable	Multivariable
Sex, Ref: Female	Male	1.07 (0.98–1.18)	1.06 (0.97–1.16)	0.98 (0.75–1.291)	1.12 (0.84–1.48)	1.11 (0.94–1.31)	1.14 (0.96–1.35)	1.00 (0.86–1.18)	1.07 (0.91–1.26)
Age at diagnosis (years), Ref: 41–50	17–30	1.02 (0.91–1.14)	1.06 (0.95–1.19)	**1.39 (1.019–1.92)**	1.29 (0.92–1.82)	1.1 (0.9–1.35)	0.95 (0.76–1.18)	**1.25 (1.06–1.48)**	1.03 (0.86–1.23)
	31–40	0.96 (0.85–1.08)	0.96 (0.86–1.09)	0.90 (0.68–1.20)	0.96 (0.72–0.28)	1.01 (0.83–1.22)	0.86 (0.71–1.04)	1.1 (0.94–1.28)	1.02 (0.87–1.20)
	51–60	**0.83 (0.70–0.98**	0.95 (0.80–1.13)	0.75 (0.55–1.03)	0.80 (0.58–1.11)	**0.67 (0.51–0.88)**	1.05 (0.80–1.38)	**0.79 (0.64–0.99)**	0.98 (0.79–1.22)
	⩾61	**0.55 (0.38–0.82)**	0.89 (0.61–1.31)	0.75 (0.42–1.31)	1.12 (0.63–1.98)	**0.36 (0.2–0.65)**	0.76 (0.42–1.37)	0.86 (0.44–1.67)	**2.11 (1.08–4.15)**
Disability, Ref: Mild	Moderate	**0.71 (0.61–0.83)**	0.94 (0.80–1.11)	0.83 (0.67–1.04)	0.92 (0.73–1.16)	0.84 (0.65–1.09)	1.02 (0.78–1.32)	0.93 (0.79–1.11)	1.09 (0.91–1.30)
	Severe	1.12 (0.28–4.49)	1.88 (0.46–7.60)	0.81 (0.53–1.24)	0.97 (0.62–1.52)	**0.59 (0.41–0.86)**	1.05 (0.72–1.54)	**0.61 (0.48–0.76)**	0.90 (0.72–1.14)
Time to diagnosis (years), Ref: 0–5	6–10	0.90 (0.76–1.06)	1.01 (0.86–1.20)	0.93 (0.70–1.22)	0.85 (0.64–1.13)	**0.74 (0.58–0.94)**	0.84 (0.66–1.08)	**0.74 (0.61–0.90)**	**0.78 (0.64–0.95)**
	11–15	**0.70 (0.55–0.90)**	0.91 (0.71–1.17)	1.18 (0.83–1.70)	1.16 (0.79–1.69)	0.72 (0.49–1.06)	1.04 (0.71–1.54)	**0.72 (0.53–0.98)**	1.16 (0.85–1.60)
	>15	**0.71 (0.52–0.97)**	1.14 (0.83–1.56)	0.82 (0.60–1.10)	1.01 (0.73–1.39)	**0.30 (0.19–0.47)**	0.81 (0.51–1.27)	**0.60 (0.44–0.82)**	0.88 (0.64–1.21)
Year of diagnosis, Ref: 2014–2016	2017–2019	**1.25 (1.14–1.36)**	**1.44 (1.32–1.58)**	1.25 (0.98–1.61)	**1.62 (1.22–2.16)**	**1.28 (1.10–1.50)**	**1.63 (1.38–1.93)**	**1.39 (1.22–1.58)**	**1.98 (1.72–2.28)**
Type of first DMT, Ref: Lower efficacy	Higher efficacy	**0.50 (0.45–0.56)**	0.50 (0.44–0.55)	0.88 (0.68–1.15)	0.81 (0.61–1.07)	1.01 (0.86–1.19)	0.90 (0.75–1.06)	**0.72 (0.63–0.82)**	**0.68 (0.59–0.78)**
Type of center, Ref: Academic	Other	**1.13 (1.00–1.26)**	1.02 (0.91–1.14)	1.08 (0.83–1.41)	1.02 (0.78–1.34)	0.98 (0.84–1.15)	0.99 (0.84–1.17)	1.10 (0.95–1.27)	1.06 (0.91–1.22)
Comorbidity, Ref: No comorbidity	⩾1	1.07 (0.88–1.28)	N/A	0.83 (0.66–1.05)	N/A	N/A	N/A	0.99 (0.77–1.28)	N/A
Type of education, Ref: Secondary or less	Higher education (technical or associates)	1.04 (0.88–1.23)	N/A	1.04 (0.71–1.51)	N/A	N/A	N/A	0.87 (0.70–1.08)	N/A
	Higher education (university)	0.93 (0.77–1.11)	N/A	1.17 (0.87–1.58)	N/A	N/A	N/A	1.10 (0.90–1.34)	N/A

Bold values mean a significant association with shorter time to first DMT.
DMT, disease-modifying therapy; GMSR, German Multiple Sclerosis Registry; MS, multiple sclerosis; *n*, number of patients; N/A, not applicable; NARCOMS, North American Research Committee on MS; Ref, reference; UK, United Kingdom; UKMSR, United Kingdom MS Registry.

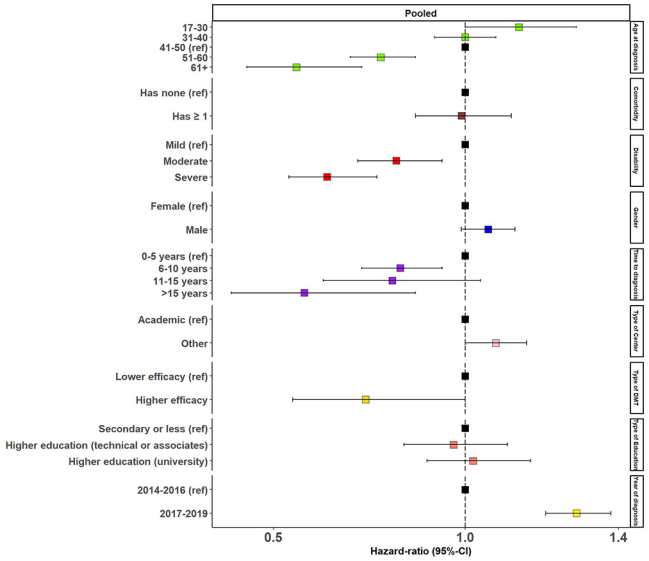


Figure 2. Graphical representation of the pooled univariable models. This forest plot shows the associations of the time to the first DMT with the pooled sociodemographic and clinical data from three MS registries (GMSR, NARCOMS, UKMSR) in a univariable Cox-regression model. The colored boxes show the values of the hazard ratios on the *x*-axis. The whiskers emanating from the boxes indicate the 95% CI of the HRs. For example, the time to first DMT was significantly longer in patients with time to diagnosis of more than 15 years [0.58 (0.39–0.87), $p < 0.01$] and treatment initiation with higher-efficacy DMT [0.74 (0.55–1.00), $p < 0.0001$].
CI, confidence interval; DMT, disease-modifying therapy; GMSR, German Multiple Sclerosis Registry; HR, hazard ratio; MS, multiple sclerosis; NARCOMS, North American Research Committee on MS; ref, reference; UKMSR, United Kingdom MS Registry.

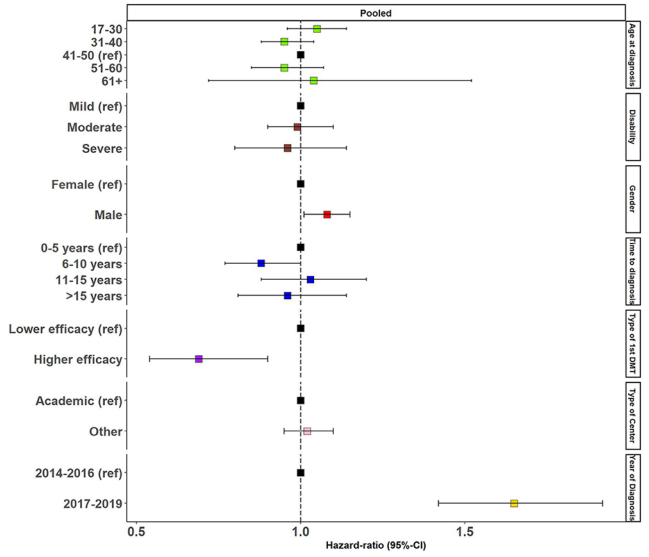


Figure 3. Graphical representation of the pooled multivariable models. This forest plot shows the associations of the time to the first DMT with the pooled sociodemographic and clinical data from three MS registries (GMSR, NARCOMS, UKMSR) in a multivariable Cox-regression model. Diagnosis between 2017 and 2019 was significantly associated with a shorter time to first DMT [1.65 (1.42–1.92), $p < 0.01$], whereas the use of a higher-efficacy treatment as first DMT was significantly associated with a longer time to first DMT [0.69 (0.54–0.90), $p < 0.0001$].
CI, confidence interval; DMT, disease-modifying therapy; GMSR, German Multiple Sclerosis Registry; MS, multiple sclerosis; NARCOMS, North American Research Committee on MS; ref, reference; UKMSR, United Kingdom MS Registry.

available, and we judged, for example, cladribine and fingolimod based on the label by EMA for highly active MS and also according to the then published EAN/ECTRIMS guidelines.

In Germany, most citizens are insured by one of the SHIs. DMT is available and reimbursed already after the first clinical episode, and no disability threshold needs to be reached prior to allowing the prescription. Furthermore, DMT can be prescribed by any outpatient neurologist not necessarily specialized in MS, and even, although a rare event, by general practitioners not specialized in neurology. Overall, the prescription of DMT is not limited to specialized hospitals or MS centers, facilitating easy and early access even in remote and rural areas. This illustrates the regulatory differences between the countries that may affect the time to DMT and also allows for discussing DMT options already during the first consultations at time of diagnosis with a PwMS. In several aspects, for example, with regard to optimal patient care and pharmaco-economics, minimal barriers for DMT prescription could also have disadvantages, but may lead to shorter times to DMT, however not necessarily the optimal DMT.

The NARCOMS data suggest a 1 month longer median time to DMT start in the United States as compared to in Germany. With a dataset of only 447 individuals analyzed from the NARCOMS Registry, the data may not be representative for early access to DMT in all areas of the United States. However, on average, this possibly reflects a heterogeneous healthcare system with respect to insurance coverage and cost of DMTs being possible barriers for early DMT start in a proportion of PwMS in the United States.[13]

The UKMSR data also suggested a delay of 6 months on average in initiating DMT in the United Kingdom compared to Germany. This possibly is explained by the process of being diagnosed in the United Kingdom. General practitioners act as gatekeepers for specialist neurologists. If MS is suspected, patients are referred to a waiting list, picked up by a specialist treatment center at which point the process of confirming the diagnosis (MRI Scan per McDonald Criteria) begins and may account for some of the lag in diagnosis and thus treatment.

Among international MS specialists, there is a large consensus that early use of DMT, ideally after the first clinical episode suggestive of MS, may have beneficial impact on longer-term outcome.[9] This view is supported by studies in patients with clinically isolated syndrome, and retrospective real-world registry data.[2,4,5,29,30] A registry-based cohort study of PwMS from two nationwide MS registries investigated long-term effectiveness outcomes in dependence of early *versus* late DMT initiation.[29] Early starters initiated the first DMT within 2 years after MS symptom onset ($n = 2316$) and late starters during 2–8 years after symptom onset ($n = 1479$). Median time from symptom onset to initial DMT was 1 year in early starters and 5 years in late starters. However, the majority of early (83.4%) and late starters (61.3%) initiated DMT within 1 year after MS diagnosis.[29] This is also reflected by our data, as median time to first DMT after MS diagnosis ranged from 2 to 9 months across the registries analyzed. Regarding the long-term outcome of the Danish cohort of PwMS, early DMT initiation was associated with longer period to reach an EDSS score of 6 (particularly in women) and lower risk of mortality (reference: late starters).[29] Furthermore, an observational study of 2648 RMS patients from the Swedish MS Registry revealed that per year of DMT delay, MS Impact Scale (MSIS) physical score worsened by 2.75 (95% CI: 1.29–4.20) points and MSIS psychological score by 2.02 (0.03–3.78) points, whereas there was no significant association between quality of life and earlier DMT start.

In recent years, the arsenal to combat MS has grown, with registration of DMT that have proven higher efficacy compared to the DMT tested in the early clinically isolated syndrome studies. Besides the higher-efficacy DMT listed above – such as alemtuzumab, cladribine, fingolimod, natalizumab, and ocrelizumab – newer S1Ps (ozanimod, ponesimod) and a subcutaneous B-cell targeting therapy (ofatumumab) have become available, tested against active comparators in phase III clinical trials.[31–33] Therefore, not only the early application of any DMT, but in particular the early application of DMT with higher efficacy, for example, within the first 2 years of diagnosis, may result in added positive effects on the long-term disease course.[6–8]

The mean delay from symptom onset to first DMT initiation among these Swedish PwMS with at least one MSIS recording was 0.7 years in

early starters (started within 2 years, $n = 1913$) and 2.6 years in later starters (start during 2–4 years, $n = 130$).[30] The observation that early DMT initiation is becoming common in PwMS is reflected in a positive trend also in our datasets: across all three registries analyzed, PwMS diagnosed after 2017 were more likely to initiate DMT earlier compared to PwMS diagnosed between 2014 and 2016. Another issue that may contribute to the prolongation of time to first DMT is the diagnostic delay of MS. A cross-sectional multi-center study of 285 Portuguese PwMS presented significant associations between diagnostic delay and older age, increased relapse activity prior to diagnosis, symptoms of motor deficit at MS onset, primary progressive MS, and previous wrong diagnosis.[34]

Measures to reduce the time to MS diagnosis may be generating more attention to MS and thus increasing the health literacy of the general population, raising the alertness of general practitioners and improving access to neurologists.[35] This may reflect increasing awareness for the relevance of early diagnosis as well as DMT initiation and could be a result of (multi-)national guidelines in favor of early DMT start.[36,37] Interestingly, we noted a prolonged time to initiate DMT in patients who started with a higher-efficacy treatment compared to traditional lower-efficacy therapies. This may reflect the need to complete additional tests to reduce (higher-efficacy) treatment associated risks. However, several laboratory assessments to exclude pregnancy, chronic viral or bacterial infections (such as serology tests for varicella zoster, HIV, hepatitis, or tuberculosis T-cell tests), or anti-JC virus antibody testing – for one of the three progressive multifocal leukoencephalopathy risk factors assessment – in patients who intent to undergo natalizumab therapy, may explain delays only by days or a couple of weeks. In contrast, the need for vaccinations prior to higher-efficacy treatment initiation may play a relevant role, as vaccinations should be completed 4–6 weeks prior to certain higher-efficacy DMT. In the light of recent discussions on SARS-CoV-2 vaccinations' effectiveness in PwMS treated with S1Ps as well as anti-CD20 DMT, the timing of vaccinations before initiating high-efficacy treatments has become a prominent discussion point amongst neurologists.[38–41] Overall, risk mitigation measures may explain the delay noted when higher-efficacy treatments are selected as initial DMT option. The comparison across the different registries and healthcare systems showed that in the United States the time to initiate higher-efficacy DMTs is shortest followed by Germany and United Kingdom.

A trend across all three registries was a shorter time to first DMT in male PwMS. We can only speculate about the possible reasons. Although the effect was small, a possible explanation is that male sex is considered to be associated with worse prognosis in PwMS.[36,37] This assumption may lead to a shorter delay to first DMT as soon as MS is confirmed. Another possible explanation may be that a proportion of female PwMS may be hesitant with regard to starting a DMT due to childbearing wishes and plans, albeit several DMTs can be applied until awareness of pregnancy, or with recent approval even throughout pregnancy (interferons and glatiramer acetate[42]).

One trend that may be unexpected is that PwMS treated with DMT in non-academic centers were initiated within a shorter time after diagnosis compared to patients in academic centers. A possible explanation could be that patients initiating treatment in academic centers might be individuals referred for a second or a third opinion, either because these patients are unsure about (the most eligible) treatment or for example, comorbidities or other factors complicate the selection of suitable DMT. Furthermore, academic centers usually deal with larger patient populations, which might result in longer turnaround times. However, considering the nature of our registry-based study and possible heterogeneity with regard to data acquisition at the different registry sites and centers, we cannot exclude a methodological explanation for this observation.

Pooling patient-level data has become less feasible, especially for European data partners under General Data Protection Regulation (GDPR)-legislation. Following joint work on employment in MS,[20] other registry consortia[43] have also collaborated using the approach we employed. Our analysis provides unique insights into the time it takes for the first DMT to be introduced to PwMS. By including the United States and German regions in our baseline population, we can capture changes in the landscape of available treatments once market authorization is granted. This situation is relatively unique to these two countries as in almost all other countries the treatments are not available until price negotiations

(reimbursement decisions) are finished. By including more than 5000 people with MS in this study who were diagnosed after 2014, subject to modern diagnostic criteria (McDonald 2015 and 2017) and have access to a wide range of DMT options, we were able to provide data on factors influencing time to first DMT in a large sample of people with relatively short disease duration, enabling to detect possible barriers to DMT access.

However, our registry-based study has obvious limitations. PwMS included in the registries may not represent all individuals in the respective healthcare system (e.g., differences in DMT prescribing related to health care environment and limitations in access),[44] already reflected by different relative coverage of the total estimated PwMS population in the registries studied (UKMSR > GMSR > NARCOMS). In addition, there is potential for selection bias in the clinical registries (e.g. the GMSR recruits PwMS solely from centers awarded a certificate by the German MS Society after fulfilling certain criteria defined by the Society) and low numbers of participants meeting the inclusion criteria in the NARCOMS Registry. However, the NARCOMS and UKMSR are both online accessible and include PwMS, regardless of participation in documentation of their treating center. Furthermore, the UKMSR-clinical in recent years has increased recruitment in more community led sites. As another limitation, we were unable to include factors such as socioeconomic status, comorbidities, race, and ethnicity in our multivariable analyses due to data not being available in all of the datasets. Conducting research with heterogenous data sources generally is challenging. The data from two patient-reported registries (NARCOMS and the portal population of the UKMSR) were used, and two registries relied on clinical sites to report patient data showed comparable results with regard to female-to-male ratio, disability status at diagnosis, and educational status (Table 1). For both NARCOMS and the UKMSR, validation efforts have been published to ascertain the usability of patient-reported data.[14,45–48] The UKMSR also has a link between patient-reported data (portal data) and clinician-reported data for an increasing proportion of its population. The study included PwMS initiating both cladribine and ocrelizumab as the last approved DMTs. However, DMTs approved later on, for example, ofatumumab and further S1Ps, are not covered by our work due to the data cut that applies for this analysis. Future work will investigate possibly changed treatment initiation patterns following the approval of additional DMTs since 2019, which offer inter alia new routes of application. We also know that a dichotomic classification in higher- and lower-efficacy drugs are not strictly evidence-based, considering the limited number of head-to-head studies performed. However, as we focused primarily on time to any first DMT we believe that this has not affected our main findings.

Moreover, analyzing EDSS progression or further indicators of therapy effectiveness after DMT initiation to assess the benefit of early DMT initiation would be a valuable follow-up investigation.

Conclusion

Differences in healthcare systems with probably the lowest barriers to (a) diagnosis and (b) DMT initiation in Germany followed by the United States may account for some of our findings, highlighting the need to advocate for better access to diagnosis and treatment still. Provided that early DMT use is beneficial for the long-term outcome of PwMS, it is reassuring that a consistent decrease in time to DMT was noted since 2017 across all registries in our study. However, to inform on beneficial effects for PwMS, time to (higher-efficacy) DMT needs to be linked to clinical effectiveness outcomes for future studies.

Declarations

Ethics approval and consent to participate

No dedicated ethics approval was required for this study, as it is covered by the ethics approval of the registries. The GMSR was approved by the institutional review board (IRB) of the Julius-Maximilians-University of Würzburg (approval code: 142/12). The IRB at the Washington University in St. Louis approved the NARCOMS Registry (approval code: 201610132). South-West Central Bristol National Research Ethics Service (initially as 16/SW/0194 and currently 21/SW/0085) approved the UKMSR. All participants included in the above registries gave a written informed permission for their de-identified information to be used for research.

Consent for publication

Not applicable.

Author contributions

Alexander Stahmann: Conceptualization; Methodology; Project administration; Writing – original draft.

Elaine Craig: Formal analysis; Visualization; Writing – review & editing.

David Ellenberger: Formal analysis; Visualization; Writing – review & editing.

Firas Fneish: Formal analysis; Visualization; Writing – review & editing.

Niklas Frahm: Writing – original draft; Writing – review & editing.

Ruth Ann Marrie: Writing – review & editing.

Rod Middleton: Data curation; Writing – review & editing.

Richard Nicholas: Writing – review & editing.

Jeff Rodgers: Formal analysis; Writing – review & editing.

Clemens Warnke: Writing – review & editing.

Amber Salter: Conceptualization; Data curation; Formal analysis; Methodology; Supervision; Visualization; Writing – review & editing.

Acknowledgements

We would like to thank all patients who have given their consent to the participating registries and to all centers contributing to the registries involved. The GMSR of the German MS Society was initiated and funded by the German MS Foundation and the German MS Society in 2001. It is operated by a not-for-profit company, the MSFP. MSFP receives funding from a broad range of public and private sponsors including the German MS Society, the German MS Foundation, the Innovation fund of the German Federal Joint Committee, and the German Retirement Insurance. In 2022, Biogen, Celgene (BMS), Merck, Novartis, Roche, and Sanofi are participating in the multi-stakeholder funding approach to support the registry's operation and to allow the collection and reporting of (pharmacovigilance) data required as part of the EMA-minimal dataset. Industry funding does neither result in restrictions to publishing data, nor do the funders have access to the raw data or have any influence over the scientific conduct of the registry. NARCOMS is a project of the Consortium of Multiple Sclerosis Centers (CMSC). NARCOMS is funded in part by the CMSC and the Foundation of the CMSC. The UKMSR is primarily funded by the MS Society. Independent specific studies have been carried out with Sanofi Genzyme, Merck KGaA, and Novartis AG. These entities have neither direct access to the data, nor do they influence data collection or scientific conduct.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was created without any specific funding. The NARCOMS Registry is supported in part by the Consortium of MS Centers (CMSC) and the Foundation of the CMSC.

Competing interests

ASta has no personal pecuniary interests to disclose, other than being the lead of the German MS Registry, which receives funding from a range of public and corporate sponsors, recently including The German Innovation Fund (G-BA), The German MS Trust, The German Retirement Insurance, Biogen, German MS Society, Biogen, Celgene (BMS), Merck, Novartis, and Roche. DE and FF have no individual pecuniary interests to declare. NF received travel funds for research meetings from Novartis. ASal received research funding from Multiple Sclerosis Society of Canada, National Multiple Sclerosis Society, CMSC, and the US Department of Defense, and is a member of editorial advisory board for *Neurology*. RAM received research funding from Canadian Institutes of Health Research, Research Manitoba, Multiple Sclerosis Society of Canada, Multiple Sclerosis Scientific Foundation, Crohn's and Colitis Canada, National Multiple Sclerosis Society, Consortium of MS Centers, the Arthritis Society, and US Department of Defense. She is supported by the Waugh Family Chair in Multiple Sclerosis. She is a co-investigator on a study funded in part by Biogen Idec and Roche (no funds to her or her institution). RM, JR and EC: The UKMSR is primarily funded by the MS Society; RM, JC and EC have no individual pecuniary interests to declare. RN has received honoraria for participation in advisory boards for Novartis, Biogen, and Roche. CW has received institutional honoraria and/or grant support from Novartis, Sanofi-Genzyme, Alexion, Janssen, Merck, Biogen, and Roche. None resulted in a conflict of interest.

Availability of data and materials

Anonymized data will be made available on request by any qualified investigator under the terms of the registries' usage and access guidelines and subject to written informed consent of the patients.

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Supplemental material

Supplemental material for this article is available online.

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