Sex-specific analysis of early disease course and treatment in a German multiple sclerosis cohort

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Abstract

Background: Understanding sex differences in relapsing–remitting multiple sclerosis (RRMS) and initiation of disease-modifying treatments (DMTs) is crucial for tailored approaches.

Objective: The objective of this study is to analyze sex-specific differences in early RRMS.

Methods: We analyzed data of therapy-naïve adults from the German NationMS cohort to describe first symptoms, onset relapse treatment, disability evolution, and DMT exposure separated by sex to investigate previously described sex differences.

Results: Relapse presentation and treatment were similar (p = n.s.). Time to Expanded Disability Status Scale (EDSS) ⩾3.0 was comparable between sexes (adjusted hazard ratio, 95% confidence interval (95% CI): 1.32 (0.95–1.81)). DMT exposure did not differ (p = 0.60). Around 5.0% of both sexes received initial high-efficacy (HE) DMT. Younger age (odds ratio (OR) (95% CI): 0.95 (0.92–0.98); p = 0.000847), higher baseline EDSS (1.79 (1.40–2.27); p = 0.00000218), and RRMS diagnosis (2.26 (1.28–4.17), p = 0.006703) were associated with initial HE-DMT, but not sex (0.99 (0.57–1.77), p = 0.943166).

Conclusion: We did not observe major sex differences in early MS as described earlier regarding initial presentation and disability evolution suggesting a change of MS course. The decision for initial HE-DMT was influenced by younger age and higher EDSS, but not sex suggesting a lower sex bias regarding the initial treatment decision, yet only investigated in specialized academic MS centers.

Keywords: Multiple sclerosis, German NationMS cohort, sex, disease-modifying treatment (DMT), relapse

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Introduction

Sex differences in multiple sclerosis (MS), as well as in other immune-mediated diseases include higher disease susceptibility in women and differential evolution of disability between sexes.[1] Especially for the relapsing–remitting disease course (RRMS), women are more frequently affected, with an estimated female-to-male ratio of 3:1,[2,3] risen over the last decades.[4] However, men tend to experience more severe disability, especially by pyramidal system involvement, and are equally affected by primary and secondary progressive forms of MS.[3,5] It is assumed that women with MS experience an increased relapse rate.[6] However, whether these assumptions hold true for more contemporary cohorts remains unclear.

The general concept of early initiation of disease-modifying treatment (DMT) is well-established.

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However, early administration of platform DMT (PL-DMT) may be associated with lower prevention of conversion into progressive MS and less reduction of disability progression.[7,8] A shift toward early administration of high-efficacy (HE) DMTs has recently been supported by data from large observational registry settings.[8–10] In a multinational cohort from academic centers in the United States and Europe, it was highlighted that women were less likely to be treated with DMT, particularly in two age groups, namely later 20s to early 40s and late 50s to late 60s.[11] This also underscores that family planning in women only represents one potential cause[12] and that other factors play a role in sex-associated health disparities.

We analyzed potential sex-specific differences in the German NationMS cohort, including 1268 participants over an observational period of up to 8 years.

Materials and methods

Ethical statement

This study was approved by the ethics committee of the Ruhr-University Bochum (Reg. No. 3714-10) and all consecutive local committees of the participating centers. Patients were included following written consent.

NationMS cohort

Data were obtained from the German NationMS cohort study of the German Competence Network Multiple Sclerosis (KKNMS) until 9 June 2022. The NationMS study is an ongoing multicenter, prospective, longitudinal, observational cohort study. Participants were recruited from 2010 to 2017 in 22 participating academic centers. Inclusion criteria comprised initially DMT-naïve adult patients with early RRMS (within 2 years after diagnosis, McDonald 2005 or 2010)[13,14] or clinically isolated syndrome (CIS, within 6 months, fulfilling additional paraclinical requirements). As demonstrated earlier, the median disease duration within the cohort at baseline was 0.33 years (interquartile range, IQR: 0.20–0.70) from the time of the initial manifestation.[15]

Patients underwent standardized clinical and cerebral magnetic resonance imaging (MRI) assessments yearly for two consecutive years and every other year thereafter.

All inclusion and exclusion criteria as well as the full assessment plan are described elsewhere.[15]

Variables of interest for this study

Demographic characteristics and features of the early disease evolution and treatment were analyzed separated by sex. To this end, we summarized type of first symptoms, treatment of the onset attack, and evolution of disability by Expanded Disability Status Scale (EDSS) up to 8 years of follow-up. Total DMT exposure (percentage of treated vs untreated men and women) and class distribution of the first DMT between sexes (platform treatment (PL): dimethyl fumarate, glatiramer acetate, interferon-beta formulations, teriflunomide, HE: alemtuzumab, B-cell-depleting monoclonal antibodies, fingolimod, natalizumab) were assessed. Likewise, distribution of single DMT classes was investigated for men and women.

Missing data

Single missing data points are indicated in Table 1. The flow chart depicts the number of participants at each follow-up time point (Figure 1).

Statistical analysis

Statistical analysis was performed using R (4.1.2). Descriptive statistics are given as number (%) (*N* (%)) for categorical or mean (standard deviation) (mean (SD)) or median [IQR] (median [IQR]) for continuous variables. All tests were performed against $\alpha = 0.05$, and 95% confidence intervals (CI) were reported.

In univariate analyses, Fisher's exact test (for categorical variables) and Welch's test (for continuous variables) were used to compare sex groups.

Association of sex with the chance of a patient's initial treatment being HE-DMT was tested via logistic regression. Unadjusted and adjusted (for measures of disease activity and severity (age at baseline visit, baseline EDSS, and disease course at baseline)) Odds ratios (OR) with 95% CI are reported.

To test the association of sex with the time to reach EDSS $\geqslant 3$, we performed a Cox regression with t_0 = baseline visit. Patients were censored at the time of an event or at follow-up 8, whichever is first. The restricted mean survival time (RMST) for both genders is also reported.

Patients with intermittent missing EDSS and/or visit dates were excluded from the Cox regression, as exact time to event could not be determined.

Table 1. Cohort characteristics.

Total ($n=1268$)	Male ($n=378$)	Female ($n=890$)
Age at baseline (years, median [IQR])	33.0 (14.0)	32.0 (15.0)
Disease course, *n* (%)		
• CIS	165 (43.7)	392 (44.0)
• RRMSa	213 (56.3)	497 (55.8)
• Missing data	0 (0.0)	1 (0.1)
Observational period (years, median [IQR])	4.0 [0–8.2]	3.9 [0–8.3]
First relapse, *n* (%)		
• Monosymptomatic	286 (75.7)	676 (76.0)
• Polysymptomatic	92 (24.3)	214 (24.0)
Treatment of first relapse, *n* (%)		
• None	75 (19.8)	189 (21.2)
• Steroids	291 (77.0)	672 (75.5)
• Steroids and plasmapheresis	4 (1.1)	16 (1.8)
• Missing data	8 (2.1)	13 (1.5)
EDSS at baseline (median [IQR] [min; max])	1.5 [1.0]	1.5 [1.0]
• Missing	1 (0.2%)	0 (0%)
First disease-modifying treatment, *n* (%)		
• None	88 (23.3)	226 (25.4)
• Platform	266 (70.4)	603 (67.8)
• High-efficacy	19 (5.0)	45 (5.1)
• Other	5 (1.3)	16 (1.8)
Start of first treatment from diagnosis (months, mean (SD))	5.35 (8.98)	5.40 (8.61)
Number of participants with at least one DMT switch, *n* (%)	178 (47.1)	364 (40.9)

[a]McDonald criteria 2005.

Unadjusted and adjusted (for age at baseline and initial DMT) hazard ratios (HRs) with 95% are reported. For visual inspection, adjusted Kaplan–Meier curves were produced by applying augmented inverse probability of treatment weighting on survival probability, as implemented in the adjusted Curves package for R.[16] Weights were determined generating a propensity score using a multinomial logistic regression model on participant sex by baseline age and initial treatment group.

Due to low patient numbers in some contributing sites, center effects were not modeled and analyses were performed on pooled data.

Results

Baseline characteristics of women and men

Data of 1268 participants from the German NationMS cohort are given in Table 1.

The female-to-male ratio was 2.4:1 (women: $n=890$, men: $n=378$). Median [IQR] age at baseline did not differ between women (32 [15] years) and men (33 [14] years). Median follow-up intervals were comparable between women (years [IQR]: 3.9 [0–8.3]) and men (4.0 [0–8.2]). The EDSS at baseline was low overall (median [IQR]: 1.50 [1.00] in men and women) without significant sex differences ($p=0.368$) (Table 1). Baseline characteristics were comparable between censored and excluded patients, and sex distribution was similar across groups; patients with progression were older and had higher baseline EDSS, consistent with clinical expectations (Supplemental Table 1).

Presentation and treatment of the onset attack

Frequencies of the first attack with monosymptomatic (women: $n=676$ (76.0%) vs men: $n=286$ (75.7%)) compared to polysymptomatic presentation (women: 214 (24.0%) vs men: 92 (24.3%), OR (95% CI):

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*Equal contribution

Data Availability Statement is included at the end of the article.

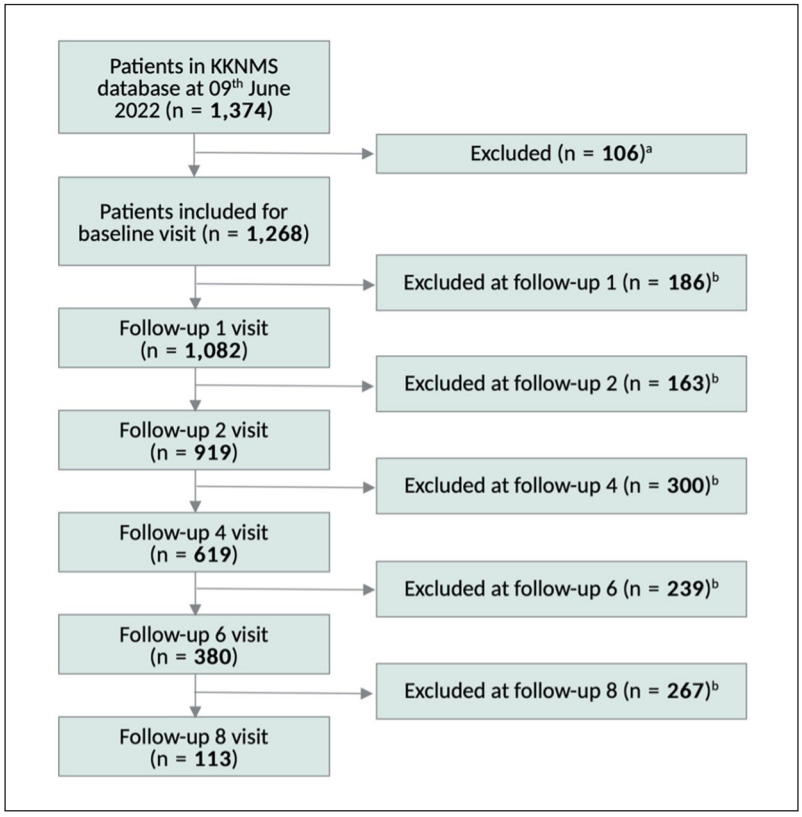

Figure 1. Flow diagram of NationMS patients included in this study.
Flow diagram of participants from the German NationMS cohort included into analysis of this study. The database was requested on 9th June in 2022 including 1374 participants. In all, 1268 participants were included for baseline visit and followed up until follow-up visit 8, with 113 remaining participants.
[a]Missing DMT onset or cessation information.
[b]Loss of follow-up or visit pending.

1.016138 (0.7579691–1.3560436), $p=0.9428$) (Table 1) did not differ between sexes. Affected functional domains did likewise not differ between men and women (Figure 2). Whether treatment was applied at first relapse did not differ significantly between the sexes (untreated events: women: $n=189$ (21.2%), men: $n=75$ (19.8%), $p=0.6493$) (Table 1).

Disability progression over time

While the median EDSS in the cohort remained stable at a low level throughout each visit (Figure 3), 172 women (19.3%) and 61 men (16.1%) reached an EDSS of 3.0 or higher during observation (Table 1).

Time to EDSS ⩾3.0 ($n=1145$, excluding 123 cases with interim missing EDSS and/or visit date) did not differ significantly between women and men (RMST (95% CI) in days: male: 2487.223 (2396.366–2568.595), female 2367.273 (2296.610–2433.217); HR (95% CI): 1.32 (0.95–1.189, $p=0.093$, adjusted for age at baseline and initial DMT) (Figure 4).

DMT patterns of women and men

Overall treatment exposure was similar for men and women in our cohort with 23.3% of men ($n=88$) without DMT over the observational period of up to 8 years and 25.4% of women ($n=226$), respectively, OR (95% CI): 1.12158 (0.839312–1.5065764), $p=0.4351$) (Table 1).

The mean interval between initial diagnosis (CIS or RRMS) and DMT start with any medication in the proportion of patients ever treated was 5.40 months ± 8.61 SD for women and 5.35 months ± 8.89 SD for men, respectively (Table 1).

Treatment switches were frequent with less than 50% of participants without any switch over the observational period. However, the proportion of therapy switches was slightly but not significantly higher among women than men (no switch: women: 40.9%, $n=364$; men: 47.1%, $n=178$, OR (95% CI): 0.7636646 (0.5698559–1.0209576), $p=0.06478$; Table 1).

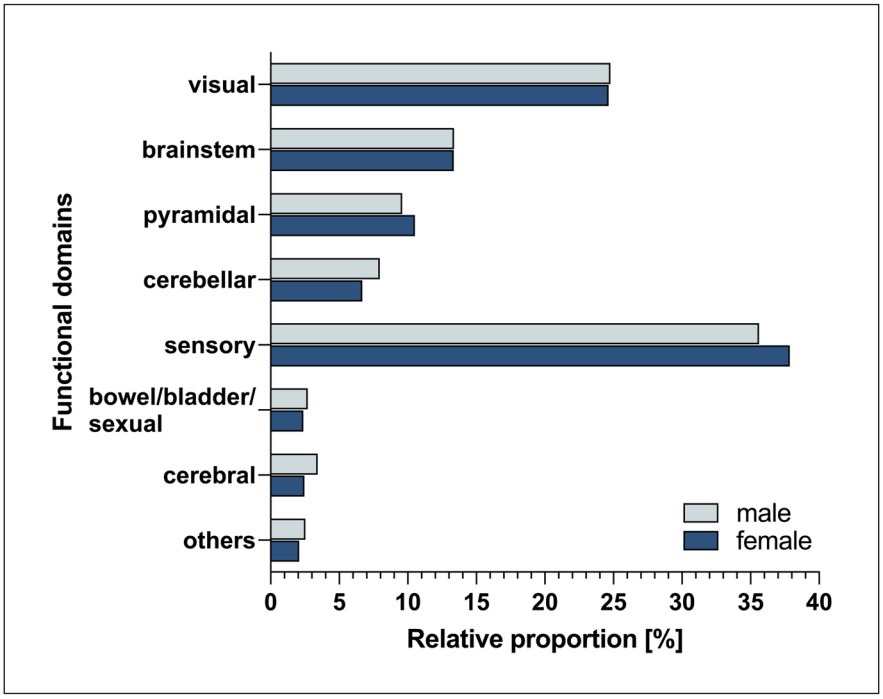

Figure 2. Affected functional domains during onset relapse in men and women.
Relative proportion of affected functional domains during onset relapse in female (dark blue) and male (light blue*f*) participants. Functional domains include the visual system, brainstem, pyramidal, cerebellar, sensory, bowel/bladder/sexual, cerebral, and others (e.g. vertigo, Lhermitte's sign).

Association of initial DMT class with sex

The chance of initially being treated with HE-DMT (5.1% of women ($n=45$) and 5.0% of men ($n=19$)) (Table 1) compared to other options (none, PL-DMT, other) did not differ significantly between the sexes (OR (95% CI): 1.01 (0.6–1.8), $p=0.979$; adjusted OR (95% CI): 0.99 (0.6, 1.8), $p=0.943166$). However, in the multivariate model, higher EDSS at baseline (OR = 1.79 (95% CI = 1.40–2.27), $p=0.00000218$), younger age (OR = 0.95 (0.92–0.98), $p=0.000847$), and an RRMS diagnosis at baseline (OR = 2.26 (1.28–4.17), $p=0.006703$) were significantly associated with the chance of the initial therapy being HE-DMT (Figure 5(a) and (b)).

Frequencies of specific HE-DMT substances applied as first treatment differed significantly between the sexes: Men were more frequently treated with fingolimod (men: $n=13/19$ (68.4%), women: $n=16/45$ (35.6%), $p=0.02682$) and women with natalizumab (men: $n=3/19$ (15.8%), women: $n=26/45$ (57.8%), $p=0.002448$). This remained significant even after correcting for baseline EDSS in logistic regression (OR (95% CI) of being female and being prescribed the substance as first DMT within the initial HE-DMT subgroup: fingolimod: 0.24 (0.07–0.78), $p=0.022$; natalizumab: 7.64 (2.10, 37.9), $p=0.005$) (Table 2).

Discussion

Within the German NationMS cohort, we did not identify sex-associated differences regarding the symptomatology and treatment of MS disease onset and early disease course with regard to EDSS over up to 8 years. Our analysis does not demonstrate differences in disease manifestation in NationMS unlike data from the German MS registry.[17] Although the German MS registry analyzed data from approximately 20,000 individuals, differences in disease manifestations were more pronounced depending on the disease form than between sexes.[17] Both the proportion of patients reaching an EDSS of 3.0 or higher and the time to EDSS of 3.0 or higher did not differ between men and women. Over the last 50 years, the prevalence and incidence of MS have increased, particularly among women.[18] However, men with MS are reported to experience a more severe disease course.[19] An MSBase analysis of over 15,000 participants demonstrated an accelerated progression of the annualized EDSS, shorter time to reach an EDSS $\geqslant$3.0 and 6.0,

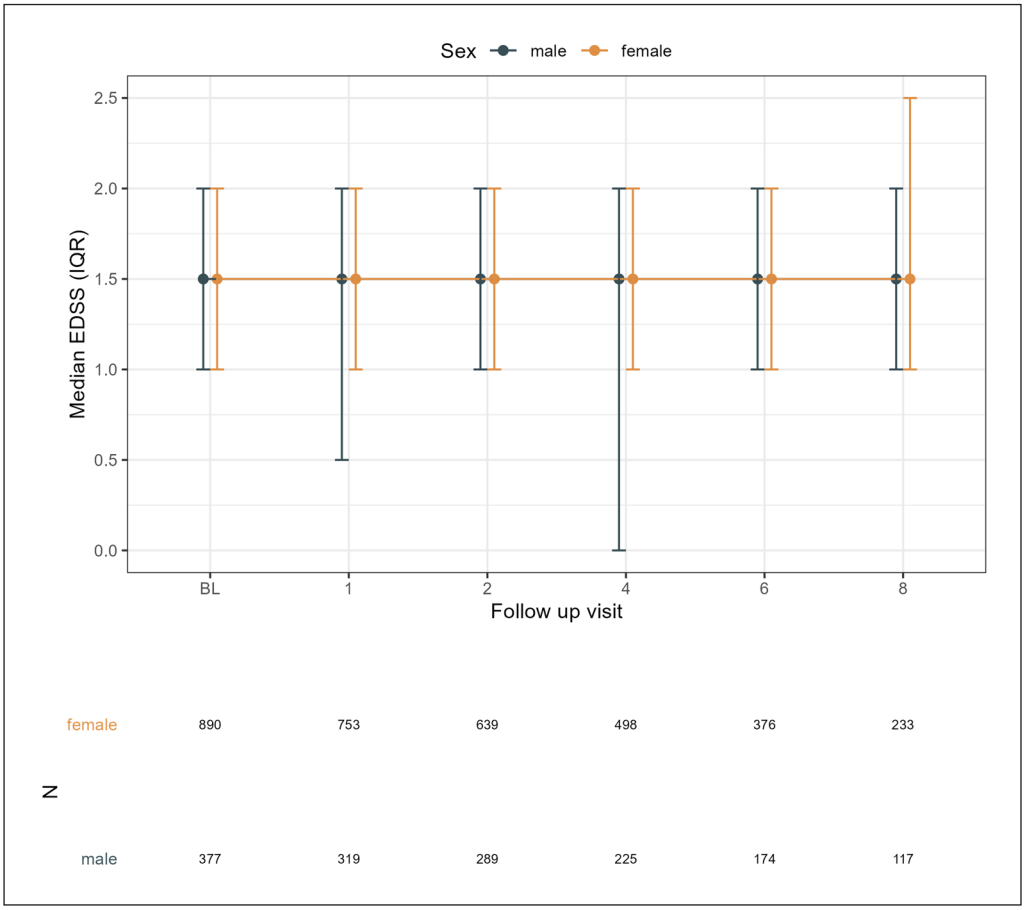

Figure 3. EDSS course of women and men up to 8 years of follow-up.
Median EDSS course of women (orange) and men (gray) from baseline up to follow-up visit 8.
EDSS: Expanded Disability Status Scale; IQR: interquartile range, $n = 1$ missing baseline EDSS.

as well as a shorter time to convert into progressive MS in male MS patients with relapsing onset MS,[20] with men reaching the milestone of EDSS of 3.0 after 8 years and women after 10 years.[21] Although, as men are equally affected by progressive forms of the disease, recently, no sex-dependent significant differences were found regarding the MS severity score (MSSS),[21] but disease progression has been shown to depend on initial presentation of the disease. The latter findings are in line with our analyses, demonstrating that younger age and higher EDSS at disease manifestation are associated with the decision to treat initially with HE-DMT, also reflecting a higher disease burden. Potentially, these[21] and our data being more recent represent a shift from earlier reported assumed sex-based differences to individual differences of MS disease presentation. Underlying reasons for such a shift will be manifold, potentially including gender-associated causes such as male persons might have adopted a different approach for seeking medical advice depending on perceived symptoms over time. However, this remains speculative.

Differences in treatment patterns between women and men are highly debated and it has been shown that men are more likely to be treated with DMTs compared to women.[11] Overall DMT exposure and the proportion of patients initially treated with HE-DMT did not differ by sex in our cohort. However, in the NationMS cohort, administration of initial HE-DMT was relatively low (around 5%). Participants were recruited from 2010 to 2017 with approval of several HE treatments only after this period. It can be assumed that, due to the wider range of treatment options and the increasing amount of data available on HE-DMTs as first-line therapy, the percentage of patients treated with HE-DMTs would be significantly higher today. In a multinational cohort from the United States and Europe, differences in treatment decisions between women and men were mainly attributed to overall

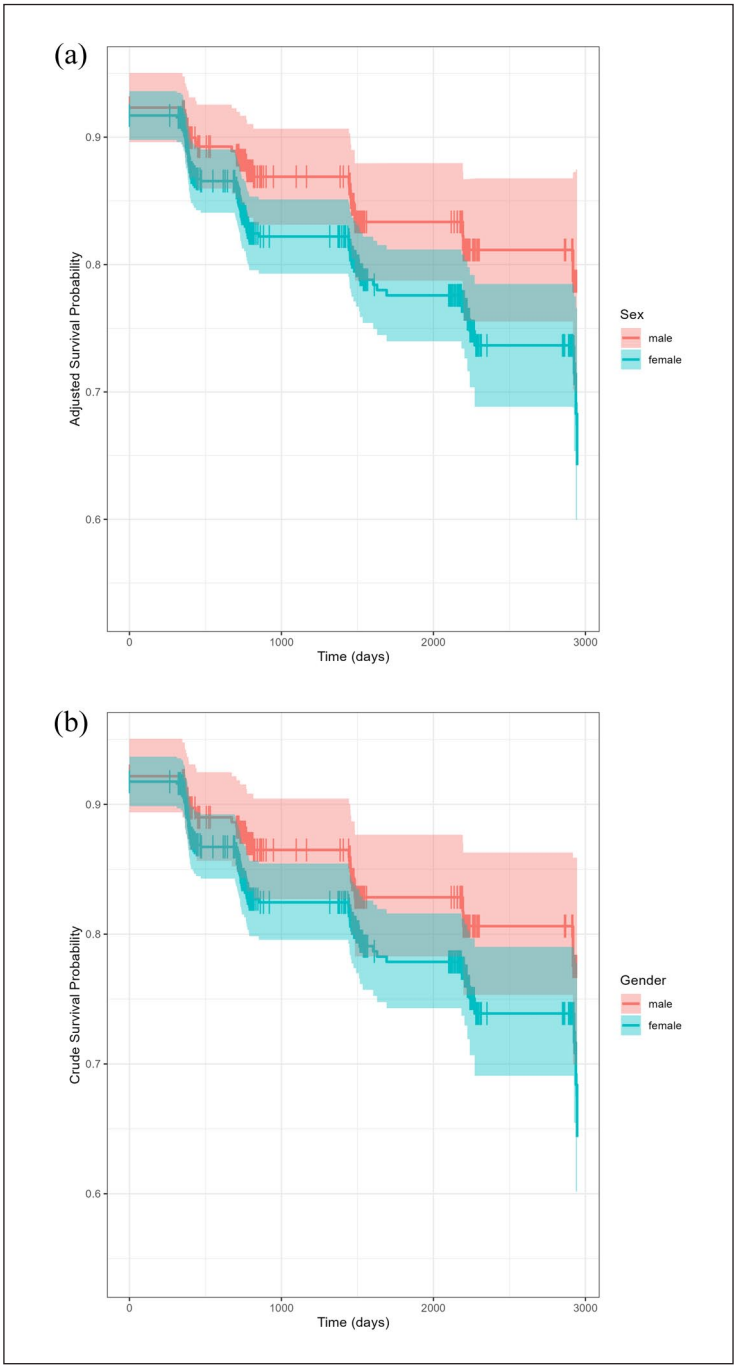

Figure 4. Survival probability of reaching an EDSS ⩾3.0. (a) Crude survival probability of reaching an EDSS ⩾3.0 including sex at baseline, hazard ratio 1.27; 95% CI: 0.92–1.75, $p=0.14$. (b) Survival probability of reaching EDSS ⩾3.0 adjusted for age at baseline and initial DMT, hazard ratio 1.32; 95% CI: 0.95–1.81, $p=0.093$.

treatment, rather than differences between HE-DMT versus PL-treatment and further associated with age and education.[11] Within the NationMS cohort, we found younger age and higher EDSS (as well as disease burden as reflected by the formal RRMS diagnosis using older versions of the McDonald criteria) at disease manifestation as predictors for the usage of HE-DMT, corroborating other data on the application of HE-DMT early in MS.[10] An analysis of a Danish cohort comprising approximately 3500 participants, starting therapy after January 2014, demonstrated that treatment choice toward HE-DMT was determined

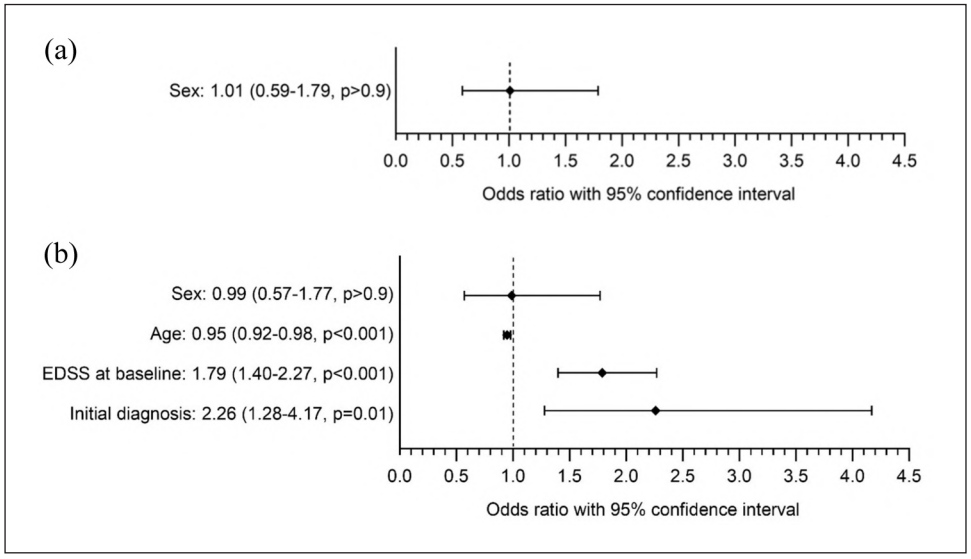

Figure 5. Logistic regression of factors associated with initial HE-DMT. (a) Logistic regression of sex as factor associated with initial HE-DMT, in an unadjusted model given as odds ratios with 95% confidence interval. (b) Logistic regression of sex, age, EDSS at baseline, and initial diagnosis as factors associated with initial HE-DMT in a multivariate model given as odds ratios with 95% confidence interval.
EDSS: Expanded Disability Status Scale.

Table 2. First disease-modifying treatment, single substance classes.

	Male	Female
First DMT, *n* (%)		
• Platform treatment	266 (70.4)	603 (67.8)
• Dimethyl fumarate	40 (10.6%)	90 (10.1%)
• Glatiramer acetate	61 (16.1%)	164 (18.4%)
• Interferon-beta formulations	156 (41.3%)	330 (37.1%)
• Teriflunomide	9 (2.4%)	19 (2.1%)
High-efficacy treatment		
• Alemtuzumab	2 (0.5%)	2 (0.2%)
• B-cell-depleting treatments (rituximab, ocrelizumab)	1 (0.3%)	1 (0.1%)
• Fingolimod	13 (3.4%)	16 (1.8%)
• Natalizumab	3 (0.8%)	26 (2.9%)
• None	88 (23.3%)	226 (25.4%)
• Other	5 (1.3%)	16 (1.8%)

Other = azathioprine, cyclophosphamide, intravenous immunoglobulins, study medication, methotrexate, mitoxantrone, triamcinolone intrathecally, daclizumab; none = no treatment during the observational period of up to 8 years.

not only by age (<40 years) but also by sex, with higher odds for men starting with HE-DMT than women.[22] These contrasting results may arise from the academic setup of our cohort, which is evaluated in MS-specialized clinics as compared to the Danish nationwide MS registry. Specialization has been shown to be associated with a reduced likelihood to delay treatment initiation or prescription of a less suitable therapy.[23] The specialized setup may thus have led to a less sex-dependent treatment decision.

Early initiation of HE-DMT in patients with relapsing onset has been demonstrated to prevent lesion formation within the central nervous system (CNS) in

comparison with administration of PL therapy.[10,24] Analyses comparing the Danish and the Swedish MS Registries depicted that initiation with HE-DMT results in a reduction in disability progression.[8] Furthermore, initiation of HE-DMT is associated with a reduced increase in EDSS[9] and a later conversion to progressive MS forms.[7] Within 2020 to 2022, in Germany and the United States, therapy initiation with HE-DMT significantly increased by 14%, accompanied by an improved compliance with the current therapy, as compared to patients initially prescribed PL treatment.[25] Initial HE-DMT or escalation to second-line DMT is associated with a reduction in relapse and higher treatment persistence.[26] In the NationMS cohort, DMT switches were frequent. Unfortunately, we were not able to analyze potential reasons in detail. The large proportion of persons with initial PL-DMT could contribute to this effect. Notably, initial HE-DMT was associated with younger age and higher initial EDSS. Within this initial HE-DMT subgroup, natalizumab was administered more often in women and fingolimod in men, potentially linked to family planning issues with restrictions for sphingosine-1-phosphate receptor modulators in women wanting to become pregnant.[12,27–30] In particular, the fact that a treatment is compatible with pregnancy seems to have a decisive influence on the substance actually used.

In summary, our analyses demonstrate that within the contemporary NationMS cohort, "traditional" sex-dependent differences regarding initial presentation of the disease and early evolution of disability were not present. This is in line with findings from another German cohort including participants with early CIS diagnosis and follow-up visits up to 4 years, which demonstrated no differences in early disease presentation and progression between women and men.[31] Sex did not play a distinct role in long-term disability progression, measured by the time to reach an EDSS score of 3 points, within our cohort.

General treatment patterns likewise did not differ by sex with some differences in the particular substance chosen between women and men. Younger age and higher initial disease burden represented by EDSS and initial diagnosis (CIS vs RRMS based on older diagnostic criteria versions) at onset seem to be the main drivers for initiating a first-line HE-DMT in the NationMS cohort. Our study did examine not only sex differences in MS course, but also influencing factors for initial treatment choice. Whether the fact that sex-independent treatment decisions were made in our cohort reflects the treatment landscape throughout Germany remains questionable. Based on our data, we conclude that sex should play a subsidiary role in the decision to favor HE-DMTs in therapy today. It can be hypothesized that sex-dependent decisions against initial HE-DMT may even lead to a long-term insufficiency of treatment given the lacking sex difference for reaching the EDSS milestone of 3.0.

Our analyses are limited by the comparably low number of participants in NationMS with initial HE-DMT and a lowering number of follow-up data at later stages of the disease, making it difficult to draw conclusions regarding the disease courses over longer time dependent on sex. An additional limiting factor is that the therapeutic landscape has changed since the start of the recruitment period, thus restricting generalizability. Follow-up analyses are thus necessary for our cohort. The sex-specific outcome analysis is limited by the fact that only the EDSS was used as a parameter. In particular, paraclinical activity and subjective disability are not investigated. As the NationMS cohort exclusively recruited in academic MS-specialized centers, a bias may be inherent to the setting as compared to registry-based data resulting in earlier diagnosis and more comprehensive treatment management.[32,33] The absence of sex influencing the choice of HE-DMT could be the result of a specialized environment. Therefore, these data cannot be used to make an unrestricted generalization about the therapy environment in Germany. As data were pooled across specialized MS centers, potential center-level variation could not be assessed; however, the participating sites operate within a comparable guideline-based care framework. These factors may contribute to a more homogeneous treatment pattern between women and men in our cohort, possibly offsetting sex effects in our analyses. As sex is considered to play a role in disease risk, etiology, onset, and progression, gender-associated factors are discussed to influence symptom recognition as well as access to care and quality of care, among others.[34] Unfortunately, gender constructs were not specifically addressed during the planning of NationMS, thereby limiting our analysis mostly to biological sex with only speculations about underlying gender-associated differences.

In conclusion, our analysis displayed less differences based on sex for early disease and treatment traits in a contemporary academic-based MS cohort as compared to other data. Factors influencing the initial decision for HE-DMT were mainly independent of sex but influenced by younger age and higher initial burden of disease (reflected by EDSS fulfillment of RRMS criteria at inclusion).

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Declaration of conflicting interests

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Data availability statement

Anonymised data are available to every qualified researcher upon reasonable request to the

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Supplemental material

Supplemental material for this article is available online.

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