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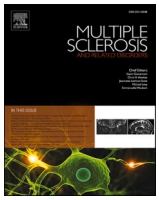

Original article

Impact of sex on clinical outcome in early Multiple Sclerosis

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ABSTRACT

Background: Previous evidence suggests sex differences in the clinical course of relapsing remitting multiple sclerosis (RRMS), but comprehensive early-stage prospective studies are lacking. We aim to quantify the impact of sex on clinical outcomes in early-stage RRMS.
Methods: Utilizing prospective cohort data, we assessed the impact of biological sex on time-to-relapse, disability progression (Expanded Disability Status Scale [EDSS]), extremity function (Nine-Hole Peg Test, Timed-25-food walk test), cognition (Paced Auditory Serial Addition Test, Symbol Digit Modalities Test), quality-of-life (Hamburg Quality of Life Questionnaire in Multiple Sclerosis, Short-Form-36), fatigue (Fatigue Severity Scale, Fatigue Scale for Motor and Cognitive functions), and depression (Beck Depression Inventory-II) in clinically isolated syndrome (CIS) or RRMS patients. Inclusion was within 12 months of symptom onset. Linear, negative binomial, mixed, and Cox models estimated male vs. female effects at the four-year follow-up including baseline-to-follow-up course.
Results: We included 149 patients (65.1 % female). Eighty-five completed four-year follow-up. No sex differences in time-to-relapse emerged (HR = 0.91;95 %CI = 0.53–1.58). Males had no increased risk of EDSS worsening (OR = 0.75;95 %CI = 0.21–2.35) compared to females. Similarly, minor/no sex differences emerged in other outcomes.
Conclusions: Four years after first manifestation, neither disease activity (disability progression and relapse rate) nor patient-reported outcomes showed sex-related disparities in this early-MS-cohort.
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1. Introduction

Multiple sclerosis (MS) is an autoimmune disease that primarily affects young adults. While its exact cause remains unclear to date, various factors contribute to its development and progression (AJ Thompson et al., 2018).

MS shows diverse clinical presentations and can vary in its course (AJ Thompson et al., 2018).

Women are more susceptible to relapsing-remitting MS (RRMS) compared to men by a ratio of approximately 2–3:1, with this sex disparity increasing in recent years (Gold et al., 2019).

However, the influence of sex on health outcomes is complex. Women seem to be disadvantaged in some respects, while men in others. For example, some studies have suggested accelerated disability accrual in males, while others have observed sex divergence in disease progression primarily among older patients, although the higher initial relapse rates found in women seem to diminish over time after disease onset (Ribbons et al., 2015; Magyari and Koch-Henriksen, 2022). In terms of cognition, women often seem to perform better in cognitive testing, however tended to self-evaluate their abilities as poorer, as compared to male patients (Motyl et al., 2024). Women often report slightly more depressive symptoms as well (Motyl et al., 2024). While there is conflicting evidence regarding which sex is more affected by fatigue and its impact on quality of life, this aspect remains relatively understudied in MS, especially concerning sex-specific considerations (Anens et al., 2014; Hadjimichael et al., 2008; Brola et al., 2016; Sabanagic-Hajric et al., 2022).

Nevertheless, most studies have primarily focused on conventional clinical outcomes like relapses and EDSS progression, leaving a gap in more detailed data regarding sex-related effects on disease activity and progression.

In this study, we investigate the impact of sex on MS relapses, disability progression and a range of other MS-specific and patient-reported outcomes (Quality of life, cognitive function, fatigue, upper limb function and maximum gait speed) in a well-characterized cohort of early MS patients.

2. Methods

2.2. Study design and population

This study is based on data from the prospective observational CIS-cohort (ClinicalTrials.gov Identifier: NCT01371071), a longitudinal study started in 2011, which included patients with diagnosis of clinically isolated syndrome (CIS) or RRMS, according to the 2017 McDonald Criteria, within six months after manifestation, and collected multidimensional data at annual study visits (AJ Thompson et al., 2018). Inclusion criteria for the CIS-cohort required participants to be at least 18 years old, provide written informed consent, and not to be currently pregnant. Exclusion criteria encompassed eye conditions affecting optical coherence tomography results, contraindications for MRI, and alcohol or substance abuse. Additionally, secondary progressive course led to exclusion, too.

For this analysis, we only selected patients with symptom onset less than 12 months at first visit (early MS), verified by medical reports, and with a minimum of four years of study participation prior to the analysis start, guaranteeing a four-year follow-up (4FU).

All patients within the study cohort were initially considered for inclusion; however, due to limitations in data availability, not all could be included in the subsequent analyses.

2.2. Patient characteristics

Baseline characteristics were assessed at time of enrollment and included demographic data, smoking history, social characteristics, and disease specific properties such as physical disability as measured e.g. by the EDSS (Table 1).

2.3. Definition of sex

Sex is considered as binary variable with subjects being either female or male.

2.4. Outcome definitions

We looked at a panel of clinical outcome measures, to obtain a comprehensive view on potential sex related differences.

We concentrated primarily on outcomes at four years after disease onset. Where we considered it useful and data permitted to carry out additional analyses that would help with clinical interpretation or provide information on the course over time, we added these to the respective outcomes. This has led to varied sample sizes within analyses (Supplemental Table I).

2.4.1. Relapses

We investigated time to first relapse after initial clinical manifestation within a 4FU period. A relapse was defined as new, MS-related symptoms lasting for at least 24 h, unrelated to other illnesses, and occurring at least 30 days after prior relapse (Polman et al., 2011). Patients reported their relapses retrospectively at each annual visit for the preceding year and experienced clinicians confirmed their validity.

3.4.2. Expanded Disability Status Scale

We compared physical disability of male to female MS patients at the 4FU, using the Expanded Disability Status Scale (EDSS), a standard measure for tracking disability progression in MS (Kurtzke, 1983). Worsening at the 4FU was defined as a 1.5-point increase for those with a baseline EDSS of 0, a 1-point increase for those with a baseline EDSS>0 and <6, and a 0.5-point increase for those with a baseline EDSS≥ 6 (Kappos et al., 2018).

2.4.3. Upper extremity function

We used the Nine-Hole Peg Test (9HPT) to assess upper extremity function (Supplemental Methods I) (Feys et al., 2017).

First, we examined sex-related differences in 4FU scores (completion time in seconds) for the dominant and non-dominant hands (i). Second, we investigated clinically significant deterioration, defined as 20 percent increase in 9HPT completion time from baseline to the 4FU (ii) (Schwid et al., 2002). Additionally, we examined (9HPT) baseline-to-follow-up course of annual 9HPT scores and the time differences between 4FU and baseline (iii, iv).

2.4.4. Lower extremity function

The lower extremities' function was examined using the Timed 25-Foot Walk (T25FW) (Supplemental Methods II) (Fischer et al., 1999).

We analyzed data analogous to the 9HPT (see i-iv).

2.4.5. Cognitive function

The impact of sex on cognitive function was assessed with the Brief Repeatable Battery of Neuropsychiatric Tests (BRB-N), comprising five subtests covering various cognitive domains (Supplemental Methods III) (Rao, 1990).

We determined cognitive impairment in patients with complete BRB-N-dataset at the 4FU as performance 1.5 standard deviations (SD) below healthy control group norms in at least two BRB-N subtests, following criteria previously used (Amato et al., 2010). Healthy control data were obtained from the VIMS ("Verlaufsuntersuchung visueller Parameter bei Patienten mit Multipler Sklerose versus gesunden Probanden zur Erstellung einer Datenbank, EA1/163/ 12) cohort.

Because the Paced Auditory Serial Addition Test (PASAT3) and the Symbol Digit Modalities Test (SDMT) are considered most sensitive to detect cognitive disabilities in MS, we calculated the impact of male vs.

Table 1
Baseline characteristics Table. N, number of patients; SD, standard deviation; IQR, interquartile range; *s*, seconds; BMI, Body-Mass-Index; EDSS, Expanded Disability Status Scale; T25FW, Timed 25-foot walk test; 9HPT, Nine-hole peg test; BRB-N, Brief Repeatable Battery of Neuropsychological Tests; SDMT, Symbol Digit Modalities Test; SRT-CLTR, Selective Reminding Test-Consistent Long-Term Retrieval; SRT-LTS, Selective Reminding Test-Long Term Storage; SRT-DR, Selective Reminding Test-Delayed recall; SPAT, 10/36 Spatial Recall Test; SPAT-DR, 10/36 Spatial Recall Test-Delayed recall; WLG, Word List Generation test; PASAT3, Paced Auditory Serial Addition Test-3; MRI, Magnetic resonance imaging; 95 %CI, 95 % confidence interval.

Parameter	All patients	Female patients	Male patients	Differences (mean/ percentage points and 95 %CI)
Number of patients, n (%)	149 (100)	97 (65.10)	52 (34.90)	
Age at onset, years, mean (SD)	32.46 (8.25)	32.38 (8.19)	32.62 (8.43)	−0.24 (−3.25–2.77)
BMI, mean (SD)	24.35 (4.76)	23.53 (4.42)	25.99 (5.04)	−2.46 (−5.40–0.48)
Current smoker, n (%)	26 (26.26)	17 (27.42)	9 (24.32)	3.1 (−12.6–18.8)
Years of school education, mean (SD)	12.36 (1.59)	12.34 (1.75)	12.39 (1.31)	−0.05 (−0.67–0.57)
Vitamin D level, nmol/l, mean (SD)	49.99 (22.38)	50.94 (22.61)	48.02 (22.24)	2.92 (−2.13–7.97)
Vitamin D deficiency (<50 nmol/l), n (%)	39 (52.70)	27 (54.00)	12 (50.00)	4 (−20.7–28.7)
Received pharmacological treatment, n (%)	48 (33.80)	30 (32.26)	18 (36.73)	−4.4 (−19.5–10.7)
EDSS baseline, median (IQR)	1.50 (1.00)	1.50 (1.00)	1.50 (1.13)	0.06*
mild (EDSS ≤2.5), n (%)	137 (91.95)	93 (95.88)	44 (84.62)	11.2 (−21.5–43.9)
moderate (EDSS 3.0–5.5), n (%)	12 (8.05)	4 (4.12)	8 (15.38)	−11.3 (−26.2–2.6)
T25FW, *s*, mean (SD)	4.17 (0.76)	4.21 (0.73)	4.11 (0.81)	0.10 (−0.17–0.37)
9HPT, dominant hand, *s*, mean (SD)	18.61 (2.48)	18.16 (2.21)	19.43 (2.74)	−1.27 (−2.26- −0.28)
9HPT, non-dominant hand, *s*, mean (SD)	19.50 (3.07)	19.39 (3.43)	19.69 (2.27)	−0.30 (−1.23–0.63)
BRB-N				
SDMT, mean (SD)	60.01 (10.75)	59.76 (9.95)	60.46 (12.14)	−0.70 (−4.58–3.18)
SRT-CLTR, mean (SD)	56.80 (13.21)	58.53 (11.86)	53.67 (14.97)	4.86 (0.47–9.25)
SRT-LTS, mean (SD)	60.10 (9.58)	61.58 (8.60)	57.43 (10.72)	4.15 (0.61–7.69)
SRT-DR, mean (SD)	11.35 (1.26)	11.52 (1.03)	11.06 (1.55)	0.46 (−0.02–0.94)
SPAT, mean (SD)	23.58 (4.37)	22.99 (4.55)	24.62 (3.86)	−1.63 (−3.04- −0.22)
SPAT-DR, mean (SD)	8.76 (1.63)	8.64 (1.71)	8.98 (1.45)	−0.34 (−0.88- 0.20)
WLG, mean (SD)	27.17 (5.96)	28.41 (5.99)	24.90 (5.24)	3.51 (1.93–5.09)
PASAT3, mean (SD)	49.20 (9.05)	48.68 (9.62)	50.16 (7.88)	−1.48 (−4.57–1.61)
MRI parameters				
T2 hyperintense lesion count, median (IQR)	13.00 (21.00)	10.50 (17.25)	16.00 (26.00)	−1.99*
Volume of T2 hyperintense lesions, ml, mean (SD)	2.12 (3.09)	1.92 (2.89)	2.50 (3.42)	−0.58 (−1.69- 0.53)

* We conducted a Mann-Whitney U test and computed Somers' D, given the ordinal nature of the data.

The proportion of missing data was less than 10 % in all parameters in Table 1, except for information on BMI (17.4 %), smoking status (33.6 %), years in school (34.9 %) and vitamin D level and deficiency (50.3 %). HAQUAMS, SF36, FSS, FSMC and BDI-II scores are not shown as part of the baseline characteristics, as they were only started to be collected during the study.

female sex on their 4FU scores (Chiaravalloti and DeLuca, 2008). In addition, we examined the baseline-to-follow-up course of cognitive function using annual PASAT3 and SDMT assessments.

2.4.6. Quality of life

We studied quality of life (QoL) at the 4FU using the German versions of the Hamburg Quality of Life Questionnaire in Multiple Sclerosis (HAQUAMS) and the Short Form 36 (SF36) (Supplemental Methods IV and V) (Gold et al., 2001; Ware and Sherbourne, 1992).

2.4.7. Fatigue

Fatigue was assessed using two different scales: the fatigue severity scale (FSS) and the fatigue scale for motor and cognitive functions (FSMC), which separates cognition and motor fatigue and is validated in MS patients (Krupp et al., 1989; Penner et al., 2009). For FSS, we analyzed four-year scores (Krupp et al., 1989). For FSMC, we examined absolute scores and categorized fatigue severity (none [<43], mild [43–52], moderate [53–62], severe [≥63]) at 4FU (Supplemental Methods VI and VII) (Penner et al., 2009).

2.4.8. Depressive symptoms

We analyzed depression using the Beck Depressions Inventory-II (BDI-II), a self-report questionnaire for measuring depressive symptom severity (Supplemental Methods VIII) (Beck et al., 1961). We examined absolute scores and the severity of depression (minimal [<13], mild [14–19], moderate [20–28], severe [≥29]) at the 4FU (Beck et al., 1961).

2.5. Statistical analysis

We summarized subject characteristics using descriptive statistics (mean, SD, median, interquartile range [IQR] boundaries, numbers, percentages) stratified by female and male MS patients. Relapse incident rate with 95 % confidence intervals (CI) was calculated separately for each sex.

For time-to-relapse analysis, we used Kaplan Meier estimation and log-rank test for group comparisons. Time-to-relapse was measured in person-years, with censoring at last contact or after 4FU. Cox proportional hazard models estimated hazard ratio (HR) for male versus female sex regarding first relapse within four years.

For continuous endpoints (EDSS, 9HPT, T25FW, PASAT3, SDMT, FSS, FSMC, HAQUAMS, SF36) at the 4FU and time differences (4FU-baseline) (9HPT, T25FW), linear regression models yielded β effect sizes for male versus female patients. Ordinal logistic regression estimated odds ratio (OR) for EDSS worsening.

We utilized negative binomial regression for skewed BDI-II data and transformed the logarithmic effect size linearly.

For baseline-to-follow-up course/over-time analyses (9HPT, T25FW, PASAT3, SDMT), we applied linear mixed models, including patient ID as random effect and sex and time-since-onset as fixed effects.

Study data were collected and managed through REDCap (Research Electronic Data Capture) – a web-based, secure application for research data capture – hosted at the NeuroScience Clinical Research Center (Harris et al., 2009).

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Descriptive and analytical statistics were conducted in R version 4.1.2.

2.6. Ethics

The study was approved by the local ethics committee (EA1/182/10) and conducted following the declaration of Helsinki.

3. Results

Between January 2011 and November 2017, a total of 180 patients had entered the CIS-cohort. Of these, we excluded 31 participants (Fig. 1), resulting in an analysis set of $n = 149$ participants, including 52 (34.9 %) male and 97 (65.1 %) female CIS/RRMS patients.

Fifty-two of patients in final analysis set (34.9 %) had CIS diagnosis at baseline. Fifty-nine patients (39.6 %) presented with optic neuritis as onset symptom. Median time to inclusion after onset of first symptoms was 136 (IQR = 90–167) days for females and 151 (IQR = 105–180) days for males. Table 1 details baseline patient characteristics, stratified by sex. There were no major differences between female and male patients at baseline, except for the MRI lesion count, where male participants were notably more affected (Table 1).

Eighty-five patients (57.0 % of 149, 63.5 % female) completed 4FU, with 53 (62.4 %) receiving MS-specific pharmacological treatment during this period. No baseline characteristic disparities were observed between patients who completed the follow-up and those who did not (Supplemental Table II and III).

3.1. Outcome data

3.1.1. Time to relapse

Out of 149 patients, 59 (39.6 %) experienced at least one relapse, with a mean time to relapse of 2.24 years (SD = 1.54). The overall relapse incidence rate was 17.38 (95 %CI = 13.46–22.81) per 100 person-years, with 18.37 (95 %CI = 13.13–25.02) in females and 16.39 (95 %CI = 9.86–25.59) in males. Kaplan-Meier analysis revealed no significant sex differences in time to relapse or relapse-free cumulative survival (log-rank test: $p = 0.74$) (Fig. 2). The HR for relapse within four years after onset was 0.91 (95 %CI = 0.53–1.58) for male versus female patients.

3.2. Physical disability

Out of 85 patients, 77 (63.6 % female) had available EDSS scores at the 4FU, with a median EDSS of 1.5 (IQR = 1.0–2.0) for females and 1.5 (IQR = 0.75–2.5) for males.

The crude coefficient (β) for EDSS at the 4FU was 0.17 (95 % CI=−0.20–0.54), indicating no EDSS score difference between males and females (Fig. 3). Sixteen patients (20.8 %) experienced EDSS worsening ($n = 77$), with 11 females (22.4 %) and five males (17.9 %). Males had an OR of 0.75 (95 %CI = 0.21–2.35) for EDSS worsening compared to females.

3.3. Upper extremity function

9HPT data at the 4FU were available for 76 patients (63.2 % female). Females averaged 17.46 s. (SD = 2.16 s.) for the dominant hand and 18.53 s. (SD = 1.71 s.) for the non-dominant hand, while males took 20.39 s. (SD = 3.46 s.) and 20.00 s. (SD = 2.49 s.), respectively. Females were slightly faster in both hands (dominant hand: β = 2.93, 95 %CI = 1.65–4.22; non-dominant hand: β = 1.48, 95 %CI = 0.51–2.44) (Fig. 3).

Four patients (5.3 % of 76, one female [2.1 %], three males [10.7 %]) showed deteriorations in the dominant hand's 9HPT and five (6.6 % of 76, two females [4.1 %], three males [10,7 %]) in the non-dominant hand's 9HPT.

Slight differences between males and females in 9HPT over time were observed (baseline individuals: 149 [65.1 % female], total observations: 629 [66,0 % female]) with females performing faster (β = 1.71, 95 %CI = 0.94–2.49 for dominant hand; β = 1.24, 95 %CI = 0.56–1.92 for non-dominant hand).

We found no sex differences for the absolute score difference between the 4FU and baseline in the 9HPT of the non-dominant hand ($n = 76$, females: mean = -0.46 s., SD = 4.08 s.; males: mean = 0.16 s., SD = 2.41 s., β = 0.62, 95 %CI = -1.07–2.31). Notable differences were observed for the dominant hand's 9HPT score difference ($n = 76$, females: mean=−0.56 s., SD = 1.58 s.; males: mean = 0.97 s., SD = 1.92 s., β = 1.53, 95 %CI = 0.72–2.35), indicating more decline among males.

3.4. Lower extremity function

T25FW data at the 4FU was available for 75 patients (62.7 % female). Females averaged 4.14 s. (SD = 0.66 s.), and males 4.23 s. (SD = 1.33 s.), with no sex differences (β = 0.09, 95 %CI=−0.37–0.55) (Fig. 3). Nine patients (12 % of 75, six females [12.2 %], three males [10.7 %]) exhibited T25FW deteriorations.

The β for course/over-time analysis (baseline individuals: 149 [65.1 % female], total observations: 625 [65.9 % female]) of the T25FW was −0.08 (95 %CI=−0.32–0.14), indicating no sex differences. The absolute T25FW score difference between the 4FU and baseline ($n = 75$, females: mean=−0.02 s., SD = 0.64 s.; males: mean = 0.07 s., SD = 0.75 s., β = 0.09, 95 %CI = −0.23–0.42) also showed no sex differences.

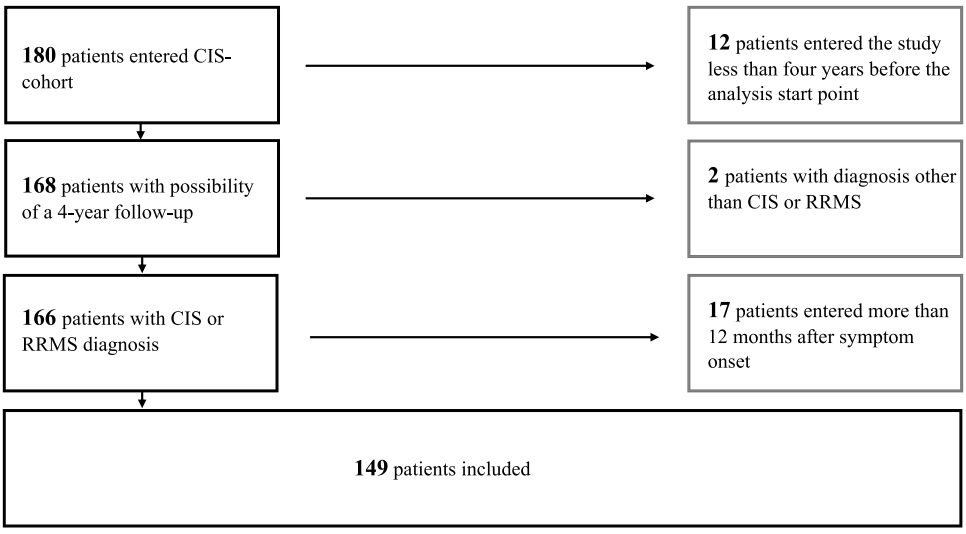

Fig. 1. Flowchart of project specific inclusion and exclusion. 149 CIS or RRMS patients with a possible follow-up of four years, who entered the CIS-cohort within 12 months after symptom onset.

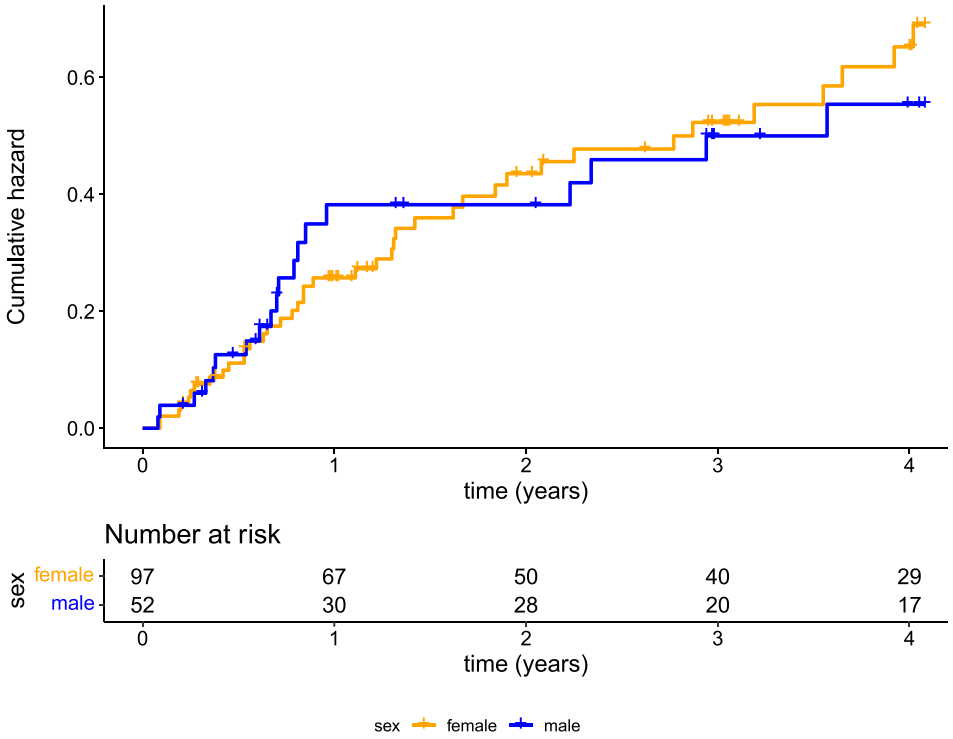

Fig. 2. Sex-specific Cumulative Hazard for Relapse in MS Patients. Cumulative hazard for new occurring relapse and risk table with number of patients at risk.

3.5. Cognitive function

Assessment of cognitive impairment at the 4FU was possible in 54 patients (59.3 % female). Six patients (11.1 %), three females (9.4 %) and three males (13.6 %), experienced cognitive impairment.

At 4FU, PASAT3 scores were available for 71 patients (63.4 % female) and SDMT scores for 72 patients (62.5 % female). Females' mean PASAT3 score was 54.18 (SD = 6.91) and mean SDMT score was 64.40 (SD = 11.57). Males' mean PASAT3 score was 55.27 (SD = 4.85) and mean SDMT score was 62.04 (SD = 16.14).

No sex differences were found in PASAT3 and SDMT scores at the 4FU or over time: The β for PASAT3 scores between males and females was 1.09 (95 %CI = −1.98–4.16), and −2.36 (95 %CI=−8.89–4.17) for SDMT scores at the 4FU (Fig. 3). Over all PASAT3 assessments (baseline individuals: 149 [65.1 % female], total observations: 608 [65.6 % female]), the β was 1.24 (95 %CI=−1.28–3.76), and −0.65 (95 % CI=−4.41–3.10) for SDMT assessments (baseline individuals: 149 [65.1 % female], total observations: 530 [65.7 % female]) over four years.

There were no systematic differences in conducted test number between female and male patients (Supplemental Results I).

3.6. Quality of life

The HAQUAMS score at the 4FU was available for 69 individuals (63.8 % female). Mean score was 1.73 (SD = 0.26) for female and 1.74 (SD = 0.44) for male patients. The β for the difference in HAQUAMS scores between female and male was 0.01 (95 %CI=−0.16–0.18), indicating no sex differences (Fig. 3).

SF36 scores at the 4FU were available for 74 participants (63.3 % female). Two subscales ("physical function" and "role limitation due to physical health") were missing in 16 females and nine males. Analyses of all SF36 subscales ("physical function", "pain", "role limitations due to physical health", "general health perceptions", "vitality", "social functioning", "role limitations due to personal or emotional problems", "emotional well-being") demonstrated no sex differences (Supplemental Table IV and Supplemental Figure I).

3.7. Fatigue

Fatigue scores (FSS and FSMC) at the 4FU were available for 72 patients (63.5 % female). No differences were found between males and females in the FSS score (females: mean = 2.49, SD = 1.26, males: mean = 2.42, SD = 1.49, β=−0.07, 95 %CI=−0.73–0.58) (Fig. 3). Mean FSMC score at the 4FU was 18.09 (SD = 16.35) for females and 17.33 (SD = 20.47) for males. No differences were found between males and females (β=−0.76, 95 %CI=−9.49–7.98) (Fig. 3). Most patients had no fatigue (40 females [88.9 %], 24 males [88.9 %]), three females (6.7 %) had mild fatigue, and one male (3.7 %) and two females (4.4 %) presented with moderate fatigue. Two males (7.4 %), but no females, experienced severe fatigue symptoms.

3.8. Depressive symptoms

BDI-II score at the 4FU were available for 69 patients (60.9 % female). Females' mean BDI-II score was 4.45 (SD = 5.33), while males' mean score was 4.81 (SD = 7.21). The analysis revealed an effect size of 0.08 (95 %CI=−0.71–0.87; linearized effect size: 0.08, 95 % CI=−0.72–0.87), indicating no impact of sex on depression (Fig. 3). Most participants had minimal depression (39 females [92.6 %], 24 males [88.9 %]), with few experiencing mild (two females [4,8 %], two males [7.4 %]) or moderate depression (one female [2.4 %]). Only one male participant (3.7 %) had severe depression.

4. Discussion

This study found no differences between male and female patients in time to relapse, physical disability, cognitive function, QoL, fatigue, and depression four years after the initial clinical manifestation of MS. Only in dominant hand motor tasks, males slightly underperformed compared to females. However, subtle differences may not have been identified due to our small sample size. Therefore, our data should be interpreted with caution and along with other studies.

Previous studies examined sex differences in disease activity

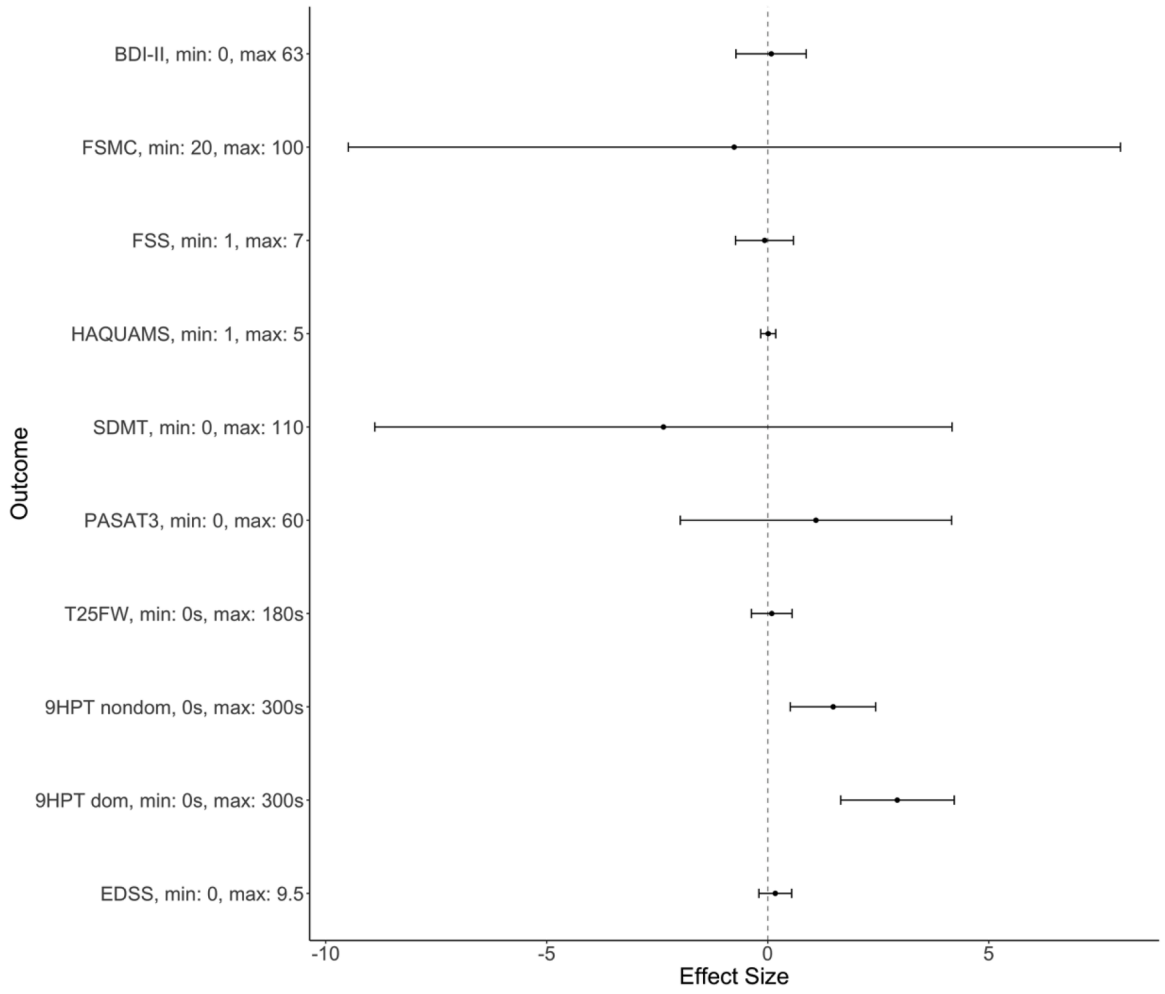

Fig. 3. Linear effect sizes of clinical outcomes. Each line represents one outcome parameter with linear effect size (β effect size or linear transformed effect size) and 95 %CI. Effect sizes greater than 0 indicate that males took longer or scored higher in the respective test or outcome parameter. EDSS, Expanded disability status scale; PASAT3, Paced Auditory Serial Addition Test-3; SDMT, Symbol Digit Modalities Test; 9HPT, Nine-Hole Peg Test; dom, dominant hand; nondom, nondominant hand; T25FW, Timed 25-foot walk test; HAQUAMS, Hamburg Quality of Life Questionnaire in Multiple Sclerosis; FSS, Fatigue Severity Scale; FSMC, Fatigue Scale for Motor and Cognitive Functions; BDI-II, Becks Depression Inventory-II; min, minimal achievable score/minimal time to be measured; max, maximal achievable score/maximal time to be measured; s, seconds.).

(disability progression and relapse rate) using cohort or registry data (Ribbons et al., 2015; Magyari and Koch-Henriksen, 2022; Kalincik et al., 2013). Our data deriving from a prospective cohort is complementary as it provides data from a rather homogenous early MS group (age, only CIS and RRMS) shortly after disease onset.

Our results align with prior research, indicating no substantial sex disparities in physical disability in early-stage MS (Magyari and Koch-Henriksen, 2022). Any differences reported in other studies were generally minor and more pronounced in later disease stages or among individuals aged 45 and older, increasing with advancing age (Ribbons et al., 2015; Magyari and Koch-Henriksen, 2022). Since our study does not include this age group, we could not confirm these reported distinctions.

Our patient cohort primarily comprises young individuals with minimal impairments, as evidenced by consistent baseline and 4FU EDSS scores of 1.5, indicating no disease progression. Many patients - without differences between sex - received early immunotherapeutic interventions. Given the cohort's stability and relative healthiness, the absence of noticeable sex differences aligns with parallel cohort data (Cree et al., 2016). Sex-related distinctions may become more apparent in later disease stages as disability progresses.

Other studies found higher relapse rates in female patients, which we could reproduce (Kalincik et al., 2013). However, those differences were statistically insignificant in our cohort.

Moreover, prior research mainly focused on broader disease activity measures like relapse rates and EDSS progression (Magyari and Koch-Henriksen, 2022; Kalincik et al., 2013). Our analysis provides additional insights into early MS, specifically regarding physical disability and functional outcomes. The 9HPT and T25FW, assessing upper and lower limb function, offer accurate disability evaluation but are infrequently reported (Koch et al., 2021).

Our team's earlier VIMS study on later-stage MS patients found that, compared to females, males performed worse in hand motor tasks but similarly in walking speed, consistent with our findings (Voskuhl et al., 2020). Our patients showed performance differences already at baseline, possibly indicating either non-MS-related inherent sex differences or early MS-related manifestations preceding clinical onset.

Some studies have described sex differences in cognitive function among MS patients (Voskuhl et al., 2020; Beatty and Aupperle, 2002). These data indicate that males perform worse in memory, visuospatial and cognitive screening tests but not in BRBN tests, aligning with our findings (Voskuhl et al., 2020; Beatty and Aupperle, 2002).

Prior research on fatigue presents conflicting findings, with some indicating greater fatigue in female RRMS patients, while others suggest more severe fatigue in males (Anens et al., 2014; Hadjimichael et al., 2008). In our data, no clear sex-related fatigue differences were evident,

with two males but no females experiencing severe fatigue.

Sex differences in MS-QoL also vary in literature. While some studies detected differences, others, like ours, found none (Brola et al., 2016; Sabanagic-Hajric et al., 2022). Similarly, we detected no differences in depression scores between male and female MS patients. Data in this regard are consistent, with no apparent sex-based differences, even in later disease stages (Chan et al., 2021).

The disease course is further shaped by complex biological interactions, including hormone fluctuations. For instance, elevated estrogen levels during pregnancy impact immune cell function, resulting in a significant reduction in MS relapse frequency, particularly notable in the latter stages of gestation (Airas and Kaaja, 2012).

Our findings highlight the necessity of moving beyond simplistic binary sex (i.e. male vs. female) divisions in medical inquiries. Regarding MS, it may be necessary to quantify sex hormone levels, as these interfere with immunological processes (Lombardo et al., 2024). Longitudinal T25FW analysis shows sex alone insufficiently predicts impairment (Gunzler et al., 2023). Socioeconomic factors and gender may provide better explanations for disease progression, as these determine behavior, lifestyle, and life experiences, which in turn determines access to and use of the healthcare system (Mauvais-Jarvis et al., 2020). For instance, concerning cardiovascular diseases, recent research revealed that gender, rather than biological sex, predicted risk of recurrent acute coronary syndrome (Pelletier et al., 2016).

4.1. Strength and limitations

Strengths of our study include enrolling participants at a consistent early disease stage, ensuring cohort homogeneity over the four-year early disease phase. Additionally, we maintained uniformity across various factors including socioeconomic status, education level, and urban environment.

However, our study's limitation is its rather small sample size, potentially hindering detection of small effects that larger registry-based studies identified previously. Large registry analyses are known to identify very small effects, which are often explained due to chance, selection bias, confounding (Hochster, 2008). Additionally, these small effects are often of questionable clinical relevance. For example, previous studies found an HR of 1.1 (95 %CI = 1.05–1.14) for the occurrence of new relapses 40 years after disease onset and a male:female ratio of 1.0216 (95 %CI = 1.003–1.029) for deterioration of EDSS points per years, concluding higher inflammatory disease activity in women and a faster disability progression in men (Magyari and Koch-Henriksen, 2022; Kalincik et al., 2013). The study conclusions are contrasting our study findings with several possible explanations. Although we previously noted the limited statistical power of our study, such samples have still revealed clinically relevant effects in the past (Voskuhl et al., 2020; Tolaymat et al., 2020). Additionally, effects identified by registry-based studies should be interpreted in the context of predefined 'minimal effect of relevance' (Thygesen and Ersboll, 2014). However, this reference benchmark is missing rendering it challenging to interpret whether these effects possess any clinical relevance. Another potential explanation for the differences in conclusions between our study and previous data is that our analysis was limited to data from the early MS phase, while the respective studies included data spanning decades. However, we believe that, particularly in this context, one should refrain from drawing too strong conclusions about apparent sex differences based on minimal estimated effects.

Limitations pertain to our outcome parameters: relapses within a year were recorded at the subsequent visit, introducing potential recall bias. To counter this, an experienced clinician validated subsequent relapses. This limitation is unlikely to impact our results since it applies to both sexes.

Furthermore, our analyses could be affected by incomplete examination data for some participants, necessitating calculations with varying patient counts.

4.2. Conclusion

Our data supports prior findings of no major sex differences in early-stage RRMS outcomes, though this could evolve as disability becomes more pronounced. Future research should investigate potential sex-related effects on inflammation and neurodegeneration biomarkers.

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Data statement

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

CRediT authorship contribution statement

N.S. Gottwald: Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **S. Asseyer:** Writing – review & editing. **C. Chien:** Writing – review & editing. **J. Brasanac:** Writing – review & editing. **A.T. Nauman:** Writing – review & editing. **R. Rust:** Writing – review & editing. **T. Schmitz-Hübsch:** Writing – review & editing. **J. Bellmann- Strobl:** Writing – review & editing. **K. Ruprecht:** Writing – review & editing. **F. Paul:** Writing – review & editing. **V. Regitz-Zagrosek:** Writing – review & editing. **S.M. Gold:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization. **P.S. Sperber:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Conceptualization.

Declaration of competing interest

N.S. Gottwald has no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2024.105749.

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