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MSJ Experimental Translational Clinical

Original Research Article

Evaluation of patient-perceived fatigue in multiple sclerosis utilizing the Finnish MS registry

Multiple Sclerosis Journal—Experimental, Translational and Clinical

January–March 2025, 1–9

DOI: 10.1177/20552173251325098

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Abstract

Objectives: To characterize patient-perceived fatigue by using the Finnish Multiple Sclerosis (MS) registry data.

Materials & Methods: Fatigue was assessed with the Fatigue Severity Scale (FSS), the Fatigue Scale for Motor and Cognitive Functions (FSMC), and the Visual Analogue Scale—Fatigue. Disease severity was evaluated with the Expanded Disability Status Scale and symptoms with the Visual Analogue Scales. Patient reported outcomes (PROs) included the Multiple Sclerosis Neuropsychological Questionnaire, the Euro Quality of Life – 5 dimensions, the 15 D, and the Multiple Sclerosis Impact Scale. For the purposes of the study, patients were classified to those without (FSS ≤ 4) and those with (FSS ≥ 5) fatigue. The FSS scores were correlated with the results of other PROs.

Results: Based on the 512 FSS scores, 47% of the patients reported fatigue (FSS ≥ 5). Fatigue was related to higher disability, lower education, and smoking. FSS correlated significantly with other measures of fatigue, cognitive, and mood symptoms, and was associated with lower Quality of Life.

Conclusions: As an invisible and debilitating symptom fatigue should be evaluated systematically. In the screening, it is important to recognize the characteristics of the different scales. Whereas the FSS may serve as an overall screen, the FSMC may help to identify aspects of cognitive and motor fatigue separately.

Keywords: multiple sclerosis, fatigue, digital patient monitoring, patient-generated data, patient reported outcomes, registry data

Date received: 7 October 2024; accepted: 13 February 2025

Introduction

Fatigue has been presented as the most common and disabling symptom of MS with the prevalence rate of up to 80%.[1–5] Fatigue has been shown to have a negative impact on overall quality of life, work capacity, mental health, cognition, and physical activities.[2,6–8] It has been defined to manifest as the decrease in physical and/or mental performance that results from changes in central, psychological, and peripheral factors. These changes depend on the task being performed, the environmental conditions it is performed in, and the physical and mental capacity of the individual.[9] As an invisible symptom fatigue remains often underdiagnosed and due to its detrimental effects, there is a call for early diagnostics.[5] Because the underlying mechanisms of fatigue are multifaceted and no clear definition for the symptom exists, its assessment is particularly challenging and relies heavily on patient report.[1,10] There are various scales for the assessment of fatigue without a consensus on which to use. The fact that fatigue often co-exists with other symptoms like depression and cognitive problems further complicates the assessment of the symptom.[1,2,8]

The Finnish national MS registry was launched in 2014 and is used in 17 out of 21 Finnish wellbeing services counties in the treatment of patients with MS.[11] In addition to the systematic follow-up of the patients, it offers the possibility to follow incidence, prevalence, and progression of MS in Finland. An

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interface for patient-reported outcome measures (PROMs) called MyMS was added to the registry in 2017, to allow for electronic collection of patient-perceived aspects of the disease, such as disability, relapses, specific symptoms, quality of life (QoL), and lifestyle factors.[12] MyMS gives patients a way to track the evolution of their disease while also providing the treating physician with the patient perspective.[12,13] Special attention has been given to the possibility to screen invisible symptoms of MS, such as fatigue, by the means of the Fatigue Severity Scale (FSS),[14,15] the Fatigue Scale for Motor and Cognitive Functions (FSMC),[16,17] and Visual Analogue Scale on Fatigue (VAS-F)[13] which have all been integrated into the patient interface of the Finnish MS registry.[12,13]

The objective of the present study is to characterize patient-perceived fatigue by using data collected through the patient interface of the Finnish MS registry. More specifically, the prevalence of self-perceived fatigue and relationship between fatigue and other PROMs were evaluated. A special emphasis was put on the analysis of the effects of fatigue on QoL and impact of the disease. Furthermore, the results of the two commonly used PROMs on fatigue, the FSS and the FSMC, were compared to better understand the specific characteristics of each scale.

Materials and methods

This is a retrospective, non-interventional, registry-based study utilizing data from the patient interface of the Finnish MS registry, which is available for all those MS patients who have been registered in the clinician-based MS registry.[12] These patients have a validated MS diagnosis and are actively treated and followed at the neurology clinics of the hospitals. MyMS is an information secure service where the patient uses a secure national e-identification service for identification. It provides the patient with a user-friendly and graphically illustrative interface for patient-generated data including validated PROMs.

The FSS[14,15] was implemented to MyMS in 2017 whereas the FSMC,[16,17] and the VAS-Fatigue[13] at the end of 2020. The FSS consists of nine fatigue-related statements with a scale from 1 (strongly disagree) to 7 (strongly agree). The mean score serves as the study variable. The FSMC consists of 20 statements related to motor and cognitive aspects of fatigue with a scale ranging from 1 (totally disagree) to 5 (totally agree). The total score (range 20–100), and separate scores for cognitive and motor fatigue (range 10–50) serve as the study variables. According to the cutoffs, a total score under 43 indicates no fatigue, 43–52 mild, 53–62 moderate and 63 and over severe fatigue. For cognitive fatigue, a score under 22 indicates no fatigue, 22–27 mild, 28–33 moderate and 34 and over severe fatigue. For motor fatigue, a score under 22 indicates no fatigue, 22–26 mild, 27–31 moderate and 32 and over severe fatigue.[16] The VAS-Fatigue score ranges from 0 (no fatigue) to 100 (worst possible fatigue).

Disability is evaluated with the Expanded Disability Status Scale (EDSS)[18] and the Patient Reported Expanded Disability Status Scale (PREDSS).[12,19] Other patient-reported outcome measures included in the analysis are the Multiple Sclerosis Neuropsychological Questionnaire (MSNQ),[17,20] VAS-Cognition (VAS-C) and VAS-Mood (VAS-M),[13] the Euro Quality of Life—5 Dimensions (EQ-5D),[21] the 15 D,[22] and the Multiple Sclerosis Impact Scale (MSIS-29).[23,24] To evaluate the characteristics of self-perceived fatigue, MyMS users were classified into those without fatigue (FSS ≤ 4) and those with pronounced fatigue (FSS ≥ 5).[25]

The data was extracted in January 2023. The sample consists of data from five out of 21 Finnish wellbeing services counties with 512 patients with FSS score. The five counties featured diverse populations, with MyMS usage varying between under 10% and over 20%.[12]

Ethical approval and statistical analyses

According to Finnish legislation, the approval of an ethical committee was not required, as the study was a non-interventional registry study in which patients were not contacted. Patients consent to the use of the data for research purposes when they log into the registry. All data use was permitted via Finnish Social and Health Data Permit Authority Findata with registry keepers permission number THL/2104/14.05.00/2023 findata-rems-2023. Clinical data was extracted from the Finnish MS registry and PROM data from the MyMS interface for patient-reported measures and recordings. StellarQ Ltd is the data processor for all the extracted data.

Date imputation as middle of the month or year was used for clinical variables with partial dates. However, date imputation was not needed for patient-reported data. Patients were assigned to two groups based on their FSS score using "worst-case scenario" selection, meaning that a patient was assigned to the group with fatigue if s/he scored ≥ 5 at any time during follow-up period, and the first corresponding date was set as the index date. Age and disease duration were calculated based on the selected index

date. Descriptive statistics for demographics included means, standard deviations, medians, and quartiles for continuous variables, and counts and proportions for categorical variables. In addition, the proportion of missing data was reported. Group comparison for continuous variables was calculated using non-parametric Wilcoxon rank-sum test and for categorical variables using the Fisher's exact test.

In correlation analyses, each paired sample was derived as the first matching date within 28 days between the FSS and other PROMs. Correlation coefficients were based on Pearson's product moment correlation. To control and check the False Discovery Rate, Benjamini-Hochberg procedure was used as correction for multiple comparisons.

Univariate and full multivariate linear regression model was fitted to model QoL variables. Beta estimates were reported with corresponding 95% confidence intervals. Underlying multicollinearity was checked, and usage of selected variables was confirmed using variance inflation factors (VIFs). Diagnostic checks were made to detect possible influential outliers. Based on studentized residuals and Cook's distance zero, influential outliers were not detected to consider refitting the model. Scatter plots were created to show the relationship between the FSS score and the scores of the FSMC.

P-values under 0.05 after the correction were considered significant. All data analyses were done using RStudio (version 2021.09.1).

Results

Based on the FSS score, 47% of the patients reported pronounced fatigue at some point during the follow up ($FSS \geq 5$; $n = 241$), 8% reported borderline fatigue ($4 < FSS < 5$; $n = 41$), and 45% did not report fatigue ($FSS \leq 4$; $n = 230$). Using less stringent criterion ($FSS > 4$), 55% of the patients reported fatigue. Patients with self-perceived fatigue ($FSS \geq 5$) were more disabled, less educated and were more often smokers than patients without fatigue (Table 1). They did not differ from the patients without fatigue with respect to age, sex, disease duration, or number of patients with relapsing remitting course of the disease. Patients with fatigue differed from the patients without fatigue on each of the PROM used. They reported higher disability, more problems with cognition and mood as well as lower QoL and more negative impact of the disease (Table 1).

The FSS score did not correlate with disease duration but correlated significantly with disability both as measured with the EDSS and the self-reported equivalent, the PREDSS (Table 2). The correlations between the FSS score and the VAS-F, VAS-C, and VAS-M were significant. Moreover, the FSS score correlated significantly with the impact of the disease (MSIS-29) and showed a strong negative correlation with measures of QoL (EQ-5D, 15D). The FSS score showed a strong correlation with both the total score, and the motor and cognitive sub-scores of the FSMC. Furthermore, the correlations between the FSS score and the MSNQ scores on cognitive problems were significant, where the strongest correlation was between the FSS and the attention-related questions of the MSNQ (Table 2).

As shown in the correlation analyses (Table 2), self-perceived fatigue was associated with lower QoL measured both with the EQ-5D and the 15D, and negative impact of the disease as measured with the MSIS-29. Univariate regression analyses showed that fatigue alone, as measured with the FSS, explained lower QoL and more negative impact of the disease (Table 3). The clinician evaluated EDSS, as well as a progressive course of the disease showed similar explanatory value. Further, smoking seemed to have a negative impact on QoL as measured with the 15D and the MSIS-29. A multivariate model confirmed that fatigue measured with the FSS, together with disability, measured with the EDSS, explained the lower QoL and the negative impact of the disease. In addition, a progressive course of the disease, as well as age and smoking, were found to be supportive variables which help to explain the negative impact on MSIS-29 and 15D, respectively.

As shown in the correlation analyses (Table 2), the FSS score showed a strong correlation with both the total score, and the motor and cognitive sub-scores of the FSMC. Figure 1 shows specifically the relationship between the FSS score and the scores of the FSMC in patients without fatigue ($FSS \leq 4$) and those with pronounced fatigue ($FSS \geq 5$), the vast majority of the patients with $FSS \geq 5$ showed severe overall, cognitive, and motor fatigue according to the FSMC.

Discussion

In the present Finnish registry sample, 47% of patients with MS reported fatigue when defined as FSS score of 5 or over. This finding is in line with the findings of the Finnish FSS validation study[15] with a prevalence rate of 48% and a UK registry study[26] with a prevalence rate of 55% when using the same criterion for fatigue.

Table 1. Comparison of patients without fatigue (FSS ≤ 4) and with fatigue (FSS ≥ 5).

Demographic and disease variables	Total (N = 512)	FSS ≤4 (n = 230)	FSS ≥5 (n = 241)	*p-value*[#]
Age at MS onset (years), Mean (SD)	32.9 (9.76) [22%]	32.7 (9.12) [20%]	33.2 (10.32) [25%]	0.65
Age at MS diagnosis (years), Mean (SD)	35.3 (10.08)	34.7 (9.59)	35.7 (10.22)	0.25
Age at data extraction (years), Mean (SD)	43.4 (10.42)	43.1 (10.63)	43.8 (9.91)	0.40
Sex (Female), n (%)	405 (79.1%)	178 (77.4%)	195 (80.9%)	0.37
Disease course (RRMS[#]), n (%)	417 (81.4%)	192 (83.5%)	195 (80.9%)	0.47
Disease duration (years), Median (Q1-Q3)	5.7 (1.3–12.5)	6.4 (1.4–12.3)	5.5 (1.3–12.9)	0.86
EDSS, Median (Q1-Q3)	2.5 (1.5–3.5) [40%]	2.0 (1.5–2.5) [38%]	3.0 (2.0–4.9) [41%]	<0.001***
Education (years), Mean (SD)	14.1 (2.67) [20%]	14.6 (2.79) [20%]	13.7 (2.54) [20%]	<0.001***
Smoking (Yes), n (%)	67 (13.3%) [2%]	18 (7.9%) [1%]	39 (16.7%) [3%]	0.005**
Patient reported outcomes				
PREDSS, Median (Q1-Q3)	3.0 (1.0–4.0) [74%]	2.0 (1.0–2.0) [77%]	3.0 (3.0–4.0) [69%]	<0.001***
VAS scores, Median (Q1-Q3)				
Fatigue	40.5 (20.0–73.2) [77%]	20.0 (15.0–30.0) [78%]	71.0 (50.0–80.0) [71%]	<0.001***
Cognition	30.0 (14.0–59.2) [81%]	16.0 (9.0–25.2) [84%]	44.0 (29.0–70.0) [71%]	<0.001***
Mood	13.5 (8.2–37.5) [82%]	9.5 (5.0–14.2) [85%]	30.0 (10.0–60.5) [74%]	<0.001***
Quality of life measures, Median (Q1-Q3)				
EQ-5D score	0.8 (0.7–0.9) [77%]	0.9 (0.8–1.0) [73%]	0.7 (0.6–0.8) [77%]	<0.001***
15D score	0.8 (0.7–0.9) [13%]	0.9 (0.8–0.9) [11%]	0.7 (0.7–0.8) [16%]	<0.001***
MSIS-29, total score, Median (Q1-Q3)	21.6 (9.5–40.5) [23%]	9.5 (4.3–17.2) [14%]	41.4 (30.6–52.6) [29%]	<0.001***
FSMC scores, Median (Q1-Q3)				
Total	66.0 (45.0–80.0) [70%]	39.5 (27.8–57.0) [69%]	80.0 (71.0–88.0) [64%]	<0.001***
Motor	34.0 (21.0–40.0) [69%]	20.0 (15.0–29.0) [68%]	40.0 (35.8–44.0) [64%]	<0.001***
Cognitive	32.0 (21.0–41.0) [69%]	21.0 (13.0–28.0) [68%]	40.5 (35.8–45.0) [64%]	<0.001***
MSNQ score, Median (Q1-Q3)	33.0 (27.5–42.0) [85%]	27.0 (25.0–30.0) [91%]	37.5 (32.0–44.0) [74%]	<0.001***

[#]Footnote to Table 1. RRMS = relapsing-remitting multiple sclerosis, EDSS = Expanded Disability Status Scale (EDSS), PREDSS = Patient-reported EDSS, VAS = Visual Analogue Scale, EQ-5D = Euro Quality of Life – 5 dimensions, MSIS-29 = Multiple Sclerosis Impact Scale – 29, FSMC = Fatigue Scale for Motor and Cognitive Functions, MSNQ = Multiple Sclerosis Neuropsychological Questionnaire, [xx%] = Percentage of missing values, ***p < 0.001 **p < 0.01.

The patients in the present study were on average ten years younger, had shorter disease duration, more often relapsing disease, and reported less disability than the patients in the two aforementioned studies. Whereas the age difference may explain the slight discrepancies in the observed prevalence rates, our findings

Table 2. Correlation between the FSS score (n = 512) and other variables.

	Pairwise comparisons	Pearson's *coef (p-value[#])*
Disease duration	512	0.00 (0.97)
EDSS[#]	343	0.40 (<0.001***)
PREDSS	197	0.42 (<0.001***)
VAS scores		
Fatigue	177	0.73 (<0.001***)
Cognition	162	0.58 (<0.001***)
Mood	148	0.39 (<0.001***)
Quality of life measures		
EQ-5D score	183	−0.61 (<0.001***)
15D score	459	−0.73 (<0.001***)
MSIS-29 scores		
Total	426	0.75 (<0.001***)
Physical	429	0.71 (<0.001***)
Psychological	438	0.68 (<0.001***)
FSMC scores		
Total	224	0.88 (<0.001***)
Motor	226	0.88 (<0.001***)
Cognitive	225	0.83 (<0.001***)
MSNQ scores		
Total	125	0.59 (<0.001***)
Memory and learning	157	0.53 (<0.001***)
Attention	201	0.62 (<0.001***)
Verbal, problem solving, and behavior	141	0.57 (<0.001***)

[#]Footnote to Table 2. EDSS = Expanded Disability Status Scale, PREDSS = Patient-Reported EDSS, VAS = Visual Analogue Scale, EQ-5D = Euro Quality of Life – 5 Dimensions, MSIS-29 = Multiple Sclerosis Impact Scale, FSMC = Fatigue Scale for Motor and Cognitive Functions, MSNQ = Multiple Sclerosis Neuropsychological Questionnaire, ***p < 0.001.

indicate that fatigue is a symptom of MS that may present early in the disease trajectory. The prevalence found in the present study is lower than that reported in a Norwegian registry study[3] and a Finnish cross-sectional study,[4] where fatigue was reported in 81 and 73% of patients, respectively. In the latter two studies, the frequency was, however, based on the FSMC instead of the FSS, which probably explains the discrepancy.

In line with previous studies,[3,4,15,26] disability as measured with the EDSS correlated significantly with fatigue. In addition, the patient-reported equivalent of the EDSS, the PREDSS, showed a similar association with fatigue, indicating that self-assessment is a valid surrogate if the clinician based EDSS evaluation is not available. In our sample, age and sex were not associated with fatigue, which is in line with the findings of a UK registry study[26] but contrary to the findings of a Norwegian registry study.[3] We also observed that fatigue was related to lower education and smoking. However, only a small proportion of the patients were smokers and, thus, the finding should be considered preliminary, although it is in line with the findings of the UK registry study.[26] In previous reports, fatigue has been associated with a higher risk of premature discontinuation of the disease-modifying treatment, leading to periods of inefficient suppression of neuroinflammation which predisposes patients to a higher risk of disability accumulation. In MS disability, fatigue, and lower quality of life are intertwined, which we observed in our data as well.[4,27]

In our sample, the FSS score showed strong correlation with the scores of two other fatigue measures, namely the VAS-F, and the FSMC. In clinical practice, it is important to know how to interpret the results of different self-rating questionnaires. For the FSS, different scores have been suggested as cutoffs for fatigue.[15] A cutoff of five or over represents a stringent criterion of fatigue, whereas cutoff of 4.5 or even 4.0 has also been used. The criteria of 4.5 or 5.0 or over typically

Table 3. Modelling factors related to QoL and impact of the disease by using demographic variables, FSS score, and clinician-rated disability.

	EQ5D[#]		15D		MSIS-29	
	Univariate model β (95% CI); p-value[#]	Multivariate model β (95% CI); p-value	Univariate model β (95% CI); p-value	Multivariate model β (95% CI); p-value	Univariate model β (95% CI); p-value	Multivariate model β (95% CI); p-value
Sex – Male	0.04 (−0.02, 0.10)	0.05 (0.00, 0.09)*	0.02 (0.00, 0.04)	0.01 (−0.01, 0.02)	−0.60 (−4.71, 3.52)	−0.05 (−2.33, 2.23)
Age	0.00 (−0.01, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.14 (−0.09, 0.37)	−0.17 (−0.31, −0.03)*
Disease duration	0.00 (−0.01, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.20 (−0.11, 0.51)	−0.11 (−0.30, 0.09)
Disease course —SP/PP	−0.09 (−0.15, −0.02)**	0.01 (−0.05, 0.06)	−0.05 (−0.07, −0.02)***	0.01 (−0.01, 0.02)	12.69 (8.12, 17.25)***	3.32 (0.18, 6.47)*
Smoking—Yes	−0.05 (−0.13, 0.03)	−0.01 (−0.07, 0.05)	−0.04 (−0.07, −0.01)**	−0.02 (−0.04, −0.01)**	6.07 (0.99, 11.14)*	2.37 (−0.46, 5.19)
FSS	−0.06 (−0.07, −0.04)***	−0.04 (−0.05, −0.03) ***	−0.05 (−0.05, −0.04)***	−0.04 (−0.04, −0.03)***	8.29 (7.47, 9.11)***	6.57 (5.77, 7.36) ***
EDSS	−0.07 (−0.08, −0.05)***	−0.05 (−0.07, −0.03) ***	−0.04 (−0.05, −0.03)***	−0.02 (−0.03, −0.02)***	7.55 (6.37, 8.74)***	4.54 (3.40, 5.68) ***

[#]Footnote to Table 3: SP = secondary progressive, PP = primary progressive, FSS = Fatigue Severity Scale, EDSS = Expanded Disability Status Scale, EQ-5D = Euro Quality of Life – 5 Dimensions, MSIS-29 = Multiple Sclerosis Impact Scale ***$p < 0.001$ **$p < 0.01$ *$p < 0.05$.

estimate a fatigue frequency of approximately 50%, with some variation depending on the background and disease-related variables of the sample.[15,26] By applying the least stringent criterion for fatigue with the cutoff of FSS > 4 the frequency rate in the present sample would have been 55% instead of 47% with the cutoff of FSS ≥ 5. For the FSMC scale, a total score of 43 or over has been interpreted as a cutoff for mild fatigue.[16] Using this criterion, the frequency estimates for fatigue have reached up to 80%.[3,4] According to the cutoffs of the FSMC, the vast majority of the patients in the present sample with FSS ≥ 5 manifest severe total, cognitive, and motor fatigue. A small proportion of patients without fatigue according to the FSS (FSS ≤ 4) showed severe fatigue according to the FSMC. Thus, it appears that the use of the FSS may give a lower prevalence and severity estimate than the use of the FSMC. In a study by Broch et al.,[3] the possibility that fatigue is over-diagnosed using the existing FSMC cutoffs was suggested. However, since the cutoffs used are based on a careful validation study showing high sensitivity and specificity, as well as excellent convergent correlation with the FSS, it may also be possible that the FSMC covers more profoundly aspects of cognitive and mental fatigue, which may remain under-diagnosed with the FSS. These discrepancies should be considered when methods for fatigue assessment are chosen. Whereas the FSS has proven to be an appropriate measure to screen the severity of overall fatigue, the FSMC may contribute to the identification of the aspects of cognitive and motor fatigue separately.

In the present sample, the FSS score correlated with the measures of cognitive symptoms, that is both the VAS-C and the total score of the MSNQ. We made a post-hoc categorization of the questions of the MSNQ into those related to attention, memory and learning, and other cognitive domains. The strongest correlation was observed between the FSS and the MSNQ score on attention. That is in line with the observation that subjective fatigue and attention lapses are related.[28] Several studies have previously shown a relationship between self-perceived fatigue and depression.[3,4,26] This was observed also in our study, as we found that the FSS score correlated with the VAS-M, although no specific scale assessing depressive symptoms was included in our analysis. As fatigue and problems with mood and cognition often co-occur in patients with MS, it is important to screen each of these symptoms separately.

In our sample, the FSS score was associated with lower quality of life as measured both with the

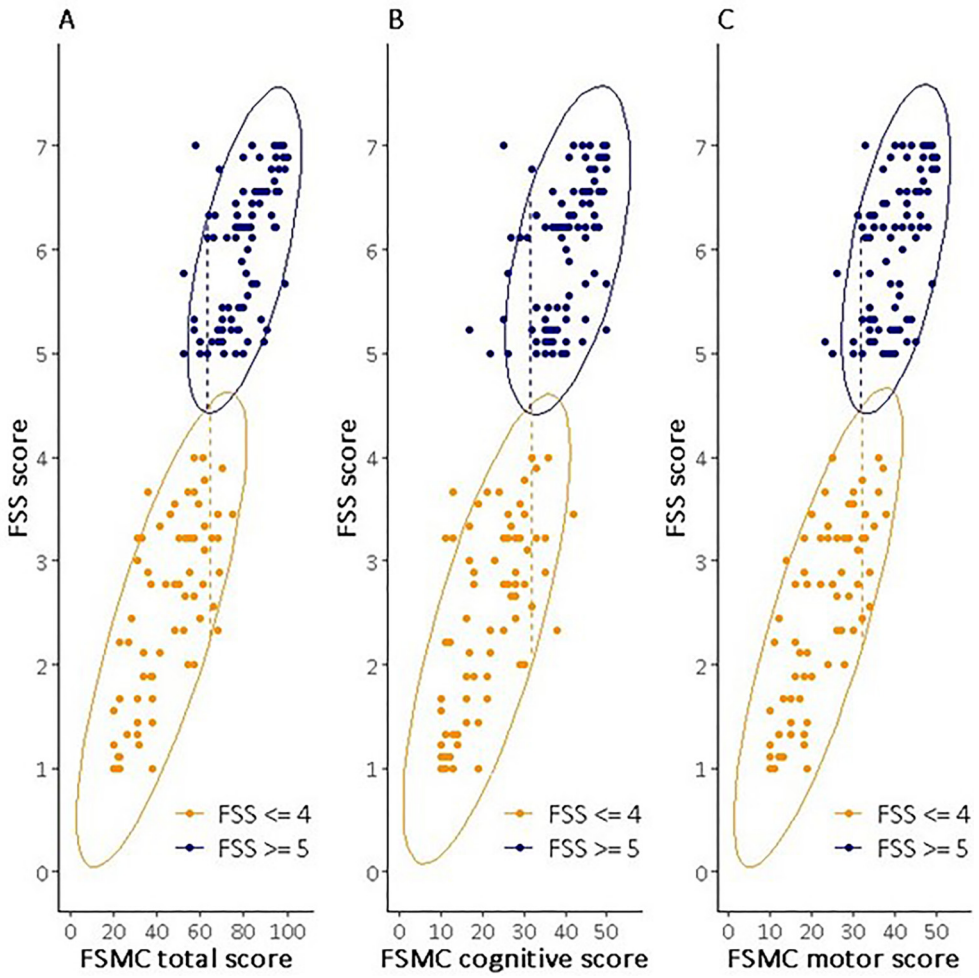

Figure 1. Scatter plot describing the relationship between the FSS score and the total, as well as cognitive and motor sub-score, of the FSMC in patients without fatigue (FSS ≤ 4) and patients with fatigue (FSS ≥ 5). Dashed line shows 90% percentile of FSMC values for FSS ≤ 4 and 10% percentile of FSMC values for FSS ≥ 5.

EQ-5D and the 15D questionnaire, in similarity to previous reports.[3,4,26] Moreover, we observed that fatigue, as measured with the FSS, is related to a more pronounced negative impact of the disease, as measured with the MSIS-29. In line with our findings, fatigue has previously been observed to have an adverse effect on physical activities, mobility, psychological wellbeing, and quality of life in a UK registry study.[26] When modelling factors related to QoL and impact of the disease, we observed that fatigue alone, as measured with the FSS, and together with physical disability measured with the EDSS or the PREDSS, explain lower QoL and more negative impact of the disease.

There are several limitations in the present study. The sample size of the present study is relatively small. It only represents the data from five out of 21 wellbeing services counties with applicable results on 512 patients. To reduce selection bias, the sample included data from various regions of Finland, representing diverse populations and wellbeing services counties with differing levels of activity in the use of MyMS. Further, the amount of missing data is high because only the FSS, the MSIS-29 and 15D have existed in the patient interface from the beginning whereas other PROMs have been in use for two years.[12,13] To better understand the evolution of fatigue, longitudinal data and a larger database are needed. Although the Finnish MS registry serves as a valuable resource for systematic data collection, it currently lacks sufficient data for more advanced or longitudinal analyses. Consequently, the results have to be considered preliminary and more data is needed to allow for more reliable interpretations. In the present study, official Finnish versions of the

PROMs with the published cutoffs were employed. However, only the FSS and the MSIS-29 have been validated with Finnish patients with MS.[15,23] Further, the evaluation of mood was restricted to one VAS question instead of using a validated questionnaire. More comprehensive evaluation of mood might be a relevant addition to the PROMs in the Finnish MS registry.

MS registries are in active use in many European countries, and the need to further develop register-based data collection is recognized worldwide.[29–31] However, patient-derived data is collected only in a few of these registers.[29] Along with the development of clinician-based registers, there is a growing need to implement patient engagement options in order to combine objective disease data to subjective patient-centered outcomes. At best, patient engagement by using PROMs empowers the patient to accomplish his or her role in the treatment process and thus promotes treatment adherence.[32,33] Patient generated data is an important data source when trying to understand multifaceted and debilitating symptoms like fatigue.

Acknowledgements

The authors gratefully acknowledge the contribution of the StellarQ IT team for building and continuously developing the Finnish MS Register IT platform. All members of the Steering committee of the Finnish MS register as well as patients who have participated in the development of MyMS are gratefully acknowledged.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The study was financially supported by Janssen-Cilag Oy as a company sponsored study. The preparation of the manuscript was in part funded by the Strategic Research Council (SRC) established within the Academy of Finland. Funding no. 358415.

Declaration of conflicting interest

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: PH is an employee of the Finnish Neuro Society and StellarQ. PH has served as an adviser or speaker for Merck, Novartis, and Sanofi.

MV None.

M S-H has served as an adviser or speaker for Biogen, Celgene (BMS), Novartis, Roche, Sanofi, and Teva; has received institutional research grants for clinical research from Bayer, Biogen, Merck, Novartis, and Roche; and support for congress participation from Biogen, Celgene (BMS), Merck, Novartis, Roche, Sanofi, and Teva.

HK has served as an adviser or speaker for Merck, Biogen, Celgene (BMS), Novartis, Roche, Jansen-Cilag Oy, Teva, Sandoz and Sanofi and support for congress participation from Merck.

MN has served as an adviser or speaker for Novartis, Roche, Merck, Sanofi and Teva; and support for congress participation from Novartis, Merck, Roche and Sanofi.

SA None.

JP None.

JR None.

MR has served as an adviser or speaker for Biogen, Novartis, Merck, Roche and Sanofi; support for congress participation from AbbVie, Merck and Novartis.

HA has received research grants from the Finnish Neurological Society, the Finnish Cultural Foundation, the Finnish MS Foundation, and the University of Oulu Scholarship Foundation, and support for conference and education session participation and honoraria for consultant services from Novartis.

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AH fulltime employee of Janssen-Cilag Oy Finland and holds stock in Johnson & Johnson.

Ethical disclosure and patient consent

According to Finnish legislation, the approval of an ethical committee was not required, as the study was a non-interventional registry study in which patients were not contacted. In the present study, patients consented to the use of the data for research purposes when they logged into the registry. All data use was permitted via Finnish Social and Health Data Permit Authority Findata with registry keepers permission number THL/2104/14.05.00/2023 findata-rems-2023.

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Data availability

The data of the presents study is from the Finnish National MS Registry. The data is owned by the Finnish wellbeing services counties. StellarQ Ltd is the data processor for all the extracted data.

References

1. Krupp L. Fatigue is intrinsic to multiple sclerosis (MS) and is the most commonly reported symptom of the disease. *Mult Scler* 2006; 12: 367–368.
2. Ramirez AO, Keenan A, Kalau O, et al. Prevalence and burden of multiple sclerosis-related fatigue: a systematic literature review. *BMC Neurol* 2021; 21: 68.

3. Broch L, Simonsen CS, Flemmen HØ, et al. High prevalence of fatigue in contemporary patients with multiple sclerosis. *Mult Scler J Exp Transl Clin* 2021; 7: 2055217321999826.
4. Ahvenjärvi H, Niiranen M, Simula S, et al. Fatigue and health-related quality of life depend on the disability status and clinical course in RRMS. *Mult Scler Relat Disord* 2023; 77:104861.
5. Lakin L, Davis BE, Binns CC, et al. Comprehensive approach to management of multiple sclerosis: addressing invisible symptoms-A narrative review. *Neurol Ther* 2021; 10: 75–98.
6. Kobelt G, Langdon D and Jönsson L. The effect of self-assessed fatigue and subjective cognitive impairment on work capacity: the case of multiple sclerosis. *Mult Scler* 2019; 25: 740–749.
7. Eizaguirre MB, Ciufia N, Roman MS, et al. Perceived fatigue in multiple sclerosis: the importance of highlighting its impact on quality of life, social network and cognition. *Clin Neurol Neurosurg* 2020; 199: 106265.
8. AlSaeed S, Aljouee T, Alkhawajah NM, et al. Fatigue, depression, and anxiety among ambulating multiple sclerosis patients. *Front Immunol* 2022; 13: 844461.
9. Rudroff T, Kindred JH and Ketelhut NB. Fatigue in multiple sclerosis: misconceptions and future research directions. *Front Neurol* 2016; 7: 22.
10. Manjaly ZM, Harrison NA, Critchley HD, et al. Pathophysiological and cognitive mechanisms of fatigue in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2019; 90: 642–651.
11. Laakso SM, Viitala M, Kuusisto H, et al. Multiple sclerosis in Finland 2018-data from the national register. *Acta Neurol Scand* 2019; 140: 303–311.
12. Hämäläinen P, Viitala M, Kuusisto H, et al. MyMS: an interface for patient-reported outcomes for Finnish individuals with multiple sclerosis. *Int J MS Care* 2024; 26: 273–280.
13. Hämäläinen P, Lämsä E, Viitala M, et al. Digital registry-based solution for screening and management of fatigue and cognitive problems in multiple sclerosis. Under submission.
14. Krupp LB, LaRocca NG, Muir-Nash J, et al. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol* 1989; 46: 1121–1123.
15. Rosti-Otajärvi E, Hämäläinen P, Wiksten A, et al. Validity and reliability of the fatigue severity scale in Finnish multiple sclerosis patients. *Brain Behav* 2017; 7: e00743.
16. Penner IK, Raselli C, Stöcklin M, et al. The fatigue scale for motor and cognitive functions (FSMC): validation of a new instrument to assess multiple sclerosis-related fatigue. *Mult Scler* 2009; 15: 1509–1517.
17. Hämäläinen P, Leo V, Therman S, et al. Validation of the Finnish version of the brief international cognitive assessment for multiple sclerosis (BICAMS) and evaluation of the applicability of the multiple sclerosis neuropsychological questionnaire (MSNQ) and the fatigue scale for motor and cognitive functions (FSMC). *Brain Behav* 2021; 11: e02087.
18. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1983; 33: 1444–1452.
19. Kobelt G, Berg J, Lindgren P, et al. Costs and quality of life in multiple sclerosis in Europe: method of assessment and analysis. *Eur J Health Econ* 2006; 7: S5–13.
20. Benedict RH, Munschauer F, Linn R, et al. Screening for multiple sclerosis cognitive impairment using a self-administered 15-item questionnaire. *Mult Scler* 2003; 9: 95–101.
21. EuroQol Group. Euroqol–a new facility for the measurement of health-related quality of life. *Health Policy* 1990; 16: 199–208.
22. Sintonen H. The 15D instrument of health-related quality of life: properties and applications. *Ann Med* 2001; 33: 328–336.
23. Hobart J, Lamping D, Fitzpatrick R, et al. The multiple sclerosis impact scale (MSIS-29): a new patient-based outcome measure. *Brain* 2001; 124: 962–973.
24. Rosti-Otajärvi E, Hämäläinen P, Wiksten A, et al. Validity and reliability of the Finnish version of the multiple sclerosis impact scale-29. *Brain Behav* 2017; 7: e00725.
25. Lerdal A, Celius EG and Moum T. Fatigue and its association with sociodemographic variables among multiple sclerosis patients. *Mult Scler* 2003; 9: 509–514.
26. Moore H, Nair KPS, Baster K, et al. Fatigue in multiple sclerosis: a UK MS-register based study. *Mult Scler Relat Disord* 2022; 64: 103954.
27. Zettl UK, Schreiber H, Bauer-Steinhusen U, et al. Hecker M; BETAPATH study group. Baseline predictors of persistence to first disease-modifying treatment in multiple sclerosis. *Acta Neurol Scand* 2017; 136: 116–121.
28. Spiegelberg N, Breuer S, Nielsen J, et al. Cognitive fatigue predicts cognitive failure in multiple sclerosis patients and healthy controls: a case-control study. *Arch Clin Neuropsychol* 2021; 36: 908–917.
29. Glaser A, Stahmann A, Meissner T, et al. Multiple sclerosis registries in Europe - an updated mapping survey. *Mult Scler Relat Disord* 2019; 27: 171–178.
30. Bebo BF Jr, Fox RJ, Lee K, et al. Landscape of MS patient cohorts and registries: recommendations for maximizing impact. *Mult Scler* 2018; 24: 579–586.
31. Ziemssen T, Hillert J and Butzkueven H. The importance of collecting structured clinical information on multiple sclerosis. *BMC Med* 2016; 14: 81.
32. Members of the MS in the 21st Century Steering Group, Rieckmann P, Centonze D, et al. Unmet needs, burden of treatment, and patient engagement in multiple sclerosis: a combined perspective from the MS in the 21st century steering group. *Mult Scler Relat Disord* 2018; 19: 153–160.
33. Brichetto G and Zaratin P. Measuring outcomes that matter most to people with multiple sclerosis: the role of patient-reported outcomes. *Curr Opin Neurol* 2020; 33: 295–299.