Multiple Sclerosis and Related Disorders 77 (2023) 104861

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

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

Original article

Fatigue and health-related quality of life depend on the disability status and clinical course in RRMS

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ARTICLE INFO

Keywords:
Multiple sclerosis
Fatigue
Quality of life

ABSTRACT

Background: Fatigue is a prominent and disabling symptom of multiple sclerosis (MS), impairing quality of life. The disease course of relapsing remitting MS (RRMS) is individual.

Objectives: We aimed to study the effects of demographic and clinical characteristics, as well as lifestyle risk factors on experienced fatigue and health-related quality of life (HRQoL) among RRMS patients, comparing benign and severe disease types.

Methods: Altogether 198 Finnish RRMS patients were recruited for this real-life cross-sectional study. Self-reported questionnaires were used to evaluate fatigue and HRQoL by using Fatigue Scale for Motor and Cognitive Functions and 15D health-related quality of life questionnaires. Patients were categorized into subgroups based on the current disability status measured by the Expanded Disability Status Scale (EDSS) cut-off value of 4.5, and by retrospective clinical course divided into benign and aggressive RRMS.

Results: All in all, 73% of the RRMS patients suffered from fatigue. Lower HRQoL had a strong correlation with more prominent fatigue ($r = -0.719$). Higher EDSS was associated with more prominent fatigue and lower HRQoL in the whole RRMS cohort. Older age at the disease onset was associated with more prominent fatigue and decreased HRQoL in the groups of aggressive RRMS and EDSS > 4.5. In the groups of EDSS ≤ 4.5 and benign RRMS, a higher number of used disease-modifying treatments (DMTs) was associated with more pronounced fatigue and reduced HRQoL. In addition, higher BMI was associated with lower HRQoL in patients with benign RRMS. Side effects (45 %) and lack of efficacy (26 %) were the most common reasons for discontinuing a DMT. Cessation due to side effects was the only reason that was significantly associated with more prominent fatigue and lower HRQoL. Use of nicotine products, gender, or disease duration were not associated with fatigue or HRQoL.

Conclusions: Individuals with severe RRMS and higher EDSS scores are more prone to experience fatigue and lower HRQoL. In addition, fatigue and lower HRQoL are more commonly observed among RRMS patients with older age at disease onset and in those with multiple DMT switches.

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https://doi.org/10.1016/j.msard.2023.104861
Received 5 January 2023; Received in revised form 1 June 2023; Accepted 29 June 2023
Available online 4 July 2023

1. Introduction

The disease course of RRMS is individual. Some patients present relatively little disease progression over time. Based on this observation, a concept of benign RRMS has been suggested, although a general agreement on the definition is still lacking (Glad et al., 2010, Reynders et al., 2017). Other patients experience aggressive symptoms and rapid deterioration of functional and cognitive capacity since the very beginning of the disease onset (Díaz et al., 2019). In a clinical setting, it is important to recognize different disease phenotypes in order to understand their differences and special features and take these factors into account in treatment.

Relapsing-remitting multiple sclerosis (RRMS) is the most common type of MS, accounting for about 85 % of all MS patients (Huisman et al., 2017). Fatigue is one of the most common and burdensome (Fisk et al., 1994, Ayache and Chalah, 2017) symptoms in MS, with an estimated prevalence of 50-80 % (Broch et al., 2021, Rooney et al., 2019, Colosimo et al., 1995, Razazian et al., 2014, Royer et al., 2022). Despite being recognized as a prominent MS symptom, the definition of fatigue still lacks consensus (Penner and Paul, 2017). Fatigue is often associated with acute relapses (Hanken et al., 2019, Mäurer et al., 2016), increased neurological impairment (Lerdal et al., 2007, Ghajarzadeh et al., 2013), longer disease duration (Ghajarzadeh et al., 2013), and impaired quality of life (QoL) (Young et al., 2021). Lower QoL has been associated with functional impairment, older age, longer disease duration (Young et al., 2021, Brola et al., 2016, Brola et al., 2017), and overweight (de Zwaan et al., 2009, Wang et al., 2012, Huang et al., 2005, Salem et al., 2014). Smoking has been associated with fatigue and lower QoL (Kahraman et al., 2021, Johansson et al., 2021, Broch et al., 2022).

In this real-life cross-sectional study, we aimed to evaluate the associations of demographic and clinical characteristics and disease-modifying treatments (DMTs), as well as lifestyle risk factors on experienced fatigue and health-related quality of life (HRQoL) of RRMS patients in the whole population and subgroups based on current disability status and retrospective clinical course.

2. Material and methods

2.1. Participants

The study cohort consisted of 198 RRMS patients examined at the University Hospitals of Oulu and Kuopio, and Mikkeli Central Hospital in Finland (Fig. 1). The patients were recruited during their normal clinical visits to the neurology outpatient clinic between the years 2015 and 2021. The inclusion criteria were a definite diagnosis of RRMS, according to McDonald (McDonald et al., 2001, Polman et al., 2011, Thompson et al., 2018) or Poser criteria (Poser et al., 1983) (patients diagnosed before 2001), a fulfilled Fatigue Scale for Motor and Cognitive Functions (FSMC) (Penner et al., 2009) or the 15D instrument of health-related quality of life (15D) (Sintonen, 2001) questionnaires and Expanded Disability Status Scale (EDSS) (Kurtzke, 1983) evaluated within a year. Patients were clinically stable three months before and after answering the questionnaires (no clinical relapses or corticosteroid treatments). Demographic and clinical characteristics are presented in Table 1.

2.2. Methods

We used the validated Finnish version of the self-reported FSMC (Penner et al., 2009, Hämäläinen et al., 2021) to quantify MS-related total, cognitive and motor fatigue. The FSMC consists of 20 items, scoring 20-100 points, with the higher score indicating more prominent fatigue. Patients with the FSMC score $\geq$ 43 were considered to experience fatigue (Penner et al., 2009). The FSMC total score ($FSMC_{tot}$) can be further divided into the cognitive ($FSMC_{cog}$) and the motor ($FSMC_{mot}$) subscores, both consisting of 10 items, scoring 10-50 points each. The

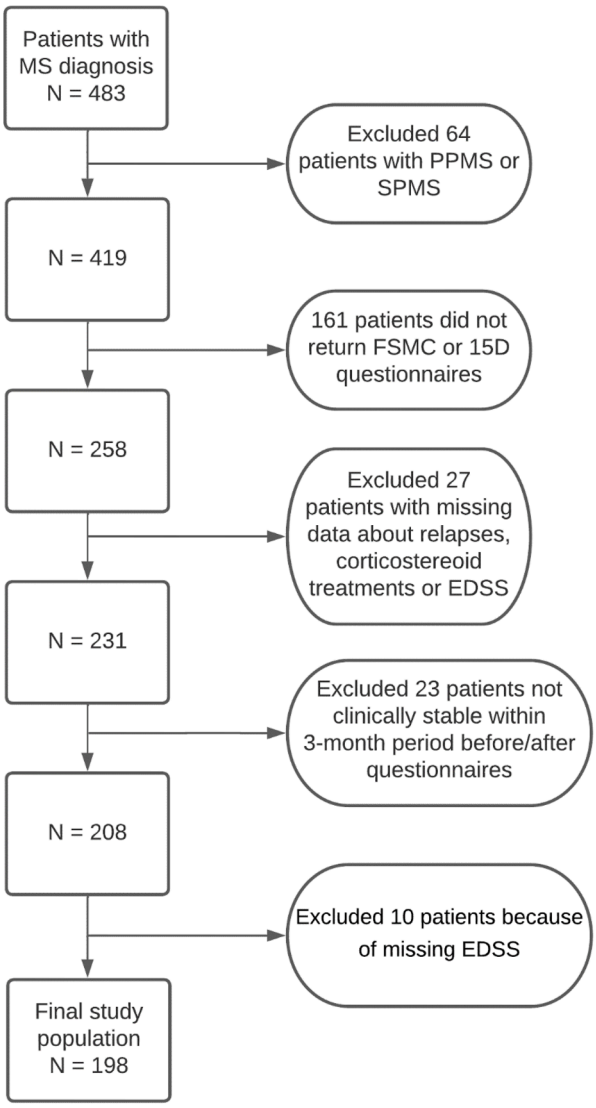

Fig. 1. Flowchart of patient inclusion process.

15D instrument of health-related QoL (HRQoL) was used to assess QoL (Sintonen, 2001). The 15D questionnaire results in a single index (the 15D score) on a 0-1 scale, representing overall HRQoL (0 = being dead, 1 = no problems on any dimension). Overall, 192 patients (97 %) returned both the FSMC and the 15D questionnaires, and 195 (98 %) patients either one of them. Lifestyle risk factors were assessed in terms of overweight and use of nicotine products. Body mass index (BMI) was calculated for each patient, and the commonly used cut-off value of 25 (World Health Organization, 2000) was used to divide patients into the categories of normal and overweight. Serum cotinine levels were measured (Männistö et al., 2016) and used to objectively identify, whether an individual actively used nicotine products (Apseloff et al., 1994). Cotinine cut-off values were based on those determined for US adults (Jain, 2018): values 4.13 ng/mL and 2.99 ng/mL were used for males (sensitivity and specificity 94.5 %) and females (sensitivity and specificity 97.1 %), respectively. For the number of used DMTs, every newly started MS drug was counted in case the active ingredient had not been used before – except for the exchanges between different interferon beta drugs, which were analyzed as a group. For subanalyses, the DMT categories were defined as follows: no medication, low-efficacy (interferon beta, glatiramer acetate, teriflunomide, or dimethyl fumarate), and high-efficacy (alemtuzumab, fingolimod, cladribine, ocrelizumab or natalizumab). DMT discontinuation was defined as an event when DMT

Table 1
Demographic and clinical characteristics of the study cohort.

	RRMS (n = 198)	BRRMS (n = 50, 25.2 % of the total cohort)	ARRMS (n = 43, 21.7 % of the total cohort)	p-value (BRRMS vs ARRMS)	EDSS ≤ 4.5 (n = 174, 87.9 %)	EDSS > 4.5 (n = 24, 14.1 %)	p-value (EDSS ≤ 4.5 vs EDSS > 4.5)
Gender, female (n)	82.3 % (163)	88.0 % (44)	72.1 % (31)	0.067[a]	82.8 % (144)	79.2 % (19)	0.775[a]
EDSS, median (IQR, range)	2.0 (1.0-3.0, 0-8.0)	1.5 (1.0-2.0, 0-2.0)	2.5 (1.5-5.0, 0-8.0)	< 0.001[b]	2.0 (1.0-2.5, 0-4.5)	6.0 (5.1-6.4, 5.0-8.0)	< 0.001[b]
Current age (years), mean (SD, range)	45 (11, 18, -79)	48 (9.7, 32-69)	44 (11, 20, -69)	0.055[c]	44 (11, 18, -79)	51 (11, 31, -69)	0.006[c]
BMI*, mean (SD, range)	26.1 (5.01, 14.8-43.6)	25.2 (3.80, 19.6-34.0)	26.8 (5.23, 17.6-43.6)	0.813[c]	26.3 (4.91, 17.6-43.6)	24.5 (5.51, 14.8-40.1)	0.102[c]
Use of nicotine products**, yes	32.5 %	30.6 %	46.3 %	0.135[a]	33.9 %	20.8 %	0.343[a]
Age at the onset of MS symptoms (years), mean (SD, range)	32 (9.6, 10-58)	30 (7.9, 16-47)	33 (10, 13-58)	0.155[c]	32 (9.3, 10-57)	33 (12, 13-58)	0.783[c]
Disease duration since onset of MS symptoms (years), median (IQR, range)	11 (5.0-19, 0-44)	17(13-22, 10-33)	9.0 (5.0-18, 0-36)	< 0.001[b]	10 (4.0-18, 0-44)	17 (9.3-28, 3-36)	0.005[b]
Number of relapses through disease history, median (IQR, range)	3.0 (2.0-5.0, 1-35)	4.0 (3.0-5.0, 1-11)	4.0 (2.0-9.0, 1-35)	0.166[b]	3.0 (2.0-4.0, 1-29)	6.5 (3.3-9.8, 2-35)	< 0.001[b]
Number of corticosteroid treatments through disease history (IQR, range)	1.0 (0-3.0, 0-32)	1.0 (0-2.0, 0-7)	2.0 (1.0-7.0, 0-32)	< 0.001[b]	1.0 (0-2.0, 0-25)	4.0 (1.0-8.8, 0-32)	< 0.001[b]
Number of DMTs, median (IQR, range)	2.0 (1.0-2.0, 0-5.0)	1.0 (1.0-2.0, 0-4.0)	3.0 (2.0-4.0, 0-5.0)	< 0.001[b]	1.0 (1.0-2.0, 0-5.0)	2.5 (2.0-3.0, 1.0-5.0)	< 0.001[b]
FSMC total score***, mean (SD, range)	57.9 (21.2, 20-100)	50.2 (17.1, 20-81)	61.3 (21.4, 20-93)	0.007[c]	56.7 (21.3, 20-98)	66.5 (19.0, 30-100)	0.035[c]
FSMC cognitive score***, mean (SD, range)	28.7 (10.7, 10-50)	25.5 (8.85, 10-41)	30.1 (11.1, 10-47)	0.028[c]	28.3 (10.8, 10-50)	31.3 (10.1, 14-50)	0.201[c]
FSMC motor score***, mean (SD, range)	29.2 (11.0, 10-50)	24.8 (8.71, 10-41)	31.1 (10.8, 10-46)	0.002[c]	28.4 (10.9, 10-50)	35.2 (9.55, 14-50)	0.004[c]
15D score***, mean (SD, range)	0.833 (0.103, 0.450-1.00)	0.871 (0.0806, 0.680-1.00)	0.805 (0.112, 0.610-1.00)	0.002[c]	0.845 (0.0971, 0.550-1.00)	0.742 (0.110, 0.450-0.920)	< 0.001[c]
Fatigue prevalence ($FSMC_{tot} \geq 43$) ***	73.3 %	61.2 %	79.1 %	0.073[a]	71.3 %	87.5 %	0.137[a]

ARRMS = aggressive relapsing remitting MS, BMI = Body Mass Index, BRRMS = benign relapsing remitting MS, DMT = disease modifying treatment, EDSS = Expanded Disability Status Scale, $FSMC_{tot}$ = Fatigue Scale for Motor and Cognitive Functions total score, $FSMC_{cog}$ = FSMC cognitive score, $FSMC_{mot}$ = FSMC motor score, IQR = interquartile range, SD = standard deviation, MS = Multiple sclerosis
a Chi-squared test
b Mann-Whitney U test
c Student's t-test
* Missing data = 13
** Missing data = 4 (valid percent reported)
*** Missing data = 3 (valid percent reported)

was discontinued due to side effects, lack of efficacy, elevated antibodies or JC virus positivity, pregnancy or desire of pregnancy, or any other reason.

2.3. Categorization

2.3.1. Disability status

Patients were divided into disability subgroups of EDSS ≤ 4.5 and > 4.5. EDSS ≤ 4.5 is the threshold value for being fully ambulatory and able to walk without aid or rest for 300 meters (Kurtzke, 1983).

2.3.2. Clinical course

Patients were categorized into benign RRMS (BRRMS) group if the disease duration was ≥ 10 years and EDSS score was ≤ 2, which is a frequently used definition for benign MS (Glad et al., 2010). Patients with BRRMS had used none or only low-efficacy DMTs in their medical history. Aggressive RRMS (ARRMS) was identified based on a highly active clinical course of MS (several or very disabling relapses in early disease history and high MRI activity) or an explicit diagnosis of a highly active MS (one relapse and high MRI activity), and use of high-efficacy DMT previously or currently.

2.4. Statistical analysis

Statistical analyses were performed with IBM SPSS Statistics version 29 for Windows (IBM Corp, Armonk, NY). The results are presented as mean (standard deviation, SD) for normally distributed and as median (interquartile range, IQR) for nonparametric data in demographic statistics. Correlations were calculated with Pearson correlation for normally distributed and Spearman correlation for nonparametric data. Two group comparisons for continuous variables were performed with Student's t-test for normally distributed and Mann-Whitney U test for nonparametric data, and multigroup comparisons with one-way ANOVA Tukey's test for normally distributed data. Group comparisons for categorical variables were calculated with the Chi-squared test. A p-value of < 0.05 was considered statistically significant.

2.5. Ethics statement

Written informed consent was obtained from all the study individuals. The research ethics committees of Northern Savo Hospital District and Northern Ostrobothnia Hospital Districts approved the study protocol (decisions 44/2014 and 109/2016). The study was performed according to the principles of the Declaration of Helsinki.

3. Results

3.1. The FSMC scores and the 15D score in the total population

In our study population, 73% (143/195) of the patients suffered

fatigue based on the $FSMC_{tot}$. There was no significant difference between males and females (p = 0.831) (Table 1).

The higher $FSMC_{tot}$ strongly correlated with the lower 15D score (r = -0.719) (Fig. 2). The association remained significant after correction for EDSS and BMI in linear regression analysis. Correlations between the $FSMC_{tot}$, the $FSMC_{cog}$, the $FSMC_{mot}$, and the 15D score are shown in Supplementary Tables 1-4, respectively. Higher EDSS had a moderate correlation with the higher $FSMC_{tot}$ (r = 0.426). The 15D score had a moderate inverse correlation with EDSS (r = -0.572).

Linear regression models were built from significantly correlated variables. In the regression model, higher EDSS (B = 3.596, p < 0.001) and a higher number of used DMTs (B = 3.549, p = 0.006) were found as significant explanatory factors for the higher $FSMC_{tot}$, as well as for the higher $FSMC_{cog}$ and the $FSMC_{mot}$ (Table 2). In the model, EDSS was a significant explanatory variable for the lower 15D score, (B = -0.032, p < 0.001) (Table 3).

Use of nicotine products was not associated with the $FSMC_{tot}$, the $FSMC_{cog}$, the $FSMC_{mot}$, or the 15D score. Gender was not associated with the $FSMC_{tot}$ or the subscores, or the 15D score.

3.2. DMT efficacy groups and reasons for DMT discontinuation

In the subgroup of EDSS ≤ 4.5, a one-way ANOVA showed a significant difference in the $FSMC_{cog}$ between the DMT efficacy groups (p = 0.034) (Supplementary Table 5). In Tukey's test, the mean value of the $FSMC_{cog}$ was significantly different between the no medication and high-efficacy medication groups (p = 0.027). Patients with ≥ 2 DMTs in the disease history had significantly higher $FSMC_{tot}$ (p = 0.002), $FSMC_{cog}$ (p = 0.006), and $FSMC_{mot}$ (p < 0.001) than those with only one DMT.

The most frequent reasons for discontinuing a DMT were side effects (45 %) and lack of efficacy (26 %). Patients with at least one DMT discontinuation had significantly higher $FSMC_{tot}$ (p = 0.002), $FSMC_{cog}$ (p = 0.003), $FSMC_{mot}$ (p = 0.002), and lower 15D score (p = 0.02). In those with at least one DMT discontinuation, a higher number of cessations due to side effects had weak correlations with the $FSMC_{tot}$ (r = 0.202) and the 15D score (r = -0.202), and very weak correlations with the $FSMC_{cog}$ (r = 0.195) and the $FSMC_{mot}$ (r = 0.182). Other reasons for cessations did not have significant associations.

3.2. Retrospective clinical course

3.2.1. The FSMC scores and the 15D score in the BRRMS group

Altogether 61 % of the patients with BRRMS had the $FSMC_{tot} \geq 43$ (Table 1). The $FSMC_{tot}$ and the 15D score had a strong inverse correlation (r = -0.672), as well as the other FSMC scores (Supplementary Tables 1-3). The lower 15D score had a moderate correlation with higher BMI (r = -0.421) and a weak correlation with a higher number of relapses (r = -0.310) (Supplementary Table 4). BMI ≥ 25 was significantly associated with the lower 15D score (p = 0.018) (Fig. 3).

In the linear regression model, higher EDSS (B = -0.032, p = 0.022), a higher number of used DMTs (B = -0.023, p = 0.041), and higher BMI (B = -0.007, p = 0.010) were found as significant explanatory factors for the lower 15D score (Table 3). A higher number of used DMTs was found as a significant explanatory variable for the higher $FSMC_{tot}$ (B = 5.941, p = 0.025) and the $FSMC_{cog}$ (B = 3.553, p = 0.009) (Table 2).

The $FSMC_{tot}$ was not associated with gender or use of nicotine products, and neither were the FSMC subscores. Gender or use of nicotine products were not associated with the 15D score.

3.2.2. The FSMC scores and the 15D score in the ARRMS group

The $FSMC_{tot} \geq 43$ was found in 79 % of the ARRMS patients (Table 1). The $FSMC_{tot}$ and the 15D score had a strong inverse correlation (r = -0.673). Similar correlations were observed between the FSMC subscores and the 15D score. See supplementary Tables 1-4.

The lower 15D score had a moderate correlation with older current age (r = -0.423) and older age at the onset of MS symptoms (r = -0.451) (Supplementary Table 4). Older age at the onset of MS correlated weakly with the higher $FSMC_{tot}$ (r = 0.352) and $FSMC_{mot}$ (r = 0.389). In addition, the $FSMC_{mot}$ had a weak correlation with EDSS (r = 0.364). See supplementary Tables 1-3.

In the regression model, older age at the onset of MS symptoms was

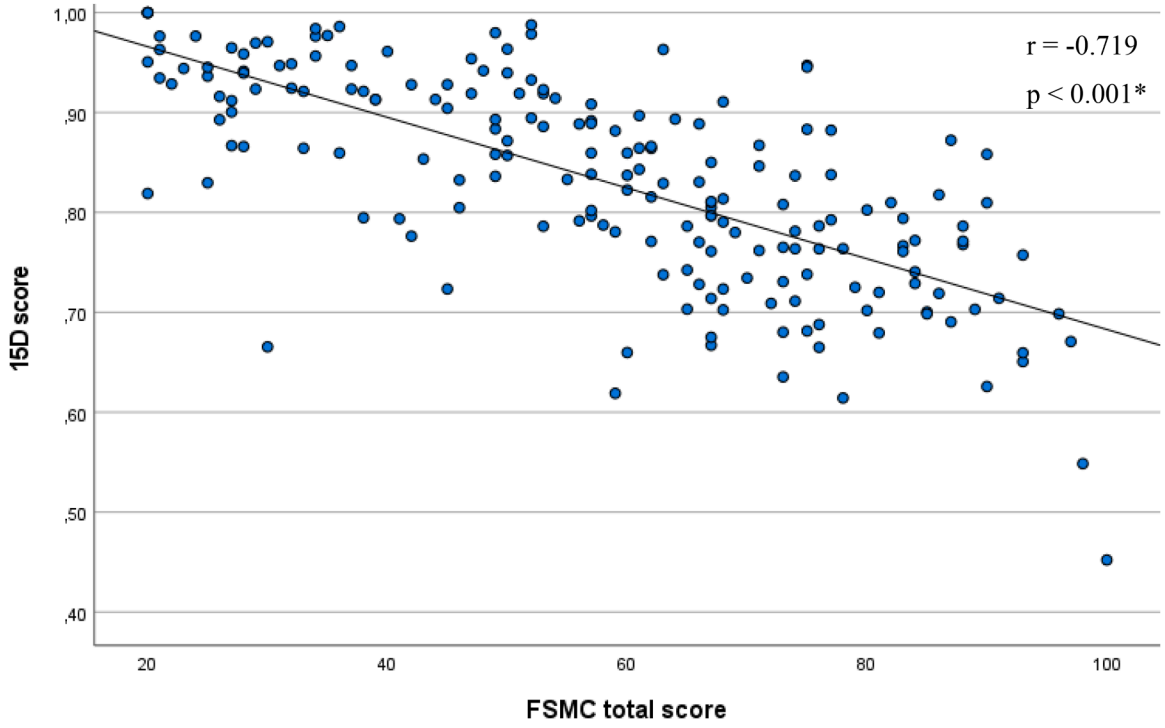

Fig. 2. Correlation of 15D score and FSMC total score. Higher 15D score stands for better health-related quality of life and higher FSMC total score stands for more fatigue. Pearson's correlation.

Table 2
Results of linear regression analysis indicating the variables which explained the FSMC total, cognitive and motor scores in total population and subgroups.

FSMC total score	Coefficient (B)	p-value	95 % Confidence interval
Total population (n = 195)			
EDSS	3.596	< 0.001	1.932–5.260
Number of used DMTs	3.549	0.006	1.046–6.051
BRRMS (n = 49)			
Number of used DMTs	5.941	0.025	0.797–11.085
ARRMS (n = 43)			
Age at the onset of MS symptoms	0.671	0.041	0.030–1.312
EDSS ≤ 4.5 (n = 171)			
EDSS	6.948	< 0.001	4.336–9.559
Number of used DMTs	4.232	0.002	1.637–6.828
EDSS > 4.5 (n = 24)			
Age at the onset of MS symptoms	0.655	0.049	0.002–1.308
FSMC cognitive score			
Total population (n = 195)			
EDSS	1.396	0.002	0.536–2.256
Number of used DMTs	1.946	0.003	0.652–3.240
BRRMS (n = 49)			
Number of used DMTs	3.553	0.009	0.948–6.157
EDSS ≤ 4.5 (n = 171)			
EDSS	3.169	< 0.001	1.825-4.513
Number of used DMTs	2.266	0.001	0.929-3.602
FSMC motor score			
Total population (n = 195)			
EDSS	2.200	< 0.001	1.354–3.045
Number of used DMTs	1.603	0.014	0.331–2.875
ARRMS (n = 43)			
Age at the onset of MS symptoms	0.361	0.030	0.038–0.684
EDSS ≤ 4.5 (n = 171)			
EDSS	3.779	< 0.001	2.445–5.113
Number of used DMTs	1.967	0.004	0.641–3.293
EDSS > 4.5 (n = 23)			
Age at the onset of MS symptoms	0.345	0.038	0.020–0.669

ARRMS = aggressive relapsing remitting MS, BRRMS = benign relapsing remitting MS, DMT = disease modifying treatment, EDSS = Expanded Disability Status Scale, FSMC = Fatigue Scale for Motor and Cognitive Functions, MS = Multiple sclerosis

found as a significant explanatory factor for the higher $FSMC_{tot}$ (B = 0.671, p = 0.041) and the $FSMC_{mot}$ (B = 0.361, p = 0.030) (Table 2). The lower 15D score was significantly explained by higher EDSS (B = -0.020, p = 0.0090) and older age at the onset of MS symptoms (B = -0.004, p = 0.010) (Table 3).

The $FSMC_{tot}$ was not associated with gender or use of nicotine products, and neither were the FSMC subscores. The 15D score was not associated with gender or use of nicotine products.

3.2.3. The differences between the groups of BRRMS and ARRMS

Patients with BRRMS had significantly lower $FSMC_{tot}$ (p = 0.007), $FSMC_{cog}$ (p = 0.028), $FSMC_{mot}$ (p = 0.002) and higher 15D score (p = 0.002) than patients with ARRMS (Table 1).

3.3. Current disability status

3.3.1. The FSMC scores and the 15D score in the EDSS ≤ 4.5 group

Of all the patients in the EDSS ≤ 4.5 group, 71 % experienced fatigue (Table 1). The 15D score and the $FSMC_{tot}$ were strongly inversely correlated (r = -0.735), as were there FSMC subscores (Supplementary Tables 1-3). Higher EDSS had moderate correlations with the higher

Table 3
Results of linear regression analysis indicating the variables which predicted the 15D the health-related quality of life score in total population and subgroups.

15D score	Coefficient (B)	p-value	95 % Confidence interval
Total population (n = 195)			
EDSS	-0.032	< 0.001	-0.039 to -0.025
BRRMS (n = 47)			
EDSS	-0.032	0.022	-0.060 to -0.005
Number of used DMTs	-0.023	0.041	-0.045 to -0.001
BMI	-0.007	0.010	-0.012 to -0.002
ARRMS (n = 42)			
EDSS	-0.020	0.009	-0.034 to -0.005
Age at the onset of MS symptoms	-0.004	0.010	-0.007 to -0.001
EDSS ≤ 4.5 (n = 172)			
EDSS	-0.043	< 0.001	-0.054 to -0.031
EDSS > 4.5 (n = 23)			
EDSS	-0.066	0.022	-0.121 to -0.011

ARRMS = aggressive relapsing remitting MS, BRRMS = benign relapsing remitting MS, DMT = disease modifying treatment, EDSS = Expanded Disability Status Scale, 15D = 15D the health-related quality of life instrument

FSMC scores and the lower 15D score (r = -0.533). The higher $FSMC_{tot}$ had weak correlations with a higher number of used DMTs and relapses (Supplementary Table 1).

In the regression model, higher EDSS (B = 6.948, p < 0.001) and a higher number of used DMTs (B = 4.232, p = 0.002) significantly explained the higher $FSMC_{tot}$ (Table 2). EDSS was the significant explanatory factor for the higher 15D score (B = -0.043, p < 0.001) (Table 3).

There was no association between gender and the $FSMC_{tot}$, the FSMC subscores, or the 15D score. There were no associations between use of nicotine products and the $FSMC_{tot}$ or the 15D score, or the FSMC subscores.

3.3.2. The FSMC scores and the 15D score in the EDSS > 4.5 group

In the EDSS > 4.5 group, 88 % of the patients had the $FSMC_{tot} \geq 43$. The $FSMC_{tot}$ had a moderate inverse correlation with the 15D score (r = -0.544). Moderate inverse correlations were observed between the 15D score, age at the onset of symptoms (r = -0.464), current age (r = -0.507), and EDSS (r = -0.436) (Supplementary Tables 1-4).

In the linear regression model, age at the onset of MS symptoms significantly explained the higher $FSMC_{tot}$ (B = 0.655, p = 0.049) and the $FSMC_{mot}$ (B = 0.345, p = 0.038), while there were no significant explanators for the $FSMC_{cog}$ (Table 2). Higher EDSS significantly explained the lower 15D score (B = -0.066, p = 0.022) (Table 3).

No association was found between gender and the $FSMC_{tot}$ or the 15D score, or the FSMC subscores. Use of nicotine products was not associated with the $FSMC_{tot}$ or the 15D score, or the FSMC subscores.

3.3.3. The differences between the groups of EDSS ≤ 4.5 and EDSS > 4.5

In the EDSS > 4.5 group, the $FSMC_{tot}$ (p = 0.035) and the $FSMC_{mot}$ (p = 0.003) were significantly higher and the 15D score lower (p < 0.001) than in patients with EDSS ≤ 4.5 (Table 1).

4. Discussion

This study set out to evaluate the associations of demographic and clinical factors, as well as lifestyle risk factors on fatigue and HRQoL in different forms and disability levels of RRMS patients. Overall, 73% of the RRMS patients experienced fatigue, which is in line with previous

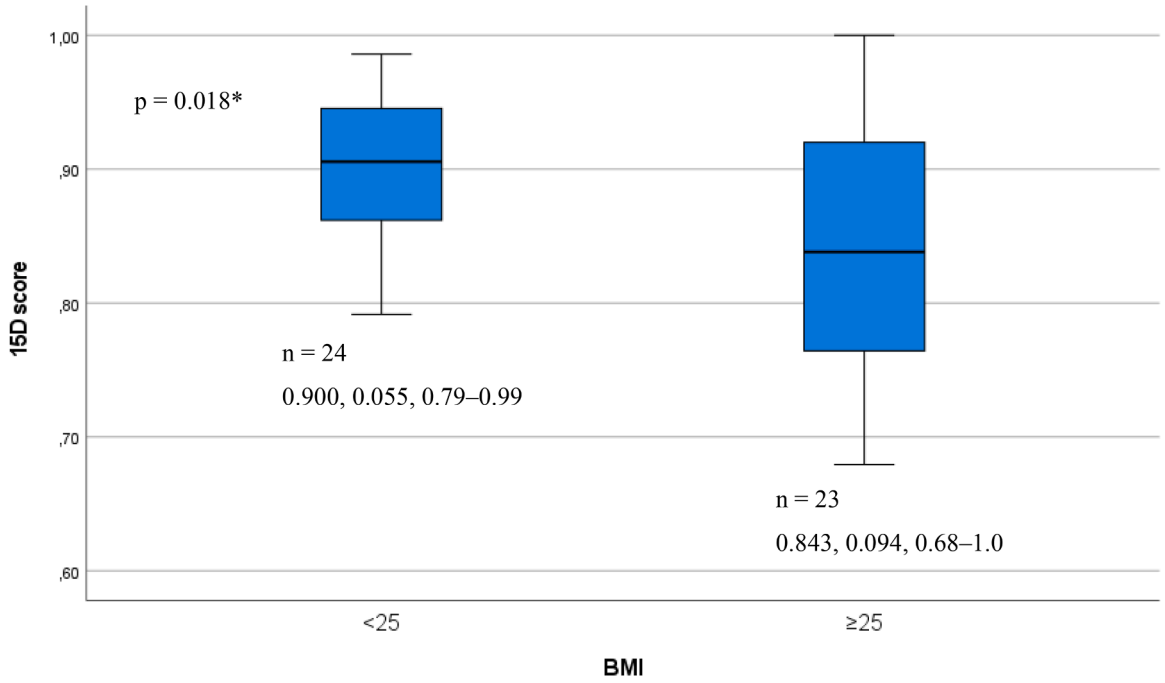

Fig. 3. Difference of 15D scores between BMI subgroups of ≥ 25 and < 25 in BRRMS patients. Lower 15D score stands for lower HRQoL. Student's t-test. Values below the boxplots: mean, standard deviation, range.

reports (Broch et al., 2021, Rooney et al., 2019, Colosimo et al., 1995, Razazian et al., 2014, Royer et al., 2022). We confirmed that RRMS patients with more pronounced overall fatigue had decreased HRQoL, confirming the findings of previous studies (Young et al., 2021, Nourbakhsh et al., 2016). Older age at the disease onset was associated with more prominent fatigue and reduced HRQoL in the patients with high EDSS or aggressive disease course. In patients with low EDSS or benign disease course, age at onset was not a significant factor, but instead, a higher number of used DMTs through disease history was associated with more pronounced fatigue and lower HRQoL. In addition, higher BMI was associated with lower HRQoL in patients with benign disease course. Generally, higher physical disability measured by EDSS was the common denominator for fatigue and impaired HRQoL at the whole population level.

Our study demonstrates that the higher number of used DMTs through the disease history is associated with more prominent fatigue and lower HRQoL in patients with benign disease course or low EDSS. However, although starting a new DMT might reflect disease activity, it may also mirror the patient́s inability to tolerate the adverse effects of DMTs due to low psychological tolerance or interindividual variability in pharmacokinetics and pharmacodynamics. Indeed, the most frequent reason for DMT discontinuation in our study was side effects (45 %), and it was the only cessation reason associated with fatigue and lower HRQoL. In a previous report, a higher grade of fatigue was associated with a higher risk of premature discontinuation of a DMT (Zettl et al., 2017). Patients with ≥ 1 DMT discontinuations had significantly more prominent fatigue than those without any discontinuations. In clinical work, this should be noticed. When an MS patient wants to change the DMT due to side effects, the underlying reasons for the request should be evaluated first and inconsiderate changes should be avoided since in every DMT switch patient loses efficient treatment time. Patients with many DMT switches may have undergone long periods without efficient therapy. Furthermore, fatigue as a possible risk factor for discontinuation should be discussed with the patient, since fatigue may also influence the patient's commitment to the DMT. In the group of low EDSS, patients with high-efficacy treatment had more cognitive fatigue than patients without medication, which is likely explained by more aggressive disease. High-efficacy treatments do not seem to promote fatigue themselves, as they have been associated with improved cognitive function (Hvid et al., 2022, Margoni et al., 2022, Cohan et al., 2018, Benedict et al., 2018) and reduced fatigue (Margoni et al., 2022, Bónitto et al., 2022).

Younger age at the onset of MS was associated with better HRQoL and less prominent motor fatigue in patients with aggressive disease course or high EDSS, independently from disease duration. Younger patients might have better resilience and coping mechanisms to adjust to their disability. Better coping mechanisms have been associated with less fatigue (Brajković et al., 2009) and higher QoL (Mikula et al., 2014). On the other hand, older age at the MS onset has been associated with faster disability progression (Cierny et al., 2017), which might also explain our findings. Disease duration was not associated with HRQoL or fatigue, which is in contradiction with previous studies from Iran (Ghajarzadeh et al., 2013) and Poland (Brola et al., 2016). Differences in the healthcare systems may contribute to this discrepancy. For instance, longer delay in treatment start has been associated with faster disease progression (Kopp et al., 2020). A Polish MS registry study demonstrated that limited access to immunomodulatory therapy was associated with lower QoL (Brola et al., 2016). Furthermore, we used different scales to estimate fatigue and QoL, which might contribute to the different results.

Overweight was associated with lower HRQoL in patients with benign disease course. This association was not found in other subgroups or the total population. Patients with aggressive disease or high EDSS might have other confounding factors affecting HRQoL, which exceed the effect of overweight. Previously, overweight has been associated with impaired QoL (de Zwaan et al., 2009, Wang et al., 2012, Huang et al., 2005, Salem et al., 2014) and cognitive dysfunction (Cherbuin et al., 2015, Gunstad et al., 2007, Raji et al., 2010). Healthcare providers should endorse exercise and healthy lifestyle choices for every MS patient.

Based on serum cotinine analysis, nicotine products were actively used by 33 % of MS patients. Interestingly, use of nicotine products is more frequent among MS patients than among the general Finnish population, of which 12 % smoke and 7 % use snus daily (Tupakkatilasto, 2020). Similar findings have been observed in a Swedish MS cohort (Manouchehrinia et al., 2022) in comparison to the general

Swedish population (The Public Health Agency of Sweden, 2022). Associations between use of nicotine products and fatigue or HRQoL were not found in our study, which is in contradiction with previous studies (Kahraman et al., 2021, Johansson et al., 2021, Broch et al., 2022). Unknown confounding factors or different fatigue and QoL scales might explain different results. As cotinine is an unspecific nicotine product use biomarker, more detailed data on use of tobacco products could be wise in future studies.

Previous studies have reported heterogeneous results on the effect of gender on fatigue (Broch et al., 2021, Broch et al., 2022, Fazli and Shayesteh-Azar, 2013, Lerdal et al., 2003) and QoL (Cichy et al., 2016, Sabanagic-Hajric et al., 2022, Kaya Aygünoğlu et al., 2015) in MS patients. We did not observe significant associations.

The means of determining fatigue and quality of life in literature have not been standardized. The scales differ in terms of coverage and focus, which might contribute to heterogeneous study results. In the present study, we used the FSMC and 15D to evaluate fatigue and HRQoL. The FSMC differs from other scales since it evaluates the cognitive and motor components of fatigue, in addition to overall fatigue. For instance, Fatigue Severity Scale (FSS) has been designed for evaluation of fatigue severity (Krupp et al., 1989) and Fatigue Impact Scale (FIS) for measuring the effects of fatigue (Fisk et al., 1994). The emphasis of the 15D is on the physical and mental aspects of one's life. While HRQoL is one aspect of QoL, it is not a synonym. Some commonly used scales, like EuroQol 5-Dimensions (EQ-5D) (The EuroQol Group, 1990), are shorter and thus give less detailed results than the 15D.

The strengths of the present study were the extensive patient history, and systematic EDSS evaluations performed by experienced neurologists. Considering limitations, anxiety or depression scales or the evaluation of depression medication usage were not included. Previous studies have indicated an increased prevalence of anxiety and depression (Boeschoten et al., 2017), which have been confirmed as risk factors for lower QoL (Rooney et al., 2019) and fatigue (Rooney et al., 2019, Beiske et al., 2008) in MS. Pain (Veličkaitė et al., 2020, Elliott et al., 2003) and certain socioeconomic factors (Broch et al., 2022) have been found to impair QoL as well but were not assessed. Adding mental health scales, pain evaluation, and more accurate sociodemographic data in further studies would provide a broader perspective on the origins of fatigue and impaired QoL.

5. Conclusions

Fatigue and lower HRQoL are more prevalent in patients with severe RRMS or older age at the disease onset. It is essential to assess fatigue in all MS patients, with particular attention to the individuals with these risk factors. Discontinuing of DMTs, especially due to side effects, appears to be also associated with more prominent fatigue and lower HRQoL. Fatigue may influence a patient's commitment to DMTs, and it is thus essential to evaluate the underlying reasons for the patient's request to switch their DMT and avoid making inconsiderate changes.

Author statement

This manuscript presents original work and is not in press or under consideration in any other journal. While under consideration at *Multiple Sclerosis and Related Disorders* this manuscript will not be submitted elsewhere. All the authors have contributed to the study, reviewed the final version of the submitted manuscript, and approved it for submission. The authors take full responsibility for the data, the analyses and interpretation, and the conduct of the research. The local ethics committee approved the research protocol.

Role of Funding

Henrik Ahvenjärvi has received a research grant from the Finnish Cultural Foundation. Marja Niiranen has received a research grant from the Finnish Medical Foundation. No funding source had any role in the design, analysis or interpretation of the results in this study.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Henrik Ahvenjärvi reports a relationship with Finnish Cultural Foundation that includes: funding grants. Marja Niiranen reports a relationship with Finnish Medical Foundation that includes: funding grants. Päivi Hämäläinen reports a relationship with Novartis that includes: speaking and lecture fees. Päivi Hämäläinen reports a relationship with Sanofi that includes: speaking and lecture fees. Päivi Hämäläinen reports a relationship with Merck that includes: speaking and lecture fees. Mervi Ryytty reports a relationship with Biogen that includes: consulting or advisory and speaking and lecture fees. Mervi Ryytty reports a relationship with Merck that includes: consulting or advisory. Mervi Ryytty reports a relationship with Novartis that includes: consulting or advisory. Mervi Ryytty reports a relationship with Roche that includes: consulting or advisory. Mervi Ryytty reports a relationship with Sanofi that includes: consulting or advisory. Johanna Krüger reports a relationship with Novartis that includes: consulting or advisory. Johanna Krüger reports a relationship with Roche that includes: consulting or advisory.

Acknowledgments

We thank the participating patients and study nurse Pirkko Holappa at the Oulu University Hospital and study nurses Ulla Kokkonen and Kirsi Tavasti at the Kuopio University Hospital for their excellent work in helping to recruit patients for this study. Many thanks to Sara Kuusiniemi for her skillful technical assistance in laboratory analyses. We are also grateful to Ph.D. Hannu Vähänikkilä for his valuable advice on statistical analyses.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2023.104861.

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