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Quality of life in multiple sclerosis: The differential impact of motor and cognitive fatigue

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Abstract

Background: Multiple sclerosis is a chronic disease leading to reduced quality of life.

Objectives: To investigate whether motor and cognitive fatigue impact differently on aspects of quality of life among patients with multiple sclerosis, independently from bodily disability.

Methods: 79 patients with multiple sclerosis from Aalborg University Hospital, Denmark were included in an observational, cross-sectional study. Each subject completed two separate questionnaires regarding fatigue (Fatigue Scale for Motor and Cognitive Functions and Modified Fatigue Impact Scale) and one regarding quality of life (Short Form 36). Disability was measured with the Expanded Disability Status Scale (EDSS)-scores obtained from patient records.

Results: All fatigue scores were significantly correlated to all areas of quality of life ($p < 0.05$). This remained significant after adjustment for age, disease duration and EDSS-score. When looking at each type of fatigue separately, cognitive fatigue correlated mainly with mental health aspects of quality of life and motor fatigue with physical health areas of quality of life.

Conclusion: Increased motor and cognitive fatigue lead to a differential reduction in physical and mental quality of life, independently of bodily disability. This underlines the importance of proper assessment and treatment of fatigue among patients with multiple sclerosis.

Keywords: Multiple sclerosis, quality of life, fatigue, motor fatigue, cognitive fatigue, EDSS

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Introduction

Multiple Sclerosis (MS) is a chronic, neurological illness characterized by autoimmune-induced demyelination of nerves in CNS leading to different degrees of disability.¹ Disability status among MS patients is most commonly measured with the Expanded Disability Status Scale (EDSS), which quantifies the severity of disability and is useful for objective monitoring of disease progression, although this tool has been criticized for its over-emphasis on motor and gait function.²

Quality of life (QOL) measurement is an alternative way to examine the impact of MS. QOL includes information on several aspects of life such as overall well-being, mental, physical and social function.^{3–5} MS patients have significantly reduced QOL compared to the general population.² This might be due

to onset in early years of adulthood, the unpredictable nature of the disease course, diffuse symptoms and lack of proper treatment.⁴ Studies have shown that this reduction in QOL can only partly be explained by the neurological disability, pointing out the inadequacy of disease monitoring with EDSS-scores solitarily.² Nonetheless, QOL is a subjective measure and might not always reflect an actual change in disease characteristics, pointing out the need for a combination of both tools.

Fatigue is often reported as the most frequent and disabling symptom among MS-patients, affecting up to 80% of all patients and classified as the symptom which interferes most with everyday life by up to 55%.¹ MS-related fatigue can be categorized due to its presentation as either motor or cognitive fatigue, or as primary fatigue (specific to MS) or

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secondary fatigue (caused by concomitant conditions).¹ The pathophysiology of primary fatigue remains unknown. Central abnormalities, inflammation and immunological factors have been found to play a role.¹ Due to the multiple types and causes of fatigue, treatment of this symptom remains a challenge.¹

This incites the question of whether the experience of fatigue plays a more crucial role in relation to QOL among MS patients than physical disability itself. Several studies have examined the relation between overall fatigue and QOL.^{3,4,6,7} However, it is now clear that unidimensional views of fatigue and QOL are obsolete, emphasizing the need for examining cognitive and motor fatigue, as well as mental and physical QOL, separately.⁸ This will contribute to a better understanding of the complex nature of fatigue and the role it plays in the daily life of MS patients, which is the first step towards improving current treatment strategies. This has only been examined in a few studies,^{9–11} pointing towards the need for further research in this field. The aim of this study is therefore to examine the impact of motor and cognitive fatigue on different aspects of QOL separately, and to investigate whether this impact exists independently of bodily disability.

Materials and methods

Patients

We conducted an observational cross-sectional study in accordance with the STROBE guidelines (Supplementary material 1).⁹ The study population consisted of 79 MS patients who were seen at the MS clinic at Aalborg University Hospital in the period from 1st November 2017 to 25th May 2018. The inclusion criteria were: a) a diagnosis of multiple sclerosis in accordance with the McDonald criteria 2010;¹⁰ b) age ≥ 18 years; and c) ability to communicate in Danish.

All study subjects completed the following three questionnaires (Supplementary material 2), all translated to Danish.

- Fatigue Scale for Motor and Cognitive Functions, FSMC.¹¹
- Modified Fatigue Impact Scale, MFIS (derived from the 40-item Fatigue Impact Scale)¹²
- Short Form 36, SF-36.¹³

The questionnaires were completed either at the hospital and returned right away, or completed at home and returned at the next appointment. EDSS-scores, disease duration and disease course were obtained from patient records. Latest EDSS-score (within 6 months) was included, scored by a trained, blinded neurologist.

Scales

FSMC consists of 20 items (10 for cognitive fatigue [FSMCcog] and 10 for motor fatigue [FSMCmot]) with 1–5 points per item. The total possible score ranges from 20–100 points. A sum score of ≥ 43 is categorized as mild fatigue, ≥ 53 as moderate fatigue and ≥ 63 as severe fatigue.¹¹ The scale has undergone validation based on a large sample of patients,¹¹ and also the Danish translation has been validated.¹⁴

MFIS consists of 21 items (9 for motor [MFISmot], 10 for cognition [MFIScog] and 2 for psychosocial fatigue [MFISps]) with 0–4 points per item. The total possible score ranges from 0 to 84. A score of 38 points is categorized as fatigue.^{14,15} This scale has been defined as one of the most discriminative fatigue-scales.¹⁵

Both scales were examined simultaneously because of the different aspects monitored: FSMC quantifies fatigue itself, whereas MFIS additionally focuses on its impact on everyday life.

SF-36 is a tool measuring perceived health status, and is not specific for MS. The SF-36 consists of eight dimensions (physical functioning, role limitations caused by physical problems, bodily pain, general health, vitality, social functioning, role limitation caused by emotional problems and mental health). Each area is individually scored and transformed into a scale ranging from 0 (poor health) to 100 (optimal health).^{13,16} SF-36 is the most widely used generic instrument and is considered to be the golden standard in measuring health status.⁴ Moreover, it is well-studied among MS-patients,⁴ and has therefore been selected as the QOL-outcome-measure. Note that while the term quality of life may include a broad range of elements, this study restricts its focus on the health-related area of life quality.

EDSS is a measure of disability. The score is assessed by a clinician based on the evaluation of eight functional systems of the CNS. It ranges from 0 (normal) to 10 (death due to MS).¹⁷ Some of the

limitations regarding EDSS include documented weakness in inter- and intra-rater reliability and sensitivity to change. However, despite this, EDSS is still accepted and preferred as the main disability-outcome measure in MS.¹⁷

Statistics

Descriptive statistics were used to calculate median age, EDSS, fatigue and QOL-scores.

Linear regression was selected as the statistical method of data analysis. This method enabled control of confounding factors, and this was necessary to answer the main research question raised. This choice of method was similar to other studies in this field.^{2,3,7,18,19}

First, a series of simple linear regression analyses were performed to examine the correlation between each fatigue subscale and SF-36 subscale, respectively. The correlation was quantified by Pearson's coefficient of correlation, *r*. Secondly, multiple linear regression was performed with EDSS scores and fatigue scores as independent values and QOL scores as the dependent value. This was done to examine the impact of fatigue on QOL, while adjusting for EDSS. β -coefficients were found and

p-values were obtained by testing the null hypothesis of $\beta = 0$. All statistics were performed using Excel. *P*-values <0,05 were considered significant.

Ethics

Written and oral consent were obtained from all participants, and the project was approved by The North Denmark Region Committee on Health Research Ethics (approval no. 20170078).

Results

Demographics

79 patients who fulfilled the inclusion criteria were identified. Median age was 44 years, median disease duration was 9 years and median EDSS-score was 2,5. The majority of the patients (90%) had relapsing remitting MS. Table 1 presents the demographic and disease related characteristics of the study population at index date, including median fatigue scores. Using the sum score cut-off points for the FSMC, 84% of patients were fatigued (scoring mild fatigue or more), and using MFIS, 63% were fatigued. Median quality of life scores for each of the eight subscales of SF-36 are listed in Table 2. All results not shown below are summarized in Supplementary material 3.

Table 1. Demographic and clinical features of the study population.

	Total sample
N	79
Median age in years (IQR)	42 (36,5–50,8)
Gender	
- Female, N (%)	60 (76)
- Male, N (%)	19 (24)
Median EDSS (IQR)	2,5 (1,5–3,75)
Median duration of disease in years (IQR)	9 (3–13,5)
Disease course, N (%)	
- Relapsing Remitting MS	71 (90)
- Secondary progressive MS	5 (6)
- Primary progressive MS	3 (4)
Median fatigue scoring (IQR)	
- FSMC _{cog}	34 (22,5–40,0)
- FSMC _{mot}	36 (25,0–41,0)
- FSMC _{tot}	66 (51,0–80,8)
- MFIS _{cog}	20 (13,0–24,8)
- MFIS _{mot}	19 (13,5–25)
- MFIS _{ps}	3 (2,0–5,0)
- MFIS _{tot}	42 (30,5–54,8)

N, number of subjects. SD, standard deviation. FSMC, Fatigue Scale for Motor and Cognitive Functions. MFIS, Modified Fatigue Impact Scale. _{cog}, cognitive subscale. _{mot}, motor subscale. _{ps}, psychosocial subscale. _{tot}, total score of the scale.

Table 2. Median quality of life score.

		Median (IQR)
QOL	Physical functioning (PF)	65,0 (40,0–95,0)
	Role limitations caused by physical problems (RP)	25,0 (0,0–75,0)
	Bodily pain (BP)	60,0 (35,0–80,0)
	General health (GH)	40,0 (30,0–55,0)
	Vitality (V)	35,0 (25,0–60,0)
	Social functioning (SF)	62,5 (60,0–62,5)
	Role limitations caused by emotional problems (RE)	66,7 (33,3–100,0)
	Mental health (MH)	64,0 (48,0–76,0)
QOL, quality of life.		

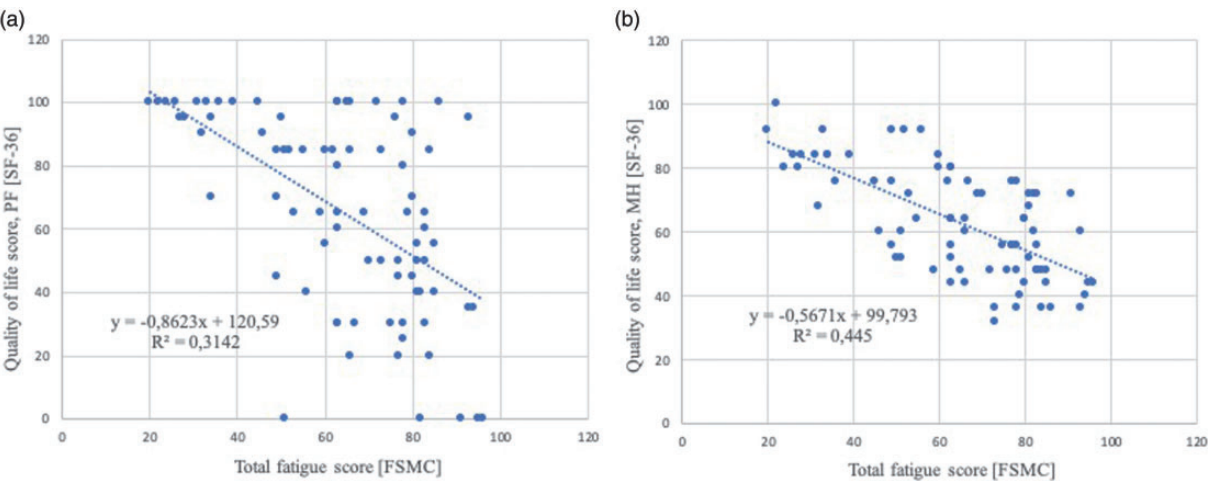


Figure 1. (a) Relationship between FSMCtot and Physical Functioning. *FSMC*, *Fatigue Scale for Motor and Cognitive Functions*. *PF*, *physical functioning*. Simple linear regression analysis was used to examine the relationship between total fatigue score on FSMC and the physical functioning dimension of QOL on SF-36. QOL decreased significantly with increasing fatigue. (b) Relationship between FSMCtot and Mental Health. *FSMC*, *Fatigue Scale for Motor and Cognitive Functions*. *MH*, *mental health*. Simple linear regression analysis was used to examine the relationship between total fatigue score on FSMC and the mental health dimension of QOL on SF-36. QOL decreased significantly with increasing fatigue.

Relationship between fatigue and QOL (unadjusted)
Simple linear regression analysis was conducted for all seven scores of fatigue and all eight scores of QOL, respectively. They showed that all fatigue scores (each subscores and total scores) were significantly related to all QOL-scores (p-value <0,05).

Looking at each QOL-scores, correlations with fatigue were strongest for the questions regarding vitality (r = −0,80 for FSMCmot), social functioning (r = −0,73 for MFISps) and role limitations caused by physical problems (r = −0,70 for MFISStot). Generally, motor fatigue scores seemed to show a stronger correlation with QOL-dimensions than cognitive fatigue scores.

The relationship between total fatigue score on the FSMC-scale and QOL-scores regarding physical functioning (PF) and mental health (MH) are shown in Figure 1(a) and (b), respectively.

Similar analyses using the MFIS-total score are shown in Figure 2(a) and (b).

Relationship between EDSS, age, disease duration and QOL (unadjusted)
Disability status (EDSS) was significantly related to all aspects of QOL except “role limitations caused by emotional problems” (RE) and “mental health” (MH), and showed the strongest correlation with “physical functioning” (Figure 3(a) and (b)).

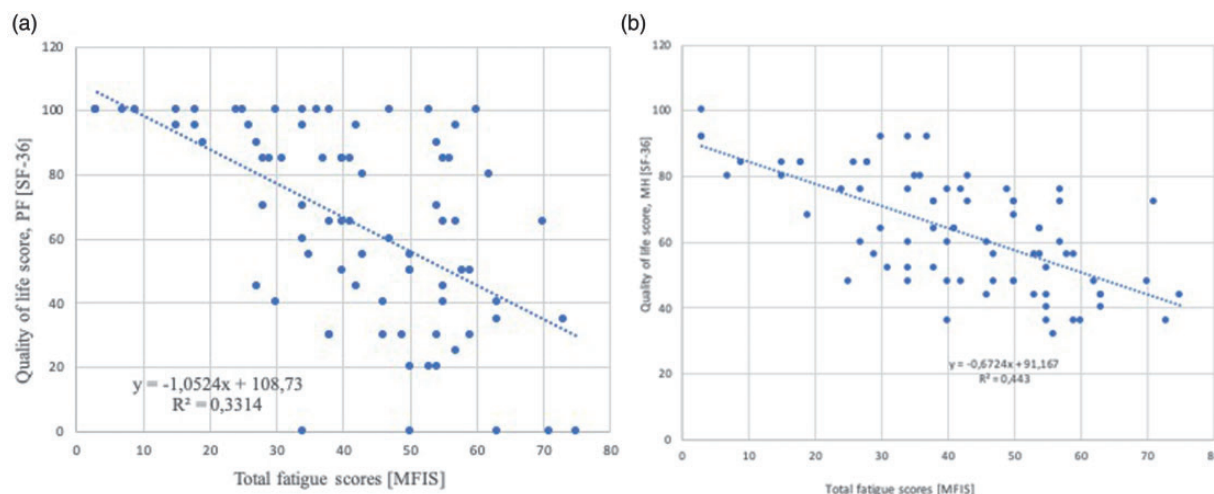


Figure 2. (a) Relationship between MFIS_{tot} and Physical Functioning. *MFIS*, *Modified Fatigue Impact Scale*. *PF*, *physical functioning*. Simple linear regression analysis was used to examine the relationship between total fatigue score on MFIS and the physical functioning dimension of QOL on SF-36. QOL decreased significantly with increasing fatigue. (b) Relationship between MFIS_{tot} and Mental Health. *MFIS*, *Modified Fatigue Impact Scale*. *MH*, *mental health*. Simple linear regression analysis was used to examine the relationship between total fatigue score on MFIS and the mental health dimension of QOL on SF-36. QOL decreased significantly with increasing fatigue.

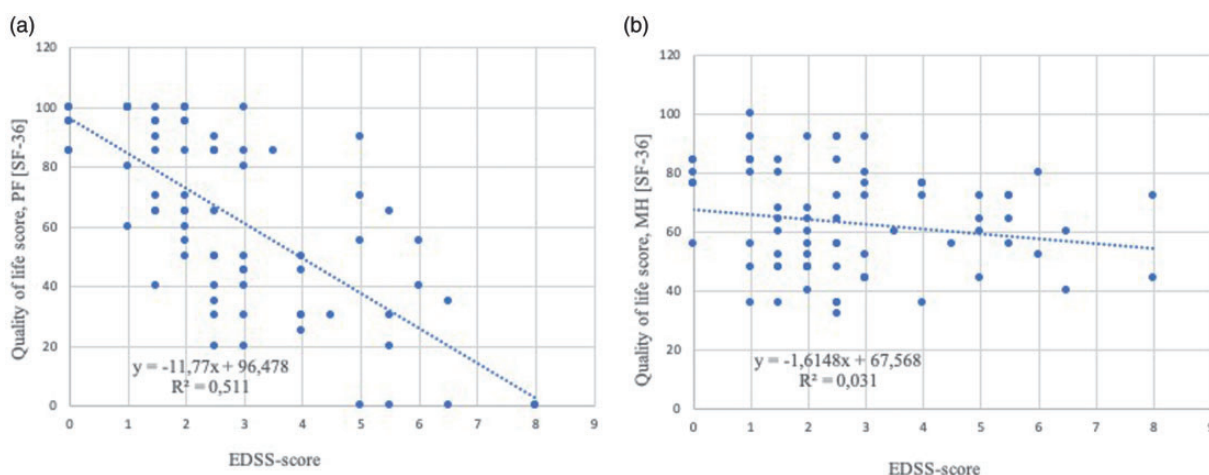


Figure 3. (a) Relationship between EDSS and Physical Functioning. *PF*, *physical functioning*. Simple linear regression analysis was used to examine the relationship between EDSS and the physical functioning dimension of QOL on SF-36. QOL-scores decreased significantly with increasing EDSS. (b) Relationship between EDSS and Mental Health. *MH*, *mental health*. Simple linear regression analysis was used to examine the relationship between EDSS and the mental health dimension of QOL on SF-36. The correlation was not significant.

Scores in “physical functioning” and “role limitations caused by physical problems” significantly decreased with increasing age. Furthermore, we saw a non-significant correlation between increasing age and better mental health.

Disease duration was only associated with “physical functioning” and “social functioning”.

Relationship between fatigue, EDSS and QOL (adjusted)

To evaluate the impact of fatigue and EDSS on QOL simultaneously, multiple linear regression was performed for each fatigue scale. First, total fatigue scores and EDSS-scores were plotted in a regression model with QOL-scores. Secondly, this was done for

each subscore of fatigue. Age and disease duration were included.

Total fatigue scores, EDSS and QOL. Total fatigue scores remained significantly associated with all aspects of QOL after adjusting for EDSS-score. Both scales were examined separately. EDSS correlated strongly with “physical functioning” in this analysis. However, the correlation between EDSS and almost every other aspect of QOL, disappeared when taking fatigue scales into account.

Fatigue subscores, EDSS and QOL. When considering the FSMC subscales separately, the motor subscale correlated with all the QOL-areas related to physical health (PF, RP, BP, GH)¹⁹ and additionally with vitality, social functioning and mental health. The cognitive subscale correlated exclusively with mental health aspects (V, SF, RE, MH).¹⁹ Thus, the two scales worked complementary to each other and jointly covered all aspects regarding QOL. Looking at the MFIS subscales, almost the same pattern was seen and additionally, QOL regarding social functioning correlated most strongly with the psyosocial subscale (Table 3).

Discussion

This study, which examined 79 MS patients in Denmark, showed that motor and cognitive fatigue were significantly and differently correlated to aspects of QOL. After adjustment for disability status, the correlation remained significant, indicating that fatigue impacts negatively on QOL independently of physical disability. Therefore, fatigue assessment provides additional information to EDSS. Supporting this statement, it was also found that EDSS was significantly associated almost exclusively with the aspect of QOL that covered physical functioning. This indicates that not all aspects of the disease burden are reflected in this score.

Relation to existing literature

Our results are consistent with previous studies showing that EDSS-score is mainly related to the physical area of QOL.^{2,3,5,18–21}

The relation between fatigue and impaired QOL has been found in several other studies as well.^{3,4,6–8,18,22} One recent study found a correlation between mental QOL and cognitive fatigue, as well as physical QOL and motor fatigue, supporting our results.⁸ Another study found similar results but noted that the different components of fatigue (physical,

cognitive, social role and psychological dimension) each correlated equally with all dimensions of QOL.²²

However, some studies conclude that mental areas of life-quality are strongly influenced by depression,^{7,18,23} which has not been measured in this study (discussed later). Mental health related QOL scores have also been found to be correlated with work status, time since last relapse, inpatient/outpatient relation and treatment.²¹

The relation between disease duration and QOL is not clarified in the literature. Some studies observe a full or partial relation,^{20,23} while others find none.²⁴ The influence of age in QOL has been reported for physical dimensions of QOL only, supporting the results of this study.^{21,24}

In our results, it was furthermore seen that increasing age seemed to be correlated to better mental health (insignificant).

The observed magnitudes of changes in QOL (for example a reduction of 1,72 points in QOL-RP, when motor fatigue increases by one, Table 4) is much greater than seen in another study, where the changes in QOL after increasement in EDSS, anxiety or depression have been measured.¹⁹ All though fatigue has not been measured in this particular study, it speaks in favor of the anticipation that this magnitude of change in QOL is of clinical relevance.

Implication of central findings

Our study implicates that 1) assessment of motor and cognitive fatigue provides us with information on distinct areas of QOL, and 2) given this correlation, treatment interventions targeted at reducing fatigue might improve QOL. This is particularly important because QOL-measurement itself has been found to be a predictor of change in disability status over time.²⁵

Assessment of fatigue can be done with questionnaires, as in this study. Studies have shown that physicians and patients have different perceptions of disability and its impact on health, thereby pointing out the necessity of using patient reported outcomes.²⁶ Some studies have found that physicians tend to focus on the physical parts of health, whereas patients are more concerned about functional capacity and a sense of well-being, which they are often able to measure themselves.²⁷

Table 3. Relationship between EDSS, fatigue [MFIS] and Quality of Life.

		EDSS	MFIS _{cog}	MFIS _{mot}	MFIS _{ps}
QOL	Physical functioning (PF)	-7,66* [-10,65; -4,69]	0,15 [-0,48;0,78]	-1,50* [-2,33; -0,68]	-1,01 [-4,33;2,30]
	Role limitations caused by physical problems (RP)	-2,09 [-6,77;2,60]	-1,62* [-2,62; -0,62]	-1,57* [-2,86; -0,27]	-1,56 [-6,77;3,65]
	Bodily pain (BP)	-0,63 [-3,96;2,70]	0,10 [-0,61;0,81]	-1,56* [-2,48; -0,63]	-1,89 [-5,60;1,82]
	General health (GH)	-3,06* [-5,81; -0,32]	-0,75* [-1,34; -0,17]	-0,28 [-1,04;0,49]	-1,62 [-4,68;1,43]
	Vitality (V)	-2,06 [-4,51;0,40]	-0,70* [-1,23; -0,18]	-1,17* [-1,85; -0,48]	-3,40* [-6,14; -0,67]
	Social functioning (SF)	-0,07 [-2,84;2,70]	-0,69* [-1,28; -0,10]	-0,35 [-1,12;0,42]	-6,45* [-9,73; -3,56]
	Role limitations caused by emotional problems (RE)	3,38 [-2,46;9,22]	-1,95* [-3,20; -0,70]	-0,65 [-2,27;0,97]	-0,56 [-7,07;5,95]
	Mental health (MH)	-0,30 [-2,24;1,64]	-0,78* [-1,19; -0,37]	-0,35 [-0,89; 0,19]	-2,39* [-4,55; -0,23]

MFIS, Modified Fatigue Impact Scale; _cog, cognitive subscale; _mot, motor subscale; _PS, psychosocial subscale; _tot, total score of the scale.

Values are expressed as β -coefficients with 95% confidence interval. They were found in an adjusted analysis, in which EDSS, fatigue, age and disease duration were entered in a multiple linear regression analysis simultaneously. Negative β 's indicate that QOL decreases with increasing fatigue. * $p < 0,05$ (p-values not shown).

Table 4. Relationship between EDSS, fatigue [FSMC] and Quality of Life.

		EDSS	FSMC _{cog}	FSMC _{mot}
QOL	Physical functioning (PF)	-8,17* [-11,2; -5,16]	0,24 [-0,37;0,84]	-1,21* [-1,87; -0,57]
	Role limitations caused by physical problems (RP)	-0,71 [-5,33;3,91]	-0,95 [-1,87; -0,02]	-1,72* [-2,71; -0,72]
	Bodily pain (BP)	-0,81 [-4,02;2,39]	-0,23 [-0,87;0,42]	-1,24* [-1,92; -0,54]
	General health (GH)	-1,89 [-4,48;0,70]	-0,47 [-0,99;0,05]	-0,74* [-1,30; -0,18]
	Vitality (V)	-1,19 [-3,50;1,12]	-0,46* [-0,93; -0,00]	-1,53* [-2,03; -1,03]
	Social functioning (SF)	0,45 [-2,63;3,52]	-0,71* [-1,33; -0,10]	-1,02* [-1,68; -0,35]
	Role limitations caused by emotional problems (RE)	4,49 [-0,93;9,91]	-2,22* [-3,31; -1,13]	-0,10 [-1,23;1,07]
	Mental health (MH)	0,29 [-1,65;2,23]	-0,74* [-1,13; -0,35]	-0,52* [-0,94; -0,10]

FSMC, Fatigue Scale for Motor and Cognitive Functions; _cog, cognitive subscale; _mot, motor subscale; _tot, total score of the scale.

Values are expressed as β -coefficients with 95% confidence interval. They were found in an adjusted analysis, in which EDSS, fatigue, age and disease duration were entered in a multiple linear regression analysis simultaneously. Negative β 's indicate that QOL decreases with increasing fatigue. * $p < 0,05$ (p-values not shown).

Treatment of fatigue includes elimination of smoking, reduction of caffeine intake and physical activity.²⁸ No pharmacological agent is yet approved for the treatment of MS fatigue, but Amantadine and Modafinil have shown efficacy.²⁸

The knowledge on the different impact of motor and cognitive fatigue may prove helpful for clinicians in predicting potential problems related to areas of QOL among MS-patients and have implications for the choice of treatment and care.⁸ For example, mental QOL and cognitive fatigue (but not physical) has shown to correlate to depression,^{7,18,23} suggesting early interventions targeted at psychological problems among this group of patients, in order to reduce fatigue and improve QOL. Moreover, Amantadine has shown to have a positive effect on fatigue, but no effect on depression, which might indicate that it is most effective on patients in whom physical fatigue is predominant.²⁹ Furthermore, one study found that those who were more physically active reported lower levels fatigue, measured on the Fatigue Severity Scale, which addresses physical fatigue only.³⁰ Finally, one study found a significant correlation between unemployment and cognitive, but not physical fatigue,³¹ which indicates the particular importance of recognizing cognitive fatigue among MS patients in order to prevent work related problems and perform appropriate rehabilitation services.

These differences in fatigue management and their differential outcomes on QOL underlines the importance of measuring and being aware of both types of fatigue separately.

Strengths and limits

The major strength of this study is that motor and cognitive fatigue has been examined separately, making it possible to investigate the diverse impact on QOL.

Furthermore, MFIS has been used for fatigue assessment. This scale is of particular interest because it has been recommended by the MS Council for Clinical Practice Guidelines based on its strong discriminative properties.¹⁵

Two other studies have used this scale in a study design similar to ours.^{8,22} However, these studies did not adjust for EDSS in the analysis, pointing out the additional information provided by our study. Finally, two different fatigue scales have been analyzed and showed the same pattern of

influence on aspects of QOL, supporting the correlation even further.

One important limitation is that depression was not examined in this study. Depression has shown to be independently associated with QOL and fatigue in several studies.^{3,7,16,18,22} Furthermore, fatigue may in some cases be a symptom of depression rather than a result of MS itself.²² However, in one cross-sectional study examining 103 MS patients, fatigue was found to be a predictor of QOL independent of depression measured through the Hamilton Rating Scale for Depression.³ Another study with prospective data collection over a 2-year period found the same correlation, supporting our results.⁶ Other factors not examined include concomitant disease, medications altering fatigue and sleep quality.^{6,7}

Secondly, misclassification due to inter-observer variation in EDSS-scoring, variance in the interval between EDSS and fatigue/QOL scoring, and misclassification of fatigue due to its fluctuating nature may occur.³² However, a recent longitudinal study found fatigue to be independently associated with some aspects of QOL in MS,³³ supporting our results.

The first version of the SF-36 was used instead of the second. Version two has several improvements, including simpler instructions and questions, improved layout, greater comparability with other translations and a few altered response choices.³⁴ Despite this, the first version was used in this study because of its well-described and well-studied status in a Danish context.³⁵

Finally, the cross-sectional design of this study makes us unable to prove a causal relationship between fatigue and reduced QOL.

The external validity of the study is threatened by the fact that our study population is only mildly disabled (EDSS 2,5), are from the same geographical place and mostly consist of patients with RRMS. However, the number of studies with the same findings, supports the validity.

Conclusion

This study shows that motor and cognitive fatigue is significantly and differentially correlated to reduced QOL, independently of bodily disability. This underlines the need for proper assessment of fatigue through the use of subjective, patient-reported measures, in order to get a holistic view of the disease

impact, which builds the foundation for development of appropriate and specific treatment interventions. These findings encourage further research in the field.

Declaration of conflicting interests

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Supplemental material

Supplemental material for this article is available online.

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