



# The Impact of Fatigue on the Quality of Life in Patients with Relapsing-Remitting Multiple Sclerosis

Senad Bajat<sup>1</sup>, Inge Klupka-Sarić<sup>2</sup>, Matea Markotić<sup>2</sup>, Selma Bajat<sup>3</sup>

<sup>1</sup>School of Medicine, University of Mostar, <sup>2</sup>Department of Neurology, Clinical Hospital Center Mostar, <sup>3</sup>Department of Anesthesiology, Resuscitation and Intensive Care, Clinical Hospital Center Mostar

## ABSTRACT

**Background:** The main objective of this study is to determine whether fatigue in patients with relapsing-remitting multiple sclerosis (RRMS) is associated with a lower quality of life.

**Methods:** The study included 50 participants with a confirmed diagnosis of relapsing-remitting multiple sclerosis. Fatigue levels were assessed using the Modified Fatigue Impact Scale, while quality of life was evaluated with the Multiple Sclerosis Quality of Life-54 questionnaire.

**Main findings:** Total fatigue and all its components demonstrated a strong negative correlation with all elements of quality of life. A greater number of relapses, higher Expanded Disability Status Scale (EDSS) scores, and the presence of comorbidities were significantly associated with overall fatigue and all its subtypes, while longer disease duration showed significant correlation with overall and physical fatigue. Although women had slightly higher average fatigue scores, this difference was not statistically significant. Age, marital status, and employment status were not significantly associated with fatigue levels, whereas participants with lower levels of education reported higher psychosocial fatigue.

**Principal conclusion:** The results of this study showed that fatigue had a statistically significant negative impact on the quality of life of patients with RRMS. The duration of the disease, a higher number of relapses, and elevated EDSS scores, as well as the presence of comorbidities, contributed to the development of fatigue, while sex, age, and sociodemographic factors, except for the level of education, did not demonstrate a significant influence.

**Key words:** relapsing-remitting multiple sclerosis, fatigue, quality of life, EDSS

### Article processing history:

Received August 4, 2025

Revised September 10, 2025

Accepted September 25, 2025

### ORCID IDs of the authors:

S.B. 0009-0005-7075-9180

I.K.S. 0000-0003-4704-9269

M.M. 0000-0001-8250-1762

S.B. 0000-0002-2789-4097

### Corresponding author:

Senad Bajat

School of Medicine, University of Mostar, 88000 Mostar, Bosnia and Herzegovina

E-mail: senadbajat00@gmail.com

### Cite this article as:

Bajat S, Klupka-Sarić I, Markotić M, Bajat S. The Impact of Fatigue on the Quality of Life in Patients with Relapsing-Remitting Multiple Sclerosis. *Annals of Biomedical and Clinical Research*. 2025;4:33-42.

<https://doi.org/10.47960/2744-2470.2025.2.4.33>

Copyright © School of Medicine, University of Mostar 2025

## INTRODUCTION

Multiple sclerosis (MS) is the most common chronic, inflammatory, and autoimmune disease of the central nervous system, characterized by demyelination, neurodegeneration, and gliosis (1). It is caused by a combination of genetic and environmental factors, including vitamin D deficiency, Epstein-Barr virus infection, and smoking (1, 2). The most common form of the disease is relapsing-remitting MS (RRMS), which may later evolve into progressive forms (3, 4). Diagnosis is based on clinical presentation, brain and spinal cord magnetic resonance imaging (MRI), cerebrospinal fluid analysis, and evoked potentials (5-7). The 2017 McDonald criteria allow for early diagnosis by confirming dissemination of lesions in time and space (7, 8).

Treatment includes immunomodulatory therapy to slow disease progression and corticosteroids for relapse management, as well as symptomatic therapy for specific issues such as spasticity, pain, and bladder dysfunction (9-11). The therapeutic approach may follow a step-wise escalation or early intensive strategy, depending on disease severity (12, 13).

Fatigue is one of the most frequent and disabling symptoms of MS, affecting up to 90% of patients (28). It is described as a persistent physical and mental exhaustion that is disproportionate to activity and not relieved by rest, significantly reducing daily functioning and quality of life (14, 15). In addition to neuroinflammation and demyelination, factors such as sleep disturbances, medication side effects, and depression can worsen fatigue (15). It is commonly assessed using tools such as the Modified Fatigue Impact Scale (MFIS), and treatment involves a combination of non-pharmacological strategies (e.g., physical activity, psychotherapy) and pharmacological agents such as modafinil (16-18).

Quality of life in MS patients is strongly influenced by disease-related symptoms, particularly fatigue, degree of disability, social support, and psychological disturbances (19, 20). Given the complexity of the disease, quality of life has become a key indicator of therapeutic success and a guide for planning individualized interventions (21, 22).

The aim of this study is to determine whether fatigue in patients with RRMS is associated with reduced quality of life. Additional objectives include examining whether fatigue intensity is significantly associated with higher Expanded Disability Status Scale (EDSS) scores, more frequent relapses, and longer disease duration, in addition to female sex, as well as exploring the potential contribution of other demographic factors and comorbidities to its development.

## PARTICIPANTS AND METHODS

### Participants

A cross-sectional study was conducted in collaboration with patients diagnosed with RRMS, in accordance with the revised 2017 McDonald criteria. The research took place at the demyelinating diseases outpatient clinic and the neurological day hospital of the Department of Neurology at the University Clinical Hospital Mostar (SKB Mostar), from January 15 to April 20, 2025. A total of 50 participants of different sexes and ages, with varying degrees of neurological impairment, were included. Eligible participants were over 18 years of age, had a confirmed diagnosis of RRMS, and had undergone individualized immunomodulatory treatment within the past three years. All patients gave informed consent after being clearly informed about the purpose of the work, and their data were fully protected. The exclusion criteria included patients with primary or secondary progressive forms of MS, as well as those not receiving immunomodulatory therapies.

## Methods

For the purposes of this study, a structured questionnaire was created in which patients provided demographic information (name and surname, age, sex, marital status, education level, and employment status) and clinical data related to their disease (disease duration, total number of relapses, most recent EDSS score, and associated comorbidities). Additionally, two standardized instruments were used: the Modified Fatigue Impact Scale (MFIS) and the Multiple Sclerosis Quality of Life-54 questionnaire (MSQoL-54) (16, 23). The MFIS assesses the perceived impact of fatigue on patients' daily functioning across physical, cognitive, and psychosocial domains, with higher scores indicating greater fatigue (23). The MSQoL-54 evaluates quality of life in MS patients through multiple domains, with higher scores reflecting better functioning and well-being. It also includes two summary indices: physical and emotional health components (23).

## Statistical analysis

Data analysis was conducted using descriptive statistical methods, with categorical variables presented as absolute and relative frequencies. Descriptive statistics also enabled the calculation of means, standard deviations, and other measures of dispersion for the numerical variables. The Chi-square test was utilized to test differences between categorical variables. The distribution of continuous variables was assessed with the Kolmogorov-Smirnov test. Depending on the distribution, differences between continuous variables were analyzed with the Student t-test, Mann-Whitney U test, and Kruskal-Wallis H test. The association between variables was examined with the appropriate correlation tests. Statistical analysis of the collected data was performed with IBM SPSS Statistics (version 25.0, SPSS Inc., Chicago, Illinois, USA) and Microsoft Excel 2019 (Microsoft Corporation, Redmond, WA, USA).

## RESULTS

As seen in Table 1, statistically significant differences were observed across all examined sociodemographic variables. Gender distribution differed significantly, indicating a disproportion between male and female participants. Educational attainment also showed significant variation, with participants unevenly distributed across different levels of education. Marital status revealed a statistically significant difference, suggesting a predominance of one category over others. Similarly, employment status varied significantly among participants, highlighting an imbalance in work-related roles within the sample.

Table 1. Sociodemographic characteristics of studied sample

	n	%	$\chi^2$	p
<b>Gender</b>			8.000	<b>0.005</b>
M	15	30.0		
F	35	70.0		
<b>Education</b>			17.680	<b>0.001</b>
Elementary school	2	4.0		
Secondary school	19	38.0		
University	9	18.0		
University	20	40.0		
<b>Marital status</b>			50.920	<b>&lt;0.001</b>
Married	40	80.0		
Single	9	18.0		
Widower	1	2.0		
<b>Working status</b>			72.400	<b>&lt;0.001</b>
Employed	38	76.0		
Unemployed	9	18.0		
Pensioner	1	2.0		
Student	2	4.0		

Disease characteristics by sex and the number of comorbidities are presented in Table 2, with no statistically significant differences found. Table 2 shows that the average disease

duration was slightly longer in men than in women with RRMS. Average relapse counts, EDSS scores, and the number of comorbidities were higher in women, although the differences were not statistically significant. Half of the participants reported having at least one additional disease besides MS, with hypertension, hypothyroidism, diabetes, and sleep disorders being the most common comorbidities.

An analysis of data from the MFIS questionnaire revealed that most patients experienced some degree of fatigue in the preceding four weeks. Average values of physical, cognitive, psychosocial, and total fatigue were somewhat higher in female participants, but without statistically significant differences between the sexes (Table 3).

Table 2. Gender differences in clinical characteristics of the disease and associated comorbidities

	Sex				t	p
	M		F			
	$\bar{X}$	SD	$\bar{X}$	SD		
Duration of disease (in years)	7.87	6.07	7.24	6.45	0.319	0.751
Number of relapses	3.13	2.47	4.00	3.45	0.879	0.384
Last EDSS	2.23	2.03	2.24	1.65	0.017	0.986
Number of associated comorbidities	0.33	0.49	0.74	0.82	1.802	0.078

Table 3. Gender differences in MFIS questionnaire scores

MFIS	Sex				t	p
	M		F			
	$\bar{X}$	SD	$\bar{X}$	SD		
Physical fatigue	11.07	12.06	14.11	10.14	0.920	0.362
Cognitive fatigue	11.53	10.15	12.69	7.28	0.454	0.652
Psychosocial fatigue	2.00	2.67	3.06	2.30	1.419	0.162
Total fatigue	24.60	24.08	29.86	18.96	0.827	0.412

A weak positive correlation was observed between age and overall fatigue level, though it was not statistically significant (Figure 1). Fatigue levels compared by marital status showed no significant differences (Figure 2). They also varied by working status (Figure 3), but again, without statistical significance.

Table 4 indicates that participants with lower educational levels (primary and secondary school) reported higher fatigue levels compared to those with higher education. The

most pronounced and statistically significant differences were found in psychosocial fatigue. Longer disease duration positively correlated with higher levels of physical and total fatigue, but not with the cognitive or psychosocial types (Table 5). Additionally, the numbers of relapses and comorbidities, as well as the last EDSS score, showed statistically significant positive correlations with total, physical, cognitive, and psychosocial fatigue.

Data from the MSQoL-54 questionnaire revealed that patients were equally satisfied

and dissatisfied with their quality of life overall. According to Table 6, the greatest impairment in quality of life was observed in physical and emotional limitations, as well as vitality, health perception, the physical health component, and health changes. While most quality-of-life subscale scores were lower in females than males, no statistically significant sex differences were found.

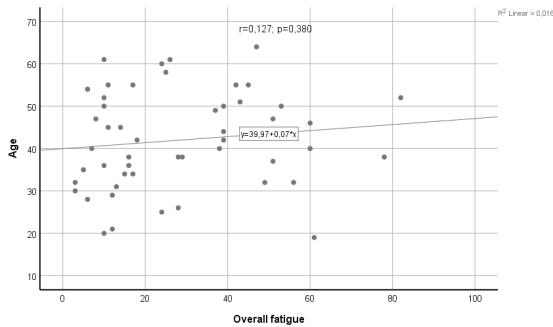


Figure 1. Relationship between participants' age and total fatigue level

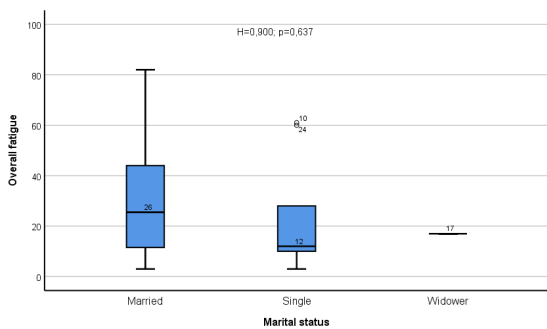


Figure 2. Relationship between participants' marital status and overall fatigue level

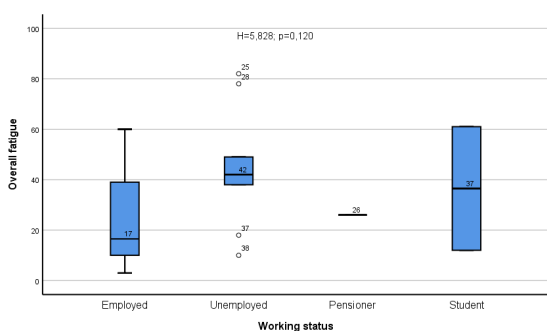


Figure 3. Relationship between participants' employment status and total fatigue level

Table 7 shows that total fatigue and all its components significantly negatively correlate with all quality-of-life subscales, indicating that greater fatigue is associated with poorer quality of life across all measured domains.

### DISCUSSION

This research examined the impact of fatigue on quality of life in RRMS patients, focusing on its association with clinical disease characteristics. The results showed that greater fatigue intensity significantly correlated negatively with quality of life. Higher EDSS scores, more relapses, comorbidities, and longer disease duration were significantly linked to increased fatigue. The relationship between fatigue and reduced quality of life aligns with previous findings. A 2024 American study demonstrated that severe fatigue in RRMS patients correlates with lower physical and mental quality-of-life components (25). A 2021 paper including all MS types identified fatigue as the most important quality-of-life factor, surpassing even disability level (26). This link reflects the complex pathophysiology of fatigue in MS, involving neuroinflammatory and neurodegenerative changes as well as psychological factors like depression and sleep disturbances, which worsen subjective quality of life (22, 27). However, some works note variability in this association (27, 28). A number of authors suggest depression and disability may have a stronger effect on perceived quality of life than fatigue, particularly in their interaction, with differences possibly due to measurement tools, cultural factors, and sample heterogeneity (28). A positive correlation between disease duration and fatigue was noted by Téllez et al., attributed to prolonged neuroimmunological burden and progressive demyelination reducing functional reserves (22). However, the lack of association between disease duration and cognitive or psychosocial fatigue here suggests these may depend more on

lesion location and psychological factors like anxiety, depression, and social support (30). Penner and Paul emphasize the multifactorial nature of fatigue, which is often dominated by psychological influences (30).

Higher EDSS scores were linked to greater fatigue, consistent with prior studies (29, 31). As an indicator of neurological disability,

EDSS reflects the physical burden experienced daily (29). While severe fatigue occurred in patients with lower EDSS, it was more pronounced in those with greater disability, possibly due to increased energy use or unrecognized neurodegeneration not fully captured by EDSS (31).

Table 4. Correlation between MFIS questionnaire scores and participants' educational level

MFIS	Education level								H	p
	Primary school		Secondary school		Postsecondary		Higher education			
	M	IR	M	IR	M	IR	M	IR		
Physical fatigue	19.50	.	16.00	19	6.00	17	11.00	19	5.458	0.141
Cognitive fatigue	19.50	.	11.00	12	7.00	5	10.00	10	6.318	0.097
Psychosocial fatigue	5.00	.	3.00	4	1.00	4	2.00	4	8.159	0.043
Total fatigue	44.00	.	26.00	32	12.00	24	24.50	31	5.828	0.120

Table 5. Correlation between disease duration, number of relapses, latest EDSS, and number of comorbidities with MFIS questionnaire variables

MFIS	Disease duration		Number of relapses		Last EDSS		Number of comorbidities	
	r	p	r	p	r	p	r	p
Physical fatigue	0.376	<b>0.007</b>	0.674	<b>&lt;0.001</b>	0.930	<b>&lt;0.001</b>	0.424	<b>0.002</b>
Cognitive fatigue	0.170	0.238	0.483	<b>&lt;0.001</b>	0.795	<b>&lt;0.001</b>	0.374	<b>0.008</b>
Psychosocial	0.208	0.146	0.553	<b>&lt;0.001</b>	0.861	<b>&lt;0.001</b>	0.367	<b>0.009</b>
Total fatigue	0.289	<b>0.042</b>	0.610	<b>&lt;0.001</b>	0.904	<b>&lt;0.001</b>	0.414	<b>0.003</b>

More relapses were also associated with higher fatigue, potentially due to cumulative central nervous system (CNS) damage (22, 32). However, Strober et al. warn that the predictive value of the relapse count decreases when accounting for depression and disability, highlighting the need to control psychosocial variables (33). Patients with more comorbidities reported higher fatigue, supporting findings by Marrie et al. and Fiest et al. (34, 35). The complex relationship between comorbidities and fatigue requires

further differentiation, as they vary in intensity and mechanisms (30).

Regarding demographics, despite a trend of higher fatigue in women, no significant sex differences were found, consistent with previous research (29, 36). Higher female fatigue may relate to hormonal fluctuations or psychosocial factors, as women report symptoms and seek care more frequently (37). Conversely, a 2021 Norwegian study identified female sex as an independent fatigue risk factor in MS (38).

Other demographic factors were generally not significantly associated with fatigue, except education level. Lower education correlated with greater fatigue, especially psychosocial, with significant differences. These results align with Patti et al., showing higher education correlates with better quality of life, likely due to better disease awareness and coping strategies affecting fatigue perception and psychosocial adjustment (39).

The limitations of this work include the small, single-center sample limiting generalizability and the use of subjective tools like the MSQoL-54 and MFIS, which may potentially be influenced by individual interpretation and mood. Future studies should involve larger samples, healthy controls, and additional tools assessing depression and sleep quality, given their known impact on MS fatigue.

In conclusion, fatigue significantly negatively impacts quality of life in RRMS patients. Its association with clinical and demographic

factors – especially disability, relapse count, and education – underscores the need for holistic, individualized care. Fatigue should be targeted directly as a key intervention goal, not merely considered a secondary symptom.

## CONCLUSION

Based on the results of this study, it can be concluded that fatigue has a significant negative impact on the quality of life of individuals with RRMS. It was observed that longer disease duration and a greater number of relapses, as well as higher EDSS scores and comorbidities, significantly contribute to the development of fatigue in these patients. On the other hand, no significantly higher frequency of fatigue was found in females compared to males. Additionally, age, marital status, and employment status were not associated with

Table 6. Sex differences in MSQoL-54 questionnaire results

	Sex				t	p
	M		F			
MSQoL-54	$\bar{X}$	SD	$\bar{X}$	SD		
Physical health	77.00	34.63	77.29	25.62	0.032	0.974
Physical role limitations	65.00	46.10	56.43	46.31	0.601	0.551
Emotional role limitations	71.11	43.40	66.67	44.28	0.327	0.745
Bodily pain	74.78	32.46	76.57	20.27	0.238	0.813
Emotional well-being	85.07	24.40	77.03	16.56	1.358	0.181
Vitality	67.47	25.38	60.34	22.07	1.000	0.322
Health perception	73.33	25.68	63.26	20.22	1.487	0.144
Social functioning	76.11	30.84	70.71	23.95	0.669	0.507
Cognitive functioning	79.00	22.61	77.00	14.46	0.376	0.709
Health distress	81.00	23.62	73.00	18.48	1.289	0.204
Sexual functioning	86.67	31.94	90.72	15.63	0.605	0.548
Change in health	55.00	25.35	49.29	18.67	0.888	0.379
Sexual satisfaction	73.33	32.00	78.57	16.21	0.771	0.444
Overall quality of life	76.78	22.65	73.40	17.96	0.562	0.576
Physical health composite score	74.65	29.87	70.10	21.93	0.602	0.550
Mental health composite score	78.75	26.58	73.32	20.96	0.773	0.443

Table 7. Correlation between fatigue and quality of life components

	Physical fatigue		Cognitive fatigue		Psychosocial fatigue		Total fatigue	
	r	p	r	p	r	p	r	p
Physical health	-0.923	<0.001	-0.812	<0.001	-0.861	<0.001	-0.907	<0.001
Physical role limitations	-0.855	<0.001	-0.767	<0.001	-0.812	<0.001	-0.848	<0.001
Emotional role limitations	-0.842	<0.001	-0.745	<0.001	-0.783	<0.001	-0.829	<0.001
Bodily pain	-0.797	<0.001	-0.706	<0.001	-0.768	<0.001	-0.788	<0.001
Emotional well-being	-0.724	<0.001	-0.837	<0.001	-0.820	<0.001	-0.808	<0.001
Vitality	-0.881	<0.001	-0.903	<0.001	-0.925	<0.001	-0.929	<0.001
Health perception	-0.910	<0.001	-0.888	<0.001	-0.922	<0.001	-0.938	<0.001
Social functioning	-0.939	<0.001	-0.883	<0.001	-0.915	<0.001	-0.950	<0.001
Cognitive functioning	-0.744	<0.001	-0.868	<0.001	-0.798	<0.001	-0.829	<0.001
Health distress	-0.845	<0.001	-0.859	<0.001	-0.870	<0.001	-0.886	<0.001
Sexual functioning	-0.730	<0.001	-0.730	<0.001	-0.697	<0.001	-0.754	<0.001
Change in health	-0.598	<0.001	-0.637	<0.001	-0.638	<0.001	-0.641	<0.001
Sexual satisfaction	-0.712	<0.001	-0.714	<0.001	-0.677	<0.001	-0.736	<0.001
Overall quality of life	-0.915	<0.001	-0.875	<0.001	-0.923	<0.001	-0.935	<0.001
Physical health composite score	-0.953	<0.001	-0.895	<0.001	-0.932	<0.001	-0.964	<0.001
Mental health composite score	-0.899	<0.001	-0.892	<0.001	-0.906	<0.001	-0.931	<0.001

higher levels of fatigue. Participants with lower educational levels reported greater fatigue, with statistically significant differences particularly evident in psychosocial fatigue.

#### ACKNOWLEDGMENTS

None.

#### FUNDING

The authors did not receive any financial support for the research, authorship, and/or publication of this study.

#### CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

#### AUTHORS' CONTRIBUTIONS

SB: contribution to study conception and design, literature review, supervision, writing of the paper, interpretation of data, critical revision of the paper; IKS: acquisition of data, contribution to study conception and design, literature

review, critical revision of the paper, assistance in writing the paper; MM and SB: acquisition of data, contribution to study conception and design, literature review.

#### ETHICAL BACKGROUND

**Institutional review board statement:** The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the School of Medicine, University of Mostar (Reg. No. 01-1-259/25).

**Informed consent statement:** Informed consent was obtained from all subjects involved in the study.

**Data availability statement:** We deny any restrictions on the availability of data, materials, and associated protocols.

#### REFERENCES

1. McGinley MP, Goldschmidt CH, Rae-Grant AD. Diagnosis and treatment of multiple sclerosis: a review. JAMA. 2021;325:765-79.

2. Brinar V, et al. Neurologija za medicinare. Drugo. obnovljeno i dopunjeno izdanje. Zagreb: Medicinska naklada; 2019.
3. Filippi M, Bar-Or A, Piehl F, Preziosa P, Solari A, Vukusic S, et al. Multiple sclerosis. *Nat Rev Dis Primers*. 2018;4:43.
4. Compston A, Coles A. Multiple sclerosis. *Lancet*. 2008;372:1502-17.
5. Ford H. Clinical presentation and diagnosis of multiple sclerosis. *Clin Med (Lond)*. 2020;20:380-3.
6. Magliozzi R, Cross AH. Can CSF biomarkers predict future MS disease activity and severity? *Mult Scler*. 2020;26:582-90.
7. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol*. 2018;17:162-73.
8. Zipp F, Oh J, Fragoso YD, Waubant E. Implementing the 2017 McDonald criteria for the diagnosis of multiple sclerosis. *Nat Rev Neurol*. 2019;15:441-5.
9. De Angelis F, John NA, Brownlee WJ. Disease-modifying therapies for multiple sclerosis. *BMJ*. 2018;27:363:k4674
10. Wang C, Ruiz A, Mao-Draayer Y. Assessment and treatment strategies for a multiple sclerosis relapse. *J Immunol Clin Res*. 2018;5:1032.
11. Zadro Matovina L, Jurašić MJ, Zavoreo I, Grbić N, Bašić Kes V. Liječenje multiple skleroze. *Acta Med Croatica*. 2018;72:385-97.
12. Oreja-Guevara C, Martínez-Yélamos S, Eichau S, Llana MA, Martín-Martínez J, Peña-Martínez J, et al. Beyond lines of treatment: embracing early high-efficacy disease-modifying treatments for multiple sclerosis management. *Ther Adv Neurol Disord*. 2024;17:17562864241284372.
13. Cerqueira JJ, Compston DAS, Geraldes R, Rosa MM, Schmierer K, Thompson A, et al. Time matters in multiple sclerosis: can early treatment and long-term follow-up ensure everyone benefits from the latest advances in multiple sclerosis? *J Neurol Neurosurg Psychiatry* 2018;89:844-50.
14. Ayache SS, Serratrice N, Abi Lahoud GN, Chalah MA. Fatigue in multiple sclerosis: a review of the exploratory and therapeutic potential of non-invasive brain stimulation. *Front Neurol*. 2022;13:813965.
15. Yi Z, Zhang Y, Du X, Kang J, Song Y, Li H, Jiang Y. Global prevalence of fatigue in patients with multiple sclerosis: a systematic review and meta-analysis. *Mult Scler Relat Disord*. 2024;59:103699.
16. Fisk JD, Ritvo PG, Ross L, Haase DA, Marrie TJ, Schlech WF. Measuring the functional impact of fatigue: initial validation of the fatigue impact scale. *Clin Infect Dis*. 1994;18:79-83.
17. Tur C. Fatigue management in multiple sclerosis. *Curr Treat Options Neurol*. 2016;18:26-38.
18. Ghazanfar S, Farooq M, Qazi SU, Chaurasia B, Kaunzner UW, Bernitsas E. The use of modafinil for the treatment of fatigue in multiple sclerosis: a systematic review and meta-analysis of controlled clinical trials. *Brain Behav*. 2024;14:e3623.
19. Patti F, Pappalardo A. Quality of life in patients affected by multiple sclerosis: a systematic review. In: Preedy VR, Watson RR. *Handbook of disease burdens and quality of life measures*. New York: Springer; 2010:3769-83.
20. Schmidt S, Jöstingmeyer P, Depression JP. Depression, fatigue and disability are independently associated with quality of life in patients with multiple sclerosis: results of a cross-sectional study. *Mult Scler Relat Disord*. 2019;35:262-9.
21. Ysraelit MC, Fiol MP, Gaitán MI, et al. Quality of life assessment in multiple sclerosis: different perception between patients and neurologists. *Front Neurol*. 2018;8:1-6.
22. Lindberg S, Sandgren S, Axelsson M, et al. Quality of life is decreased in persons with relapsing-remitting multiple sclerosis experiencing progression independent of relapse activity. *Mult Scler Relat Disord*. 2025;53:103063.
23. Vickrey BG, Hays RD, Harooni R, Myers LW, Ellison GW. A health-related quality of life measure for multiple sclerosis. *Qual Life Res*. 1995;4:187-206.
24. Larson RD. Psychometric properties of the modified fatigue impact scale. *Int J MS Care*. 2013;15:15-20.
25. Le HH, Ken-Opurum J, LaPrade A, Maculaitis MC, Sheehan JJ. Exploring humanistic burden of fatigue in adults with multiple sclerosis: an analysis of US National Health and Wellness Survey data. *BMC Neurol*. 2024;24:51.
26. Young CA, Mills R, Rog D, Sharrack B, Majeed T, Constantinescu CS, et al. Quality of life in multiple sclerosis is dominated by fatigue, disability and self-efficacy. *J Neurol Sci*. 2021;426:117437.
27. Induruwa I, Constantinescu CS, Gran B. Fatigue in multiple sclerosis – a brief review. *J Neurol Sci*. 2012;323:9-15.
28. Amtmann D, Bamer AM, Kim J, Chung H, Salem R, Askew RL, et al. People with multiple sclerosis report significantly worse symptoms and health-related quality of life than the US general population as measured by the PROMIS instruments. *Qual Life Res*. 2018;27:1415-24.
29. Téllez N, Río J, Tintoré M, Nos C, Galán I, Montalban X. Fatigue in multiple sclerosis persists over time: a longitudinal study. *J Neurol*. 2006;253:1466-70.
30. Penner IK, Paul F. Fatigue as a symptom or comorbidity of neurological diseases. *Nat Rev Neurol*. 2017;13:662-75.
31. Bakshi R, Shaikh ZA, Miletich RS, Czarnecki D, Dmochowski J, Henschel K, et al. Fatigue in multiple sclerosis and its relationship to depression and neurologic disability. *Arch Neurol*. 2000;57:930-4.
32. Krause I, Werner P, Rothstein Y, Steiner-Birmanns B, Gur A, Milo R. Comorbidity increases the risk of relapse in multiple sclerosis: a prospective study. *J Neurol Sci*. 2017;381:112-16.
33. Strober LB, Arnett PA. A longitudinal examination of the neuropsychological predictors of fatigue in multiple sclerosis. *Neuropsychology*. 2009;23:706-13.
34. Marrie RA, Horwitz R, Cutter G, Tyry T, Campagnolo D, Vollmer T. The burden of comorbidity in multiple sclerosis: frequent, underdiagnosed, and under-treated. *Mult Scler*. 2015;21:263-72.
35. Fiest KM, Walker JR, Bernstein CN, Graff LA, Beck CA, Patten SB, et al. Systematic review and meta-analysis of interventions for fatigue in multiple sclerosis. *Mult Scler*. 2016;22:2234-44.
36. Flachenecker P, Kämpfel T, Kallmann B, et al. Fatigue in multiple sclerosis: a comparison of different rating scales and correlation to clinical parameters. *Mult Scler*. 2002;8:523-6.
37. Maier S, Bajkó Z, Roşescu R, Bărcuţean L, Sărmăşan E, Voidăzan S, Bălaşa R. Sociodemographic and

- Clinical Determinants of Fatigue in Multiple Sclerosis. *Life (Basel)*. 2023;13:2132.
38. Broch L, Simonsen CS, Flemmen HØ, Berg-Hansen P, Skardhamar Å, Ormstad H, et al. High prevalence of fatigue in contemporary patients with multiple sclerosis. *Mult Scler J Exp Transl Clin*. 2021;7:2055217321999826.
39. Patti F, Pozzilli C, Montanari E, Pappalardo A, Piazza L, Levi A, Onesti E, Pesci I; Italian Study Group on Quality of Life in MS. Effects of education level and employment status on HRQoL in early relapsing-remitting multiple sclerosis. *Mult Scler*. 2007;13:783-91.