

Access this article online

Quick Response Code:



Website:

https://journals.lww.com/jehp/

DOI:

10.4103/jehp.jehp\_2079\_24

<sup>1</sup>Neurology Research Center, Kerman University of Medical Sciences, Kerman, Iran, <sup>2</sup>Health in Disasters and Emergencies Research Center, Institute for Futures Studies in Health, Kerman University of Medical Sciences, Kerman, Iran, <sup>3</sup>Faculty of Nursing, Kerman University of Medical Sciences, Kerman, Iran, <sup>4</sup>Clinical Research Development Center, Pastor Education Hospital, Bam University of Medical Sciences, Bam, Iran, <sup>5</sup>Department of Biostatistics and Epidemiology, Faculty of Public Health, Kerman University of Medical Sciences, Kerman, Iran

#### Address for correspondence:

Dr. Simin Jafari,  
Neurology Research Center, Kerman University of Medical Sciences, Kerman, Iran.  
Tel: +98-9132962994,  
E-mail: jafarisimin93@gmail.com  
Dr. Parya Jangipour Afshar,  
Health in Disasters and Emergencies Research Center, Institute for Futures Studies in Health, Kerman University of Medical Sciences, Kerman, Iran.  
Tel: +98-9133998773,  
E-mail: parya.afshar@gmail.com

Received: 26-11-2024

Accepted: 21-01-2025

Published: 31-03-2026

# Invisible symptoms and associated factors in multiple sclerosis patients

Behnaz Sedighi<sup>1</sup>, Parya Jangipour Afshar<sup>2</sup>, Maryam Abedini Parizi<sup>1</sup>, Somayeh Goudari Mohammadalian<sup>3</sup>, Amir Reza Salehi<sup>4</sup>, Fatemeh Ajam<sup>5</sup>, Simin Jafari<sup>1</sup>

## Abstract:

**BACKGROUND:** The invisible symptoms and associated factors have remained controversial especially about the effect of invisible symptoms on the Expanded Disability Status Scale (EDSS) and the daily life of individuals with multiple sclerosis (MS) patients. So, this study aimed to determine the invisible symptoms and associated factors in MS patients.

**MATERIALS AND METHODS:** This cross-sectional study analyzed data from 155 patients with MS registered at a referral clinic in Kerman during 2023–2024. Regression was utilized to identify factors associated with the invisible symptoms (fatigue, mood disorder, cognitive impairment, pain, and sexual dysfunction).

**RESULTS:** Out of 155 participants in the study, 135 were women (87.1%). The average MS disease duration for these subjects was  $9.0 \pm 5.5$  years. The most common invisible symptoms were fatigue and mood disorder. According to the regression results, the EDSS component had a positive association with sexual impairment ( $B = 0.559$ ), and women had more sexual impairment than men ( $B = 0.516$ ). Age and EDSS had a negative association with mood disorder and quality of life ( $B = -0.269$  and  $B = -0.695$ , respectively). EDSS had positive association with fatigue intensity ( $B = 0.259$ ), additionally physical disease and EDSS showed significant positive association with the Pain Disability Index ( $B = 0.224$ ,  $B = 0.270$ , respectively). Having physical disease increased cognitive impairment ( $B = 1.051$ ).

**CONCLUSION:** The findings suggest that EDSS is associated with almost all aspects of the invisible symptoms in people with MS, except cognitive impairment. Also, the more physical disease one has, the more pain and cognitive impairment one may experience.

## Keywords:

Invisible symptoms, Iran, multiple sclerosis

## Introduction

Multiple sclerosis (MS), one of the most disabling central nervous system (CNS) diseases, is an autoimmune inflammatory demyelinating condition that affects approximately 2.8 million people worldwide, the prevalence of MS in Iran is 100 per 100,000 and 31.5 per 100,000 population in Kerman Province and 57.3 per 100,000 population in Kerman City.<sup>[1-5]</sup>

MS disease leads to neurodegeneration and manifests through a variety of visible

and invisible symptoms, including fatigue, mood disorder, Cognitive impairment (CI), pain, bladder and bowel dysfunction, and sexual dysfunction.<sup>[6,7]</sup>

Invisible symptoms are prevalent in patient with MS, they may influence aspects of both physical and psychosocial symptoms which could have profound effect on the daily life of individual with MS. Invisible symptoms may also contribute more to patients' perception of their health than visible symptoms, causing a reduction in quality of life (QOL), EDSS, and even magnetic resonance imaging (MRI) changes.<sup>[6-9]</sup>

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 License (CC BY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

For reprints contact: WKHLRPMedknow\_reprints@wolterskluwer.com

**How to cite this article:** Sedighi B, Afshar PJ, Parizi MA, Mohammadalian SG, Salehi AR, Ajam F, et al. Invisible symptoms and associated factors in multiple sclerosis patients. J Edu Health Promot 2026;15:117.

The invisible symptoms of MS and their associated factors remain a topic of debate, particularly regarding their impact on the EDSS and QOL.<sup>[6-9]</sup> This highlights the need for further investigation into these symptoms and their contributing factors in MS patients [Figure 1]. The findings from this study could play a pivotal role in advancing cognitive rehabilitation strategies and developing tailored therapeutic interventions targeting invisible symptoms. Such interventions have the potential to significantly enhance patient adaptation, improve daily functioning, and elevate overall QOL. Additionally, the study focuses on MS patients in Iran—a region with a distinctive MS prevalence. By investigating this population, the research provides culturally and regionally specific insights that may differ from global or Western contexts, thereby addressing a critical gap in localized MS research.

## Materials and Methods

### Study design and setting

This study is a cross-sectional descriptive-analytical study in which the study population was selected using the sample size estimation formula for a proportion, the participants were patients with multiple sclerosis in a referral clinic in Kerman, one of Iran's largest cities, between 2023-2024.

### Study participants and sampling

A total of 155 MS patients from a referral clinic in Kerman were included in this study. The included patients had no other neurological diseases, no clinically isolated syndrome (CIS), were able to read and write, and were fluent in Persian. Patients with a history of learning disabilities, chronic comorbidities (such as diabetes, congestive heart failure, psychiatric or mental disorders, or genitourinary pathologies), those receiving corticosteroid pulse therapy, experiencing an MS relapse within 12 weeks prior to the assessment, or having physical impairments that could affect neuropsychological (NP) tests were excluded. Additionally, individuals who were not sexually active in the past six months or did not agree

to participate were also excluded. The final diagnosis of MS in this registry was confirmed by neurologists affiliated with Shafa Hospital and Kerman University of Medical Sciences, based on the revised McDonald criteria (2017).<sup>[10]</sup>

### Data collection tool and technique

Data were collected using seven questionnaires: A) demographic and clinical information form to assess the age, gender, education level, employment status, place of residence (urban or rural), no common comorbidities (diseases accompanying MS other than diabetes, hypertension, cardiovascular, cerebrovascular, and respiratory diseases), tobacco, alcohol, and substance abuse (opioids, heroin, methamphetamine, or other stimulants) and the patient's clinical conditions including duration of disease, fatigue, psychiatric symptoms, CI, pain, sexual disorder, B) the EDSS, C) Fatigue Severity Scale (FSS); an unidimensional questionnaire of 9 statements evaluating the severity but also the impact of fatigue in patients with MS. Items are scored from 1 to 7 (1 = completely disagree to 7 = completely agree). The reliability and validity of the Persian version of the questionnaire were reported as 0.93 and 0.96 by Shahvarughi-Farahani *et al.*,<sup>[11]</sup> D) patient health questionnaire-9 (PHQ9); is the depression module, which scores each of the 9 DSM-IV criteria as "0" (not at all) to "3" (nearly every day), scores of 5, 10, 15, and 20 have represented mild, moderate, moderately severe, and severe depression, respectively. The validity and reliability of the Persian version of the questionnaire by Ardestani *et al.*<sup>[12]</sup> were reported between 0.91 and 0.93 based on Cronbach's alpha. E) The Persian-adapted Brief International Cognitive Assessment for MS (BICAMS) tests which is a valid instrument for the routine NP assessment of MS patient included; California Verbal Learning Test (CVLT-II) to assess auditory or verbal episodic memory, Symbol Digit Modalities Test (SDMT) to assess visual processing speed and working memory, Brief Visuospatial Memory Test-Revised (BVM-T-R) to assess visual or spatial episodic memory. Impairment is defined as a score that was at least 1.5 SDs below the mean normative value for each cognitive test. The reliability of the Persian version of the questionnaire was assessed and confirmed by Eshaghi *et al.*,<sup>[13]</sup> with good discriminant validity and reliability. F) Pain Disability Index (PDI). The PDI is brief, yet comprehensive in the domains of life that assesses how pain affects the performance of routine daily activities with seven equations that scales are from 0 to 10. A response choice of 0 indicates normal performance, whereas 10 indicates a complete inability to carry out a particular activity. The possible range is between 0 and 70. The seven equations include daily activities, such as family and home responsibilities, recreation, social activities, occupations, sexual behaviors, self-care, and life-support activities.

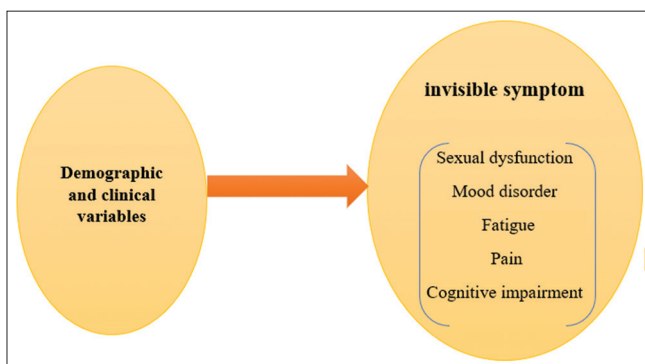


Figure 1: Conceptual figure of the theoretical framework

The validity and reliability of the Persian version of the questionnaire by Marbouti *et al.*,<sup>[14]</sup> was 0.80 based on Cronbach's alpha. G) The Multiple Sclerosis Intimacy and Sexuality Questionnaire-19 (MSISQ-19); which is self-report questionnaire contains 19 items. This scale rates how various MS symptoms have interfered with the patient's sexual activity over the previous 6 months. It assesses three dimensions of sexual dysfunction: Primary (five items), secondary (nine items), and tertiary (five items). Each item is rated on a five-point Likert scale (1, never; 2, rarely; 3, occasionally; 4, almost always; 5, always). The original validation study of the MSISQ-19 found it to demonstrate reliability, as well as construct, criterion, and concurrent validity, on measures of (a) marital satisfaction (specifically satisfaction with affective communication, satisfaction with problem-solving communication, and sexual satisfaction); (b) MS related neurological impairment and level of disability; (c) psychological distress and well-being; and (d) global sexual dysfunction.<sup>[15]</sup> Cronbach's alpha coefficient was 0.90 for total MSISQ-19 score, with values of 0.85, 0.90, and 0.78 for the subscales assessing primary, secondary, and tertiary sexual dysfunction, respectively by Mohammadi *et al.*<sup>[16]</sup>

EDSS of MS patients was designed by John Kurtzke. It assesses the functioning of systems such as pyramidal, cerebellar, brainstem, sensory, bowel, and bladder, visual and cerebellar regions.<sup>[17]</sup> The score varies from 0 (a normal neurological state) to 10 (MS-induced death): 0-2.5 refers to people with a mild degree of disability, 3-5 refers to people with a moderate degree of disability, and 5.5-10 refers to people with a severe degree of disability.

All questionnaires were filled by the patients in a calm and private environment under the supervision of a neurologist and the EDSS was assessed by a neurologist. The records were kept and analyzed anonymously.

### Ethical consideration

This study was approved by the Ethics Committee of Kerman University of Medical Sciences with id number: (IR.KMU.REC.1402.271). Written informed consent was obtained from all the participants.

### Statistical analysis method

SPSS 26 was used to analyze data. Descriptive statistics were used to describe qualitative (number and percentage) and quantitative variables (mean and standard deviation). A linear regression model was used to determine the factors related to the invisible symptoms such as fatigue, mood disorder, pain, and sexual dysfunction, and logistic regression was used to determine the associated factors on CI in the patients with MS. In both linear and logistic regression, the backward method was employed. A significant level of 0.05 was considered.

## Result

### Descriptive

Among the 155 persons who entered the study, 135 were women (87.1%), while the rest were men (12.9%). The majority of patients were older than 30 years (86.5%) and were unemployment (67.7%). Only 12.3% had physical disease, and 7.1% were addict [Table 1].

The majority of participants had mild EDSS (78.7%), and the most common symptoms they stated were fatigue and mood changes [Table 2].

**Table 1: Demographic variables of patients with MS (n=155)**

| Variables         | Categories    | Total patients<br>(n=155) Number | Percent |
|-------------------|---------------|----------------------------------|---------|
| Age               | <30           | 19                               | 12.3    |
|                   | ≥ 30          | 134                              | 86.5    |
| Gender            | Men           | 20                               | 12.9    |
|                   | women         | 135                              | 87.1    |
| Education (years) | <12           | 23                               | 14.8    |
|                   | 12-16         | 107                              | 69.0    |
|                   | >16           | 25                               | 16.1    |
| Job               | Unemployed    | 130                              | 67.7    |
|                   | Self-employed | 29                               | 15.1    |
|                   | Employed      | 28                               | 14.6    |
| Location          | Urban         | 148                              | 95.5    |
|                   | Rural         | 6                                | 3.9     |
| Physical disease  | No            | 136                              | 87.7    |
|                   | Yes           | 19                               | 12.3    |
| Addiction         | No            | 144                              | 92.9    |
|                   | Yes           | 11                               | 7.1     |

Missing cases may result in a low number and percentages

**Table 2: Clinical details of patients with MS (n=155)**

| Variables                    | Categories                              | Total patients<br>(n=155) |         |
|------------------------------|-----------------------------------------|---------------------------|---------|
|                              |                                         | Number                    | Percent |
| EDSS                         | (0-2.5) Mild                            | 122                       | 78.7    |
|                              | Moderate (3-5)                          | 27                        | 17.4    |
|                              | Sever (5.5-10)                          | 6                         | 3.9     |
| Type of drugs                | Injectable                              | 24                        | 15.5    |
|                              | Anti CD20                               | 63                        | 40.6    |
|                              | S1P receptor modulator (Fingolimod)     | 11                        | 7.1     |
|                              | Natalizumab                             | 0                         | 0       |
|                              | Oral (Dimethyl fumarate, Teriflunomide) | 33                        | 21.3    |
|                              | None                                    | 24                        | 15.5    |
| Type of problem <sup>1</sup> | Fatigue                                 | 148                       | 95.5    |
|                              | Mood                                    | 117                       | 75.5    |
|                              | Cognition                               | 70                        | 45.2    |
|                              | Pain                                    | 53                        | 34.2    |
|                              | Sexual disorder                         | 29                        | 18.7    |
|                              | Sphincteric                             | 32                        | 20.6    |

Missing cases may result in a low number and percentages, 1=The number of patients who have each of these symptoms has been reported. Each individual may experience one or more symptoms

The average duration of MS disease for these participants was  $9.0 \pm 5.5$  years, with a minimum time of 6 months and a maximum of 25 years [Table 3].

### Analytical

Regression results for all people investigated invisible factors (sexual dysfunction, mood disorder, Fatigue intensity, Pain Disability Index, and CI). It demonstrated that in sexual dysfunction, the EDSS factor was effective and had a positive association with sexual impairment ( $B = 0.559, P = 0.026$ ) while women had more sexual dysfunction than men ( $B = 0.516, P = 0.038$ ). About the mood disorder variable, age and EDSS had negative association with mood disorder ( $B = -0.269$  ( $P = 0.014$ ),  $B = -0.695$  ( $P < 0.001$ ), respectively). EDSS had a positive association with fatigue intensity ( $B = 0.259, P = 0.03$ ); in addition, physical disease and EDSS had significant positive association with Pain Disability Index ( $B = 0.224$  ( $P = 0.008$ ),  $B = 0.270$  ( $P = 0.001$ ), respectively). In CI, having physical disease increased CI ( $B = 1.05, P = 0.044$ ) [Table 4].

### Discussion

This study has investigated the invisible symptoms and associated factors in patients with MS. In this study, the majority of patients with MS had mild EDSS and the most common invisible symptoms were fatigue and mood disorders. EDSS was significantly linked to sexual

dysfunction and fatigue, while both age and EDSS were associated with mood disorders. Pain was influenced by physical comorbidities and EDSS, and CI was significantly associated with physical disorders. These results emphasized the multifactorial nature of invisible symptoms in MS, underscoring the need for targeted interventions to address these complex challenges.

In this study, the majority of patients with MS had mild EDSS, consistent with findings from several previous studies.<sup>[18]</sup> This could be attributed to early diagnosis and improved access to treatments, including disease-modifying therapies, which are effective in delaying disease progression and maintaining lower levels of disability. Additionally, the younger age of most patients and their early stage of disease may further explain the predominance of mild disability scores in this population.

In this study, fatigue was the most common invisible symptom in patients with MS, which was in line with other studies; it could be due to the multifactorial nature of fatigue in MS, including CNS damage, immune dysregulation, physical inactivity, and psychological factors such as depression and anxiety.<sup>[19,20]</sup>

The results demonstrated a significant positive association between EDSS and fatigue intensity, which was consistent with findings from previous studies. This relationship might be attributed to the multifaceted challenges faced by patients with MS, as increased disability often exacerbates psychological, physical, and cognitive fatigue. These interconnected factors likely contributed to the heightened fatigue experienced by individuals with higher levels of disability.<sup>[19-21]</sup>

The second most common invisible symptom in patients with MS was mood disorder. The results indicated that factors associated with mood disorders, which also significantly affected QOL, include age and EDSS. Specifically, both age and EDSS were found to have a negative association with QOL, aligning with findings from other studies.<sup>[21-23]</sup> In this study, mood disorders were notably more prevalent (75.5%) among individuals with MS in Iran compared to the general Iranian population, which was consistent with previous research.<sup>[24]</sup> Furthermore, the prevalence of mood disorders in this study was higher than reported in other studies on the MS population in Iran,<sup>[25]</sup> potentially due to increased healthcare utilization, such as higher rates of hospitalization and frequent physician visits, compared to the general population.<sup>[26]</sup>

In this study, cognitive impairment (CI) had a positive association only with physical disease. The impact of body health on brain function has been well-established in clinical practice, with acute confusional states

**Table 3: Mean and standard deviation of variables related to patients**

| Variables                 | Total patients<br>Mean $\pm$ SD | Min | Max |
|---------------------------|---------------------------------|-----|-----|
| Age (year)                | 39.3 $\pm$ 8.8                  | 19  | 66  |
| The duration of MS (year) | 9.0 $\pm$ 5.5                   | 0.5 | 25  |
| EDSS                      | 1.5 $\pm$ 1.6                   | 0   | 7   |

**Table 4: Factors influencing invisible symptoms (sexual dysfunction, mood disorder, fatigue, pain, and cognitive impairment) with regression for all patients (n=155)**

| Variables             | Standardized coefficient (Beta) | P      |
|-----------------------|---------------------------------|--------|
| Sexual dysfunction    |                                 |        |
| Gender (female)       | 0.516                           | 0.038  |
| EDSS                  | 0.559                           | 0.026  |
| Mood disorder         |                                 |        |
| Age                   | -0.269                          | 0.014  |
| EDSS                  | -0.695                          | <0.001 |
| Fatigue intensity     |                                 |        |
| EDSS                  | 0.259                           | 0.003  |
| Pain Disability Index |                                 |        |
| Physical disease      | 0.224                           | 0.008  |
| EDSS                  | 0.270                           | 0.001  |
| Cognitive impairment  |                                 |        |
| Physical disease      | 1.051                           | 0.044  |

(i.e., delirium, CI) frequently occurring during physical illnesses. Extensive research demonstrated a strong association between individual physical diseases such as diabetes, heart disease, vascular conditions, and cancer with poor cognitive performance.<sup>[6,27]</sup> In this study, the prevalence of CI was 45.2%. CI in patients with MS varied throughout their lifetime, with a high variability in prevalence rates (30% to 70%), indicating that it could be a significant symptom even in the early stages of MS.<sup>[6,21,28]</sup>

The results showed that Pain Disability Index had significant positive association with physical disease and EDSS. The relationship between pain and disability, as measured by the EDSS in patients with MS, has been found in several studies.<sup>[28-32]</sup> Patients with chronic pain showed higher scores on the EDSS and also had physical disease. Might be it's due to the higher the EDSS score, the more MS patients suffered from spasticity, paresis, and postural abnormalities, resulting in an increase in both neuropathic and nociceptive pain.<sup>[29,32]</sup>

The results of this study demonstrated that sexual dysfunction in patients with MS was significantly influenced by the EDSS score and female gender. Specifically, increasing EDSS scores were associated with greater sexual impairment, consistent with findings from recent studies.<sup>[33,34]</sup> This suggested that worsening physical impairment and higher disability levels exacerbated sexual dysfunction in MS patients. Additionally, factors such as muscle tightness, body spasms, and physical incapacity may further hinder sexual activity and reduce sexual satisfaction.<sup>[33,34]</sup>

Female patients were found to experience more sexual impairment compared to males, aligning with other studies conducted in Iran on sexual satisfaction.<sup>[33,35,36]</sup> This disparity might be attributed to the different clinical presentations of MS in male and female patients, including hormonal differences, such as fluctuations in estrogen levels, which have been shown to influence disease progression and symptom severity.<sup>[37]</sup> Additionally, psychological factors like higher rates of anxiety and depression among female patients, as well as sociocultural factors, including stigma and gender norms, could further contribute to this disparity.<sup>[38]</sup>

### Limitations and recommendations

This study, like all studies, had some limitations. First, it was a cross-sectional study, so it is not possible to express a causal relationship. Second, some patients did not cooperate, and the sample size was small third, there have been few studies conducted on this subject so far. It is recommended to increase the sample size and conduct a longitudinal study in future research for more robust results. Additionally, it is suggested that similar studies be carried out in different cities.

The family helps patients stay healthy, and it is the family who ultimately cares for the patient. And to treat the family is to provide the patient with essential care. Invisible symptoms can have severe psychological effects on the families and caregivers of patients, therefore their families who give them care face several clinical challenges. On the other hand, the importance of recognizing invisible symptom in MS for patient and patient's family is that can seek help from the family for their management. Family caregivers need to be educated about the MS and its symptoms. In this direction, there are various supportive and educational programs for MS patients' families and numerous studies have evaluated these programs. A study which was done in Iran showed the efficacy of group psycho-education in reduction of family caregivers' psychological burden in MS patients.

### Conclusion

This study investigated the invisible symptoms and associated factors in patients with MS, with a particular emphasis on addressing key health policy benchmarks. The findings highlight significant associations between EDSS and various invisible symptoms, including mood disorders, fatigue, pain, and sexual dysfunction, all of which impact QOL and healthcare outcomes. Early detection and management of these symptoms are crucial to prevent progression and complications while promoting patient-centered care that addresses both physical and psychosocial needs. This approach enhances the comprehensive management of MS. The study's insights align with key health policy priorities, which emphasize reducing the burden of chronic diseases through early intervention, effective symptom management, and personalized treatment plans. By focusing on invisible symptoms and their associated factors, healthcare providers can better meet policy objectives aimed at enhancing the well-being, social adaptation, and independence of MS patients.

### Acknowledgement

The researchers would like to thank all the patients with MS for participating in this study. This study was approved by the neurology research center of Kerman University of Medical Sciences.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

### References

1. Mirmosayyeb O, Shaygannejad V, Bagherieh S, Hosseinabadi AM, Ghajarzadeh M. Prevalence of multiple sclerosis (MS) in Iran: A systematic review and meta-analysis, *Neurol Sci* 2022;43:233-41.

2. Walton C, King R, Rechtman L, Kaye W, Leray E, Marrie RA, *et al.* Rising prevalence of multiple sclerosis worldwide: Insights from the Atlas of MS. *Mult Scler* 2020;26:1816-21.
3. Jeanjean M, Bind M-A, Roux J, Ongagna J-C, De Sèze J, Bard D, *et al.* Ozone, NO<sub>2</sub> and PM<sub>10</sub> are associated with the occurrence of multiple sclerosis relapses. Evidence from seasonal multi-pollutant analyses. *Environ Res* 2018;163:43-52.
4. Shaygannejad V, Mohamadirizi S. Spiritual health in women with multiple sclerosis and its association with self-esteem. *J Educ Health Promot* 2020;9:64.
5. Kamal MN, Samouei R, Sarrafzadeh S, Tamannaefar S, Ghaebi N, Behrouzi R. Relation between personality disorders and characteristics of multiple sclerosis patients and their parents. *J Educ Health Promot* 2018;7:106.
6. Lakin L, Davis BE, Binns CC, Currie KM, Rensel MR. Comprehensive approach to management of multiple sclerosis: Addressing invisible symptoms—A narrative review. *Neurol Ther* 2021;10:75-98.
7. Parker L-S, Topcu G, De Boos D, das Nair R. The notion of “invisibility” in people’s experiences of the symptoms of multiple sclerosis: A systematic meta-synthesis. *Disabil Rehabil* 2021;43:3276-90.
8. Green R, Cutter G, Friendly M, Kister I. Translational, Clinical. Which symptoms contribute the most to patients’ perception of health in multiple sclerosis? *Mult Scler J Exp Transl Clin* 2017;3:2055217317728301.
9. Yalachkov Y, Soydaş D, Bergmann J, Frisch S, Behrens M, Foerch C, *et al.* Determinants of quality of life in relapsing-remitting and progressive multiple sclerosis. *Mult Scler Relat Disord* 2019;30:33-7.
10. 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.
11. Shahvarughi-Farahani Az, A’zimian M, Fallah-Pour M, Karimlou M. Evaluation of reliability and validity of the persian version of fatigue severity scale (FSS) among persons with multiple sclerosis. *J Arch Rehab* 2013;13:84-91.
12. Ardestani MSS, Ashtiani RD, Rezaei Z, Vasegh S, Gudarzi SS. Validation of Persian version of PHQ-9 for diagnosis of major depressive episode in psychiatric wards in Iran. *Int J Appl Behav Sci* 2019;5:2.
13. Eshaghi A, Riyahi-Alam S, Roostaei T, Haeri G, Aghsaei A, Aidi MR, *et al.* Validity and reliability of a Persian translation of the Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS). *Clin Neuropsychol* 2012;26:975-84.
14. Marbouti L, Jafari H, Noorzadeh DS, Behtash H. Pain-related disability measurement: The cultural adaptation and validation of “pain disability index (PDI)” and “pain disability questionnaire (PDQ)” among Iranian low back pain patients. *Med J Islam Repub Iran* 2011;25:27-34.
15. Sanders AS, Foley FW, LaRocca NG, Zemon V. The multiple sclerosis intimacy and sexuality questionnaire-19 (MSISQ-19). *Sex Disabil* 2000;18:3-26.
16. Mohammadi K, Rahnama P, Montazeri A, Foley FW. The multiple sclerosis intimacy and sexuality questionnaire-19: Reliability, validity, and factor structure of the Persian version. *J Sex Med* 2014;11:2225-31.
17. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS). *Neurology* 1983;33:1444-52.
18. Kucharczuk M, Juraszek KM, Krajewski S, Surman-Wika M, Tkaczyński K. The assessment of the patients disability degree using the EDSS scale in various forms of multiple sclerosis. *J Educ Health Sport* 2018;8:278-92.
19. Manjaly Z-M, Harrison NA, Critchley HD, Do CT, Stefanics G, Wenderoth N, *et al.* Pathophysiological and cognitive mechanisms of fatigue in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2019;90:642-51.
20. Morrow SA, Conway D, Fuchs T, Wojcik C, Unverdi M, Yasin F, *et al.* Quantifying cognition and fatigue to enhance the sensitivity of the EDSS during relapses. *Mult Scler J* 2021;27:1077-87.
21. Yigit P, Acikgoz A, Mehdiyev Z, Dayi A, Ozakbas S. The relationship between cognition, depression, fatigue, and disability in patients with multiple sclerosis. *Ir J Med Sci* 2021;190:1129-36.
22. Asadollahzadeh E, Ebadi Z, Owji M, Rezaeimanesh N, Sahraian MA, Moghadasi AN, *et al.* Exploring the relationship between disability status, depression, and quality of life in individuals with multiple sclerosis. *Mult Scler Relat Disord* 2024;87:105629.
23. Rahimi H, Pirmoradi M, Lavasani FF, Farahani H. The effectiveness of group intervention focused on intolerance of uncertainty on psychological distress and quality of life in multiple sclerosis patients. *J Educ Health Promot* 2023;12:29.
24. Shafiee A, Soltani H, Athar MMT, Jafarabady K, Mardi P. The prevalence of depression and anxiety among Iranian people with multiple sclerosis: A systematic review and meta-analysis. *Mult Scler Relat Disord* 2023;78:104922.
25. Peres DS, Rodrigues P, Viero FT, Frare JM, Kudsi SQ, Meira GM, *et al.* Prevalence of depression and anxiety in the different clinical forms of multiple sclerosis and associations with disability: A systematic review and meta-analysis. *Brain Behav Immun* 2022;24:100484.
26. Marrie RA, Walld R, Bolton JM, Sareen J, Patten SB, Singer A, *et al.* Effect of mood and anxiety disorders on health care utilization in multiple sclerosis. *Mult Scler* 2021;27:1411-20.
27. Alizadehfard S, Alipour A. Relationship between multimorbidity and cognitive decline moderated by social health. *Avicenna J Neuropsychophysiology* 2021;8:157-61.
28. Scherder RJ, Prins AJ, van Dorp MJ, van Klaveren C, Cornelisz I, Killestein J, *et al.* Pain, cognition and disability in advanced multiple sclerosis. *Scand J Pain* 2021;21:754-65.
29. Solaro C, Cella M, Signori A, Martinelli V, Radaelli M, Centonze D, *et al.* Identifying neuropathic pain in patients with multiple sclerosis: A cross-sectional multicenter study using highly specific criteria. *J Neurol* 2018;265:828-35.
30. Young J, Amatya B, Galea MP, Khan F. Chronic pain in multiple sclerosis: A10-year longitudinal study. *Scand J Pain* 2017;16:198-203.
31. Veličkaitė G, Jucevičiūtė N, Balnytė R, Laucius O, Vaitkus A. Pain characteristics and associations with quality of life in patients with multiple sclerosis in Lithuania. *Medicina* 2020;56:596.
32. Ghajrzadeh M, Jalilian R, Sahraian MA, Moghadasi AN, Azimi A, Mohammadifar M, *et al.* Pain in patients with multiple sclerosis. *Maedica* 2018;13:125.
33. Sedighi B, Abedini Parizi M, Haghdoost AA, Jangipour Afshar P, Shoraka HR, Jafari S. How does multiple sclerosis affect sexual satisfaction in patients’ spouses? *Front Psychol* 2023;14:1110884.
34. Altmann P, Leutmezer F, Leithner K, Monschein T, Ponleitner M, Statmann M, *et al.* Predisposing factors for sexual dysfunction in multiple sclerosis. *Front Neurol* 2021;12:618370.
35. Zegeye B, Woldeamanuel GG, Negash W, Shibire G. Sexual satisfaction and its associated factors among married women in Northern Ethiopia. *Ethiop J Health Sci* 2020;30:169-78.
36. Amiri M, Khosravi A, Nouri M, Ahmadianfar F, Kebria MH, Raei M. Sexual satisfaction and related factors among Iranian married women, 2017. *Malays J Med Health Sci* 2020;16:29-33.
37. Ysraelit MC, Correale J. Impact of sex hormones on immune function and multiple sclerosis development. *Immunology* 2019;156:9-22.
38. Joyeys J, Marrie RA, Bernstein CN, Bolton JM, Fisk JD, Graff LA, *et al.* Sex differences evident in elevated anxiety symptoms in multiple sclerosis, inflammatory bowel disease, and rheumatoid arthritis. *Front Psychiatry* 2023;14:1260420.