



Podcast

High odds of multiple sclerosis following major life stressors: Evidence from a population-based case-control study in Northern Iran

Received: 09 Mar. 2025
Accepted: 05 May 2025

Nazanin Hoseinimayvan¹, Tahmineh Shojaee¹, Seyed Mohammad Baghbanian²

¹ School of Medicine, Mazandaran University of Medical Sciences, Sari, Iran

² Department of Neurology, School of Medicine, Booolisina Hospital, Mazandaran University of Medical Sciences, Sari, Iran

Keywords

Multiple Sclerosis; Psychosocial Stress; Case-Control Studies; Life Experiences; Iran

Abstract

Background: Psychological stress has been proposed as a trigger of multiple sclerosis (MS) onset, yet population-based evidence remains inconsistent across cultures. This study examined the association between major stressful life events and MS susceptibility in Northern Iran.

Methods: In a case-control study conducted between 2023 and 2025 in Mazandaran Province, Iran, 300 patients with definite MS and 300 age- and sex-matched healthy controls were enrolled. Exposure to major stressful life events during the five years preceding disease onset (for cases) or interview (for controls) was assessed using the validated Persian version of the Environmental Risk Factor Questionnaire (EnvIMS-Q). Logistic regression was

used to estimate adjusted odds ratios (ORs) with 95% confidence intervals (CIs).

Results: Exposure to at least one major stressful life event was reported by 92.7% of MS cases and 62.7% of controls ($P < 0.001$). After adjustment for demographic variables, six independent stressors were significantly associated with MS: marital separation (OR = 8.95, 95% CI: 1.92-41.6), financial debt (OR = 4.72, 95% CI: 2.73-8.16), death of a close relative (OR = 3.57, 95% CI: 2.25-5.66), unemployment or financial dependency (OR = 4.19, 95% CI: 1.64-10.7), serious personal illness or injury (OR = 2.66, 95% CI: 1.64-4.32), and marriage (OR = 3.99, 95% CI: 2.15-7.40). The identification of marriage as a stressor is contextually novel and may reflect region-specific psychosocial pressures.

How to cite this article: Hoseinimayvan N, Shojaee T, Baghbanian SM. High odds of multiple sclerosis following major life stressors: Evidence from a population-based case-control study in Northern Iran. *Curr J Neurol* 2025; 24(3): 241-6.

Conclusion: Major life stressors appear to contribute to MS susceptibility, with certain stressors such as marriage showing culture-dependent associations. These findings provide new insight into sociocultural factors influencing MS risk in Iranian populations. These findings should be interpreted with caution and confirmed in longitudinal studies.

Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) and is a major cause of disability in young adults, particularly women. While the global prevalence of MS has risen over recent decades,¹ registry-based studies from Iran show an even sharper increase, turning several provinces into high-risk areas. Region-specific environmental and lifestyle factors may contribute to the growing susceptibility to MS in this population.²

Psychological stress has been proposed as a trigger of MS onset. Psychosocial stress activates the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system, leading to altered cortisol secretion and upregulation of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α). These mediators can disrupt immune tolerance, promote autoreactive T-cell activation, and impair blood-brain barrier (BBB) integrity – mechanisms that are increasingly implicated in MS pathogenesis. Previous studies examining the association between stressful life events and MS have reported inconsistent findings, with some demonstrating significant associations and others finding no relationship – differences that may partly reflect variation in how stress has been defined and measured across populations.³

Cultural and social stressors differ across populations,⁴ and data from the Middle East remain limited.¹ Investigating psychosocial risk factors in this region may reveal culturally specific stress patterns that are not captured in Western studies.

We, therefore, examined whether major stressful life events during the five years preceding disease onset were associated with MS risk in Mazandaran Province, Northern Iran, using the validated Persian version of the Environmental Risk Factor Questionnaire (EnvIMS-Q).

Materials and Methods

Study design and setting: A population-based, case-control study was conducted in Mazandaran Province, to investigate environmental and

psychosocial risk factors for MS. The study site was the Neurology Department and MS Clinic of Boobalishina Hospital in Sari City, Mazandaran Province, the primary referral center for MS in the province. Cases were patients with definite MS who were diagnosed during the study period between 2023 and 2025. Each diagnosis was confirmed by neurologists according to the 2017 McDonald criteria.⁵ Controls were healthy individuals from the same source population, selected by random-digit dialing and frequency-matched to cases by age and sex.

Inclusion and exclusion criteria: Eligible cases were adults aged 15-50 years with confirmed MS and no other neurological disorder. Controls were permanent residents of Mazandaran Province within the same age range who had no history of MS or other neurological diseases. Exclusion criteria for both groups included inability to provide informed consent, a history of severe head injury with loss of consciousness, and current pregnancy. From 1540 telephone numbers generated, 324 eligible controls were recruited after applying the Kish household-selection method;⁶ 24 were excluded, yielding 300 controls.

Data collection and questionnaire: Data were collected through standardized telephone interviews performed by two medical doctors (the first and second authors), both trained in patient communication and familiar with the EnvIMS-Q questionnaire.^{7,8}

Each interviewer followed a structured script to ensure uniform phrasing and confirm participant understanding. During each interview, responses were recorded directly by the interviewers on printed copies of the Persian EnvIMS-Q questionnaire, which were used for data entry and statistical analysis. All completed questionnaires are securely archived and available for verification upon reasonable request to the corresponding author, pending institutional ethics approval. All calls were recorded with participant consent and reviewed by the supervising attending neurologist (a fellowship-trained MS specialist) to verify completeness and consistency. Any discrepancies identified during review were resolved under supervision before data entry. This multistep process – real-time documentation, audio verification, and expert supervision – was implemented to enhance data quality and minimize interviewer or information bias. This questionnaire collects demographic variables and exposure to major stressful life events. In this

standardized instrument, the time frame for assessing life events is predefined as the five years preceding disease onset (for cases) or the interview date (for controls). This interval is, therefore, determined by the questionnaire's original design and ensures methodological consistency with prior multinational EnvIMS-Q studies. Events included death or serious illness of close relatives, marital separation, financial difficulties, unemployment, imprisonment, relocation, and other major life disruptions.

Data were analyzed with SPSS software (version 22, IBM Corporation, Armonk, NY, USA). Descriptive data were presented as mean \pm standard deviation (SD) or frequency (percentage). Between-group comparisons for categorical variables were performed using the chi-square test or Fisher's exact test, as appropriate. For continuous variables, the independent samples t-test was used. To identify factors associated with MS, backward logistic regression analysis was employed. The results were presented as odds ratios (ORs) with 95% confidence intervals (CIs). A P-value of less than 0.05 was considered statistically significant.

Results

A total of 600 participants were included, comprising 300 patients with MS and 300 matched healthy controls. The mean age was 37.1 ± 8.5 and $36.59 \pm$ years in the case and control groups,

respectively ($P = 0.035$). Women represented 75.3% of the MS group and 68.3% of controls. As shown in table 1, patients with MS were more frequently married and had lower personal and parental educational levels compared with controls (all $P < 0.05$).

Exposure to at least one stressful life event within the previous five years was reported by 92.7% of MS cases versus 62.7% of controls ($P < 0.001$). The most common stressors were the death of a close relative, serious personal illness or injury, financial debt, severe illness in a family member, marriage, and unemployment (Table 2). Stressful events reported by fewer than 3% of participants, such as imprisonment, homelessness, or migration, were considered rare and excluded from regression analyses.

In univariable analysis, several stressors were significantly associated with MS. After adjusting for demographic factors, six stressors remained independently associated with MS in the multivariable logistic regression model: marital separation, financial debt, marriage, death of a close relative, unemployment or financial dependency, and serious personal illness or injury (all $P < 0.01$) (Table 2). Among demographic predictors, male sex was inversely associated with MS, consistent with well-established epidemiological patterns, whereas lower educational level and being married were associated with higher odds of disease.

Table 1. Demographic characteristics of patients with multiple sclerosis (MS) and healthy controls

Variable	MS cases (n = 300)	Controls (n = 300)	P
Age (year) (mean \pm SD)	37.1 \pm 8.5	36.5 \pm 9.3	0.035
Sex [n (%)]			0.057
Men	74 (24.7)	95 (31.7)	
Women	226 (75.3)	205 (68.3)	
Marital status [n (%)]			0.021
Single	80 (26.7)	101 (33.7)	
Married	211 (70.3)	181 (60.3)	
Divorced/widowed	9 (3.0)	18 (6.0)	
Education level [n (%)]			< 0.001
Primary	72 (24.0)	37 (12.4)	
Secondary	104 (34.7)	68 (22.7)	
Diploma/associate	122 (40.7)	154 (51.3)	
Bachelor's or higher	33 (11.0)	63 (21.0)	
Father's education at age 15 (%)			< 0.001
Illiterate/primary	42.3	24.3	
Secondary/diploma	53.0	50.0	
University or higher	4.7	25.7	
Mother's education at age 15 (%)			< 0.001
Illiterate/primary	45.0	31.0	
Secondary/diploma	50.0	55.0	
University or higher	5.0	14.0	

MS: Multiple sclerosis; SD: Standard deviation

Table 2. Association of stressful life events with multiple sclerosis (MS): Frequency distribution and adjusted odds ratios (ORs) (multivariable logistic regression)

Stressful life event	MS cases (n = 300) (%)	Controls (n = 300) (%)	Adjusted OR (95% CI)	P
Death of a close relative	52.6	19.7	3.57 (2.25-5.66)	< 0.001
Serious personal illness or injury	51.2	16.4	2.66 (1.64-4.32)	< 0.001
Financial debt	48.6	9.0	4.72 (2.73-8.16)	< 0.001
Severe illness in a family member	38.6	16.1	1.94 (1.11-3.38)	0.021
Marriage (as a stressor)	28.3	9.4	3.99 (2.15-7.40)	< 0.001
Unemployment/financial dependency	18.1	3.0	4.19 (1.64-10.70)	0.003
Marital separation/divorce	7.0	1.0	8.95 (1.92-41.60)	0.005
Family breakdown (major conflict)	11.0	5.0	2.41 (0.95-6.14)	0.065
Other rare events (each < 3%) [†]	-	-	-	-

Adjusted odds ratios (ORs) are derived from a multivariable logistic regression model including age, sex, education, marital status, and parental education.

[†]Rare stressors include imprisonment, homelessness, migration, death of spouse, suicide in family, retirement, and high-stakes examinations.

MS: Multiple sclerosis; OR: Odds ratio; CI: Confidence interval

Overall, the analysis indicated that exposure to multiple major stressful life events during the five years preceding onset was strongly associated with the risk of developing MS in this population.

Discussion

In this population-based, case-control study from Northern Iran, we found that six independent psychosocial stressors were associated with an increased risk of MS: marital separation, financial debt, death of a close relative, unemployment or financial dependency, serious personal illness or injury, and marriage. Notably, marriage – a factor previously regarded as protective in Iranian studies – emerged as a significant stressor, suggesting that sociocultural and economic contexts may modify how life events influence disease susceptibility. This discrepancy highlights the potential influence of sociocultural and economic contexts on the stress-MS relationship and underscores the need for culturally sensitive interpretations of psychosocial risk.

Among the identified stressors, marital separation or divorce showed the strongest association with MS risk in this study. Individuals who had experienced divorce had approximately nine-fold higher odds of developing MS compared with those without such experience, suggesting that marital dissolution may act as a major psychosocial stressor influencing disease onset. This finding contrasts with the large Danish cohort study, which reported no increased MS risk following divorce or separation.⁹ The strong association in our study may be related to how divorce is experienced in this setting, where it often has severe social and financial consequences. In the

Iranian context, divorce often leads to a reduction in social support and financial instability, which may contribute to chronic psychological stress.¹⁰

In contrast to an earlier Iranian case-control study conducted in 2018 that identified marriage as a protective factor against MS,¹¹ we found that marriage was independently associated with an increased risk of MS. This discrepancy may reflect economic changes over the past decade that have altered the psychosocial meaning of marriage. In Iran, marital relationships often entail considerable financial obligations and family expectations that may act as chronic stressors, particularly among younger couples with limited resources.⁴ Chronic exposure to such stress may contribute to HPA axis and inflammatory dysregulation, as previously discussed.³ These findings highlight that psychosocial risk factors can be time-sensitive, even within similar cultural contexts.

In addition to divorce and marriage, several other major life events were independently associated with MS in this study, including financial debt, bereavement, unemployment or financial dependency, and serious personal illness or injury. Although a large Swedish population-based study found no association between unemployment and MS risk,¹² we found it associated with higher odds of MS. This discrepancy may reflect Sweden's robust social welfare system, which buffers the stress impact of unemployment. Financial strain and job instability in Iran, particularly in regions with limited socioeconomic support such as Mazandaran Province, may result in sustained insecurity and diminished coping capacity. Overall, our results support a role for psychosocial stress in MS and

indicate that further studies are needed.

Some stressors, including family breakdown, severe illness of a first-degree relative, and job loss showed significant associations with MS in bivariate analyses but did not remain significant in the multivariable logistic model. This attenuation likely reflects intercorrelations among stressors – such as overlap between family breakdown and divorce – and the removal of weaker predictors during backward regression in the presence of stronger variables. In addition, several stressors – such as imprisonment, homelessness, death of a spouse, suicide of a close relative, migration, and retirement – occurred rarely in both groups, and therefore lacked sufficient statistical power to demonstrate meaningful associations. Underreporting of socially sensitive experiences may also have contributed to data variability. Because of this, the lack of statistically significant associations for these stressors should not be interpreted as evidence of no effect. Larger studies are needed to clarify their role. Moreover, because psychosocial stressors were assessed through self-report without external verification, some response bias cannot be ruled out. However, the use of the validated Persian version of the EnvIMS-Q and the assurance of confidentiality during interviews likely minimized socially desirable responding.

These findings are consistent with the hypothesis that sustained psychosocial stress may influence MS susceptibility through neuroendocrine-immune interactions. Chronic activation of the HPA axis and accompanying elevations in cortisol and pro-inflammatory cytokines may disrupt immune regulation and compromise BBB integrity, making autoimmune reactions more likely.³ The relatively higher effect sizes observed in our population, compared with European populations, may reflect amplification of these biological pathways by sociocultural and economic stressors.

The observed associations between major life stressors and MS are biologically plausible. Chronic psychosocial stress activates the HPA axis and the sympathetic nervous system, leading to dysregulated cortisol secretion and increased pro-inflammatory cytokines such as IL-6 and TNF- α . These mediators can impair BBB integrity and promote autoreactive immune responses, thereby contributing to demyelinating processes. Such neuroendocrine-immune interactions may help explain the elevated MS risk observed among individuals exposed to sustained psychosocial

stress in our study.³

Nevertheless, several limitations should be acknowledged. First, as a retrospective case-control study, exposure data were based on participants' recall of past life events, which may cause recall bias. Patients with MS might be more likely to remember or attribute stressful events to their illness compared with controls. To minimize this bias, we used the validated Persian version of the EnvIMS-Q questionnaire administered by trained interviewers following identical procedures for both groups. Second, several parallel comparisons were performed, raising the possibility of type I statistical error. However, the main findings were consistent across related variables and matched existing hypotheses about stress and immune function. Third, because interviews were conducted by telephone rather than face-to-face, the level of interpersonal interaction was limited, which could affect how participants interpreted some questions. Nonetheless, the interviews were administered by trained medical doctors using a standardized questionnaire, recorded with consent, and reviewed by a supervising neurologist, which likely minimized misclassification and improved data reliability. In addition, although MS pathophysiology may begin years before clinical onset, the five-year exposure window was predefined by the validated EnvIMS-Q instrument to enable consistency with previous epidemiological studies and to minimize recall inaccuracies. Residual confounding cannot be entirely excluded, as unmeasured factors such as coping style or genetic susceptibility may influence both stress exposure and disease onset. Given these limitations, the findings should be interpreted cautiously and viewed as indicative rather than causal. They are, however, consistent with prior epidemiological and mechanistic studies linking psychosocial stress to immune dysregulation and MS risk.^{11,12}

Finally, because this research was conducted in Northern Iran, the generalizability of the results to other cultural or socioeconomic contexts may be limited. At the same time, this regional focus provides valuable insight into culturally specific stressors that may be underrepresented in Western literature. Future longitudinal and mechanistic studies in diverse populations are warranted to confirm temporal relationships and further elucidate the biological pathways underlying these associations.

Conclusion

Major stressful life events were associated with increased odds of MS. Psychosocial stressors such as divorce, financial strain, unemployment, and marriage all showed independent associations with disease onset. The observation that divorce and unemployment may act as stressors contrasts with European studies,^{9,12} and the identification of marriage as an independent risk factor is novel and contextually nuanced within Iranian research;¹¹ together, these findings underline the influence of sociocultural and economic contexts on the stress-MS relationship. While these results provide new insight into the psychosocial determinants of MS in Iran, they are derived from retrospective analyses and should be interpreted with caution until

replicated in larger longitudinal investigations.

Conflict of Interests

The authors declare no conflict of interest in this study.

Acknowledgments

The study protocol was approved by the Research Ethics Committee of Mazandaran University of Medical Sciences, Sari (approval ID: IR.MAZUMS.REC.1404.92), and conducted in accordance with the Declaration of Helsinki. Confidentiality of participant information was strictly maintained. All participants provided written informed consent before enrollment.

References

1. Wang LY, Wang WF, Hui SY, Yang L, Liu YX, Li HJ. Emerging epidemiological trends of multiple sclerosis among adults aged 20-54 years, 1990-2021, with projections to 2035: a systematic analysis for the global burden of disease study 2021. *Front Neurol* 2025; 16: 1616245.
2. Etemadifar M, Nikanpour Y, Neshatfar A, Mansourian M, Fitzgerald S. Incidence and prevalence of multiple sclerosis in Persian Gulf area: A systematic review and meta-analysis. *Mult Scler Relat Disord* 2020; 40: 101959.
3. Nunez SG, Rabelo SP, Subotic N, Caruso JW, Knezevic NN. Chronic Stress and Autoimmunity: The Role of HPA Axis and Cortisol Dysregulation. *Int J Mol Sci* 2025; 26(20).
4. Pourhaji F, Taraghdar MM, Peyman N, Jamali J, Tehrani H. Explaining the burden of cultural factors on MS disease: A qualitative study of the experiences of women with multiple sclerosis. *BMC Womens Health* 2024; 24(1): 477.
5. 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(2): 162-73.
6. Kish L. A Procedure for Objective Respondent Selection within the Household. *JASA* 1949; 44(247): 380-7.
7. Pugliatti M, Casetta I, Drulovic J, Granieri E, Holmøy T, Kampman MT, et al. A questionnaire for multinational case-control studies of environmental risk factors in multiple sclerosis (EnvIMS-Q). *Acta Neurol Scand Suppl* 2012; (195): 43-50.
8. Sahraian MA, Naghshineh H, Shati M, Jahromi SR, Rezaei N. Persian adaptation of a questionnaire of environmental risk factors in multiple sclerosis (EnvIMS-Q). *Mult Scler Relat Disord* 2016; 10: 82-5.
9. Nielsen NM, Bager P, Simonsen J, Hviid A, Stenager E, Brønnum-Hansen H, et al. Major stressful life events in adulthood and risk of multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2014; 85(10): 1103-8.
10. Nikparvar F, Stith S, Dehghani M, Liang JG. The Process of Adjusting to Divorce after Leaving Violent Marriages: A Case Study of Iranian Women. *J Interpers Violence* 2021; 36(7-8): Np4468-np94.
11. Abdollahpour I, Nedjat S, Mansournia MA, Eckert S, Weinstock-Guttman B. Stress-full life events and multiple sclerosis: A population-based incident case-control study. *Mult Scler Relat Disord* 2018; 26: 168-72.
12. Jiang X, Olsson T, Hillert J, Kockum I, Alfredsson L. Stressful life events are associated with the risk of multiple sclerosis. *Eur J Neurol* 2020; 27(12): 2539-48.