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Structural Modeling of the Relationship Between Neuropsychological Functioning and Quality of Life with the Mediating Role of Anxiety Sensitivity in Patients with Multiple Sclerosis

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A B S T R A C T

Multiple sclerosis (MS) is characterized by sensory-motor, visual, bladder, and cerebellar impairments, along with emotional difficulties, which lead to functional disability and a lower quality of life. The present study aimed to determine the structural relationships between neuropsychological functioning and quality of life in patients with MS, with anxiety sensitivity as a mediator. This study employed a descriptive-correlational design based on structural equation modeling (SEM). To achieve the research objective, 390 patients diagnosed with MS and registered in the MS Association of Sari were selected through purposive sampling. Participants completed the Neuropsychological Functioning Questionnaire (Nejati, 2013), the Multiple Sclerosis Impact Scale (MSIS-29) (McGuigan & Hutchinson, 2004), and the Anxiety Sensitivity Index-Revised (ASI-R) (Taylor & Cox, 1998). Data were analyzed using structural equation regression modeling in SPSS 24 and Amos 22. The results indicated a significant positive direct relationship between neuropsychological functioning and anxiety sensitivity with the quality of life of patients with MS. Both variables significantly predicted the quality of life of individuals with MS. Additionally, findings revealed that anxiety sensitivity mediated the relationship between neuropsychological functioning and quality of life. Overall, the calculation and analysis of goodness-of-fit indices demonstrated that the proposed model exhibited an acceptable fit. Given the significant role of neuropsychological functioning and anxiety sensitivity in the quality of life of patients with MS, physicians, psychiatrists, counselors, and psychologists can consider these factors in their treatment approaches to enhance and improve patients' quality of life.

Keywords: *Neuropsychological functioning, quality of life, anxiety sensitivity, multiple sclerosis.*

1. Introduction

Multiple sclerosis (MS) is the most common disorder involving demyelination of neurons in the central nervous system, characterized by recurrent episodes of neurological dysfunction and remission periods (Dehghani, 2024). This disease is associated with sensory-motor, visual, bladder, and cerebellar impairments, as well as emotional difficulties, leading to functional disability and a lower quality of life (Fahy, 2024; Marsool et al., 2024). The course of the disease is heterogeneous and includes different subtypes, which play a role in identifying the type of MS and establishing reasonable treatment expectations. MS and the side effects of its medications negatively impact patients' health and well-being, interfering with their quality of life (Sandesjö et al., 2024; Schlindwein et al., 2024). According to the World Health Organization, quality of life refers to an individual's perception of their position in life within the context of their culture and value system, in relation to their goals, expectations, standards, and concerns (Vaheb, 2024). Patients with MS generally report significantly lower quality of life compared to the general population and individuals with other medical conditions. In the biomedical field, health-related quality of life (HRQoL) is defined as satisfaction with one's health status, incorporating both physical health and emotional responses to these conditions (Marques et al., 2018). Research indicates that individuals with MS experience lower quality of life than patients with epilepsy, diabetes, or inflammatory diseases (Gil-González et al., 2020). Other studies have confirmed a significant relationship between MS and quality of life, with this association becoming more pronounced as the disease progresses (Han, 2021).

Studies (Fernández-Jiménez & Arnett, 2015; Lanzillo et al., 2016) indicate that due to neurological complications in MS, neuropsychological functions—essential for superior organization and integration and associated with attentional and memory systems—are significantly affected in MS. Since neuropsychological functioning facilitates the use of novel assessments and provides greater cognitive resources for maintaining sustained attention, it plays a crucial role in emotion regulation in daily life. However, in MS patients, neuropsychological dysfunction is linked to poorer quality of life (Rainone et al., 2017). According to the findings of Lanzillo et al. (2016), neuropsychological functioning significantly impacts the quality of life of individuals with MS from the onset of the disease and has a primary association with this variable (Lanzillo et al., 2016). Further studies (Jabbari Amiri et al., 2015; Kos et al., 2017; Motaharinezhad et al., 2016; Vazirinejad et al., 2016) confirm a significant relationship between neuropsychological functioning and quality of life.

Another vulnerability factor affecting MS that appears to influence patients' quality of life is anxiety sensitivity. Anxiety is more prevalent in MS patients compared to the general population. Fear of pain, disability, and the unpredictability of the disease can exacerbate anxiety (Rogers, Kauffman, et al., 2019; Rogers, Shepherd, et al., 2019). Anxiety sensitivity, or fear of fear, refers to an individual's fear of bodily sensations associated with arousal, such as increased heart rate, shortness of breath, and dizziness, due to the belief that these symptoms may lead to potentially harmful social, cognitive, or physical consequences (Rogers, Kauffman, et al., 2019; Rogers, Shepherd, et al., 2019). Based on the natural etiology theory, anxiety in MS patients results from the endocrine system's response to perceived threats and is linked to situations that signal personal danger. Anxiety thus functions as a mechanism that reduces physiological performance, which in turn affects quality of life in MS patients (Timpano et al., 2016).

The findings of Tajoddini et al. (2019) indicate that emotional problems in MS patients, alongside disease-related complications, are significantly influenced by high anxiety sensitivity (Tajoddini et al., 2019). In another study, Saadat et al. (2020) found that anxiety was the most significant predictor of quality of life in MS patients, affecting their employment status and social functioning (Saadat et al., 2020).

Given these findings, identifying the cognitive and individual factors associated with MS is crucial for improving quality of life and mitigating the impact of the disease on patients and their families (Jongen et al., 2016). Providing new forms of support, increasing individual support resources, and teaching better coping strategies for dealing with life challenges can positively impact patients' lives. Therefore, in the present study, neuropsychological functioning is examined as a predictor variable, and anxiety sensitivity as a mediator, to develop a model for understanding quality of life in MS patients.

2. Methods and Materials

2.1. Study Design and Participants

The present study employed a descriptive-correlational research design. The target population included all patients

diagnosed with multiple sclerosis (MS) who were registered with the MS Association of Sari in 2019. A total of 390 individuals were selected through purposive sampling. After obtaining approval from the MS Association of Sari, the sample size was determined using Sample Power software, accounting for potential participant attrition (390 individuals). The inclusion criteria included a confirmed diagnosis of MS (of any type) and informed consent to participate in the study. After determining the sample size and coordinating with the MS Association, participants completed the study questionnaires in adherence to ethical research principles. These principles included informed consent, an explanation of the response process and the necessity of honest cooperation, respectful conduct, confidentiality of personal data, the option to withdraw from the study at any time, and the prevention of data fabrication or distortion.

2.2. Measures

2.2.1. Neuropsychological Functioning

This questionnaire was developed by Nejati (2013) to assess cognitive abilities required for daily life activities. It consists of 30 items and seven subscales: memory, inhibitory control and selective attention, decision-making, planning, sustained attention, social cognition, and cognitive flexibility. Responses are provided on a four-point Likert scale, with scores ranging from 1 to 4 for each item. In Nejati's (2014) study, the construct and convergent validity of the questionnaire were confirmed, and its overall reliability, measured using Cronbach's alpha, was reported as 0.834. Pearson's correlation coefficient for test-retest reliability was significant at the 0.01 level. All subscales, except for social cognition, showed significant correlations with academic performance at the 0.01 level (Nejati, 2014). Gorjian and Abdollahi (2016) reported a Cronbach's alpha of 0.79 for the questionnaire (Gorjian & Abdollahi, 2016). In the present study, Cronbach's alpha values for the subscales were as follows: memory (0.89), inhibitory control and selective attention (0.82), decision-making (0.84), planning (0.82), sustained attention (0.73), social cognition (0.73), and cognitive flexibility (0.80).

2.2.2. Anxiety Sensitivity

This self-report questionnaire was developed by Taylor and Cox (1998) to assess anxiety sensitivity. It comprises 36 items and four subscales: fear of cardiovascular, gastrointestinal, and autonomic symptoms; fear of respiratory symptoms; fear of publicly observable anxiety reactions; and fear of cognitive dyscontrol. Responses are given on a five-point Likert scale, with scores ranging from 0 to 4 for each item, yielding a total score range of 0 to 64. Psychometric evaluations by the original authors demonstrated acceptable construct and convergent validity, with a Cronbach's alpha of 0.90 for the overall scale (Taylor & Cox, 1998). Moradimanesh et al. (2007) confirmed the construct and convergent validity of the ASI-R and reported a Cronbach's alpha of 0.93 for the total scale (Moradimanesh et al., 2007). In the present study, Cronbach's alpha values for the subscales were as follows: fear of cardiovascular symptoms (0.90), fear of respiratory symptoms (0.92), fear of publicly observable anxiety reactions (0.91), and fear of cognitive dyscontrol (0.85).

2.2.3. Multiple Sclerosis

This questionnaire was developed by McGuigan and Hutchinson (2004) to assess the quality of life in MS patients. It consists of 29 items and two subscales: physical impact and psychological impact of MS. Responses are provided on a five-point Likert scale, with scores ranging from 1 to 5, where higher scores indicate lower quality of life. In terms of psychometric properties, McGuigan and Hutchinson (2004) reported a Cronbach's alpha of 0.80 for the overall questionnaire. The convergent validity of the physical impact subscale was demonstrated through strong correlations with other physical disability measures. In the assessment of discriminant validity, the correlation between the physical impact subscale and the Beck Depression Inventory-II was found to be 0.49 (McGuigan & Hutchinson, 2004). In Iran, Ayatollahi et al. (2006) confirmed the construct and convergent validity of the MSIS-29. The internal consistency reliability, measured using Cronbach's alpha, was reported as 0.70 for the total scale, 0.68 for the physical impact factor, and 0.65 for the psychological impact factor, with an overall internal correlation coefficient of 0.70 (Ayatollahi et al., 2006). In the present study, Cronbach's alpha values for the physical impact and psychological impact subscales were 0.92 and 0.87, respectively.

2.3. Data Analysis

After collecting the questionnaires and excluding incomplete responses (7 participants), the final dataset included 383 valid questionnaires, which were analyzed using SPSS 24 software.

3. Findings and Results

The analysis of demographic data in the present study revealed that out of the total 383 MS patients participating in the study, 193 (50.4%) were women, and 190 (49.6%) were men. Regarding education levels, 169 participants (44.1%) had a high school diploma, 95 (24.8%) held a bachelor's degree, 68 (17.8%) had an associate's degree, 40 (10.4%) had less than a high school diploma, and 11 (2.9%) had a master's degree or higher. Additionally, demographic data analysis indicated that 133 participants (34.7%) were most frequently in the age range of 20–30 years, while 28 participants (7.3%) were the least frequent group, being over 50 years old. Descriptive findings showed that 209 participants (54.6%) had a high quality of life, 133 (34.7%) had a moderate quality of life, and 41 (10.7%) had a low quality of life.

The descriptive indices for neuropsychological functioning, anxiety sensitivity, distress tolerance, and quality of life were calculated, and the results are presented in Table 1.

Table 1

Descriptive Indices of Research Variables in MS Patients (n = 383)

Variables	Statistical Indices	Mean	Standard Deviation	Minimum	Maximum
Anxiety Sensitivity					
	Fear of cardiovascular, gastrointestinal, and autonomic symptoms	19.16	10.16	0	39
	Fear of respiratory symptoms	13.85	8.19	0	28
	Anxiety reactions	16.25	8.55	0	32
	Cognitive control	9.83	5.72	0	20
Neuropsychological Functioning					
	Inhibitory control and selective attention	17.82	6.7	6	30
	Decision-making	15.18	6.03	5	25
	Planning	8.78	3.96	3	15
	Sustained attention	9.01	3.66	3	15
	Social cognition	9.09	3.69	3	15
	Cognitive flexibility	11.62	4.82	4	20
	Memory	18.32	7.61	6	30
Quality of Life					
	Physical impact	61.36	17.33	20	100
	Psychological impact	28.02	9.05	9	45

To assess the statistical assumptions of the collected data, skewness and kurtosis were examined to evaluate the normality of variable distributions. The results indicated that the data distribution was normal, with skewness and kurtosis levels within an acceptable range. Additionally, the Kolmogorov-Smirnov test was performed to further assess data normality. The results of this test indicated that the data were not normally distributed. To address this issue, outliers were identified using Mahalanobis distance analysis. Data points deviating significantly were removed, ensuring the final dataset was fully normalized.

Table 2

Model Fit Indices Derived from Data Analysis

Index	Goodness-of-Fit Criteria	Desired Value	Obtained Value	Result
Absolute Fit Indices				
	Chi-square goodness-of-fit test	Nil	232.94	-
	Goodness-of-fit index (GFI)	> 0.90	0.94	Acceptable Fit
	Adjusted goodness-of-fit index (AGFI)	> 0.90	0.93	Acceptable Fit
Comparative Fit Indices				
	Standardized fit index (NFI)	> 0.90	0.92	Acceptable Fit
	Comparative fit index (CFI)	> 0.90	0.93	Acceptable Fit
	Relative fit index (RFI)	> 0.90	0.91	Acceptable Fit

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Parsimony Fit Indices				
	Normed fit index (NFI)	> 0.90	0.90	Acceptable Fit
	Root mean square error of approximation (RMSEA)	< 0.08	0.046	Acceptable Fit
	Chi-square divided by degrees of freedom	< 3	2.55	Acceptable Fit
	Degrees of freedom		91	
	p-value		0.000	Acceptable Fit

The results presented in Table 2 indicate that the RMSEA value was 0.046, which is below the 0.10 threshold, suggesting an appropriate model fit. Additionally, the chi-square to degrees of freedom ratio (2.55) fell within the acceptable range of 1 to 3. Furthermore, the GFI, CFI, and NFI indices were all approximately equal to or greater than 0.90, confirming that the structural model of the study variables is a suitable model, thus validating the proposed model.

Figure 1

Final Research Model

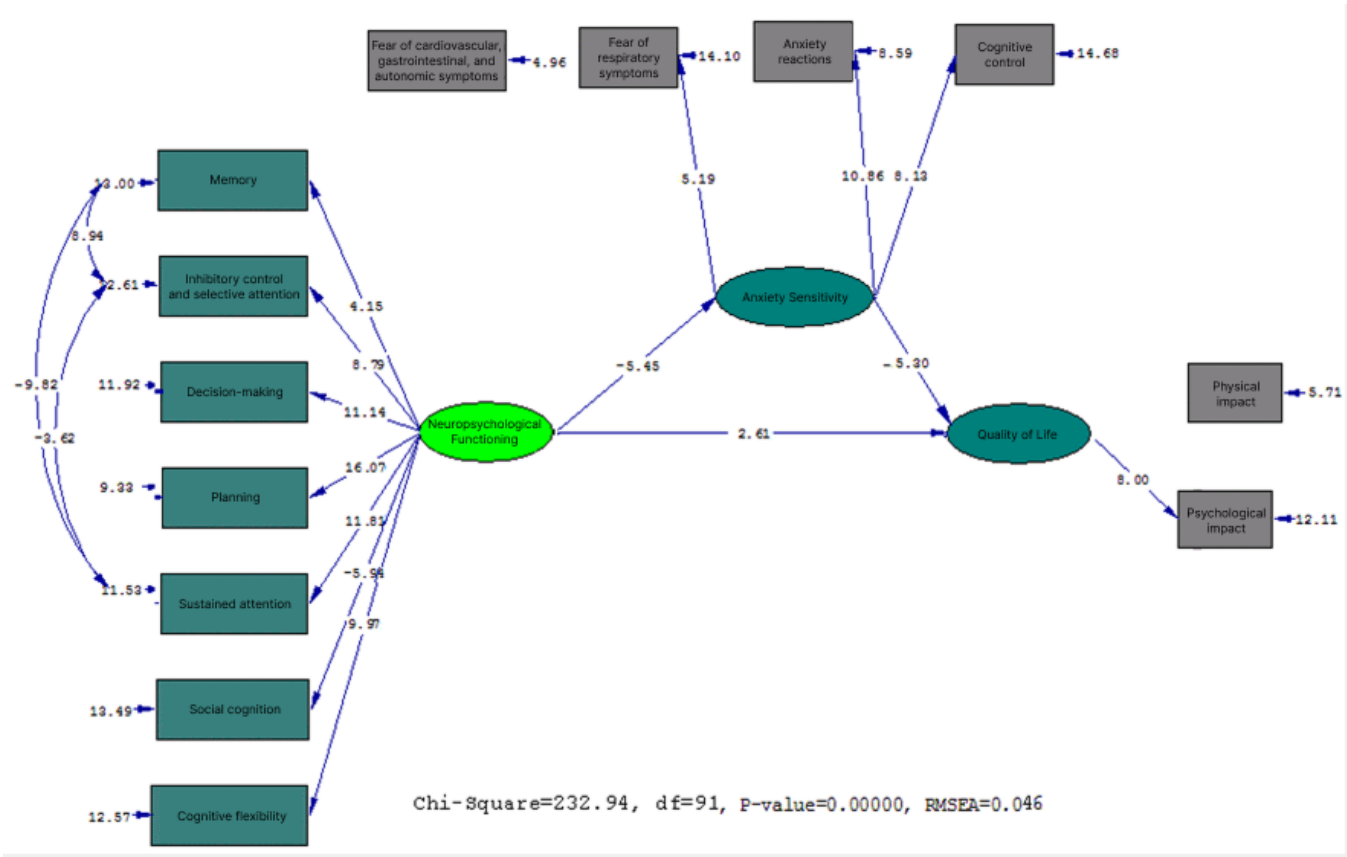

Table 3

Regression Weights and Critical Ratios for the Effects of Neuropsychological Functioning and Anxiety Sensitivity on Quality of Life

Path Direction	Standardized Parameter	Unstandardized Parameter	Standard Error	t-value
Neuropsychological Functioning → Quality of Life	0.22	0.25	0.095	2.61
Anxiety Sensitivity → Quality of Life	-0.44	-0.42	0.093	-4.47

Based on Table 3, the t-statistic for the structural equation modeling of neuropsychological functioning on quality of life (2.61) is greater than the critical t-value at a 95% confidence level (1.96). Therefore, the hypothesis of a significant relationship between neuropsychological functioning and quality of life is confirmed. Additionally,

the findings in the table indicate that the t-statistic for anxiety sensitivity on quality of life (-4.47) is smaller than the critical t-value at a 95% confidence level (-1.96). Consequently, the hypothesis of a significant relationship between neuropsychological functioning and anxiety sensitivity with quality of life in MS patients is supported.

Table 4

Regression Weights and Critical Ratios of Research Variables

Path Direction	Standardized Parameter	t-value	Sobel Test	Result	Direct Effect	Indirect Effect	Total Causal Effect
Neuropsychological Functioning → Anxiety Sensitivity → Quality of Life	Neuropsychological Functioning → Anxiety Sensitivity	-0.46	-5.45	4.25	Hypothesis Confirmed	0.33	0.184
Anxiety Sensitivity → Quality of Life	-0.40	-5.30					

According to the findings in Table 4, the standardized coefficient for the relationship between neuropsychological functioning and anxiety sensitivity is -0.46, with a t-statistic of -5.45. Additionally, the standardized coefficient for the relationship between anxiety sensitivity and quality of life is -0.40, with a t-statistic of -5.30. To examine the mediating effect of anxiety sensitivity in the relationship between neuropsychological functioning and quality of life, the Sobel test was used, yielding a test statistic of 4.25. This result indicates a significant relationship between neuropsychological functioning and quality of life mediated by anxiety sensitivity. Furthermore, based on the unstandardized coefficients, the direct effect of neuropsychological functioning on quality of life is 0.33, the indirect effect through anxiety sensitivity is 0.184, and the total causal effect is 0.514.

4. Discussion and Conclusion

The present study aimed to model the structural relationships between neuropsychological functioning and quality of life, with the mediating role of anxiety sensitivity in patients with multiple sclerosis (MS). Overall, the analysis of model fit indices indicated that the proposed model for predicting the quality of life in MS patients, based on neuropsychological functioning with the mediating role of anxiety sensitivity, had an acceptable fit. The validated model provides explanatory pathways and suggests strategies for improving the quality of life of MS patients.

The first finding confirmed that neuropsychological functioning significantly predicts quality of life in MS patients. This means that there is a significant positive relationship between neuropsychological functioning and quality of life in individuals with MS, and neuropsychological functioning is a significant predictor of their quality of life. The results of previous studies (Jabbari Amiri et al., 2015; Kos et al., 2017; Motaharinezhad et al., 2016; Vazirinejad et al., 2016) align with these findings and support this hypothesis. The most common neuropsychological dysfunctions in MS patients include impairments in working memory (MV), attention, information processing speed, abstract reasoning, and executive functioning (Covey et al., 2018). MV is a cognitive system responsible for temporarily storing and processing information necessary for performing complex cognitive tasks such as comprehension, reasoning, calculation, and learning (Bayliss et al., 2005). Executive dysfunction and reduced processing speed are key features of many cognitive disorders, including MS (Feizipour et al., 2019). Executive functions encompass cognitive abilities such as task initiation (quick and easy initiation of activities), inhibition (thinking before acting and emotional regulation), planning, organization, self-regulation, and more (Kenworthy et al., 2014). Cognitive impairment affects many aspects of daily life, including family management, full participation in society, employment retention, and overall quality of life (Baumstarck et al., 2013; Chiaravalloti & DeLuca, 2008). This is particularly problematic for young patients who need to learn and retain large amounts of information. Cognitive deficits also disrupt social and familial relationships, leading to decreased self-confidence and increased frustration among patients (Feizipour et al., 2019). Recent studies have shown a significant inverse relationship between the severity of cognitive impairment in MS patients and their quality of life (Marrie et al., 2018). Fernández-Jiménez and Arnett (2015) found a significant relationship between neuropsychological dysfunction, anxiety, depression, and quality of life in individuals with MS (Fernández-Jiménez & Arnett, 2015). Similarly, the study by Ebrahimzadeh et al. (2016) examined the correlation between working memory and quality of life in MS patients compared to healthy individuals. Their findings,

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based on a sample of 35 MS patients and 30 healthy individuals, showed that auditory and spatial working memory were impaired in MS patients, negatively impacting their quality of life (Ebrahimzade et al., 2016).

The second hypothesis demonstrated a significant relationship between anxiety sensitivity and quality of life in MS patients. Anxiety sensitivity was found to be a significant predictor of quality of life in individuals with MS. These findings are consistent with the results prior studies (Hayter et al., 2016; Marrie et al., 2018). Anxiety sensitivity contributes to cognitive biases and heightened attention to threatening stimuli, increasing the perceived severity of internal and external threats and leading to more avoidance and coping behaviors (Robinson & Freeston, 2014). This heightened state of vigilance causes individuals to remain excessively alert to warning signals of adverse events, aiming to prevent negative outcomes. In this state, individuals rely on physiological signs such as heart rate, blood pressure, dizziness, and pallor as critical indicators of being at risk (Raines et al., 2014). In other words, individuals focus on their anxiety-related bodily sensations, shaping the physical concern component of anxiety sensitivity (García-Campayo et al., 2010). Consequently, this process reduces overall functionality in all life domains, leading to persistent worry about anxiety symptoms, which results in catastrophizing not only during stressful life events but also in routine situations. This cognitive appraisal contributes to adverse life outcomes, posing significant risks to physical and mental health. Given that anxiety sensitivity leads to severe anxiety disorders, it becomes a fundamental factor in reducing quality of life.

The third hypothesis confirmed a significant relationship between neuropsychological functioning and quality of life, mediated by anxiety sensitivity, in MS patients. The prior findings support this result (Kos et al., 2017; Rainone et al., 2017; Saadat et al., 2020). Cognitive changes frequently occur in MS patients and affect various functions, including processing speed, attention, learning, memory, visuospatial abilities, and language deficits (Silveira et al., 2019). Information processing biases occur when individuals interpret information through specific cognitive filters, such as attention and interpretation biases (Sheehan, 2012). Living with a chronic, physically debilitating disease places individuals under constant stress. When this stress is accompanied by maladaptive coping strategies, individuals become more vulnerable to psychological disorders and heightened sensitivity to bodily symptoms (Timpano et al., 2016). According to cognitive theories of anxiety, anxiety sensitivity plays a crucial role in the cognitive appraisal processes that generate anxiety (Rogers, Kauffman, et al., 2019; Rogers, Shepherd, et al., 2019). Chiaravalloti and DeLuca (2008) found that in MS patients, psychological issues are the primary source of disability, social impairment, and decreased quality of life (Chiaravalloti & DeLuca, 2008). Many of the challenges faced by MS patients stem from interpersonal issues, particularly in establishing and maintaining close relationships. They may struggle to live with loved ones and express their emotions effectively. Social and community support can function as a group mechanism, providing essential information about the disease, coping strategies for various challenges, appropriate social interactions, and effective emotional expression, thus fostering intellectual, emotional, and psychological growth. MS patients with high anxiety sensitivity tend to catastrophize normal anxiety symptoms. These individuals exhibit a heightened negative appraisal and intense fear of routine anxiety symptoms, which leads to exaggerated reactions that, in turn, exacerbate anxiety. This vicious cycle perpetuates itself, ultimately lowering their quality of life (Lyyra & Parviainen, 2018).

One of the limitations of this study was the restriction of the sample population to a single city, limiting the ability to examine the variables of interest across different types of MS. Additionally, the use of purposive sampling and the inability to include interviews alongside self-report questionnaires were other limitations. Due to the subjective nature of measurement and the simultaneous and cross-sectional administration of questionnaires, causal relationships cannot be inferred. The generalization of findings should be approached with caution due to the cross-sectional nature of the study, as reverse causality remains a possibility. That is, the predictor variables (neuropsychological functioning, anxiety sensitivity, and distress intolerance) could themselves be influenced by the study outcome (quality of life). Therefore, it is recommended that future studies employ different sampling methods and investigate various MS subtypes to comprehensively assess the quality of life in MS patients. Additionally, future research should incorporate alternative data collection methods, such as interviews and observations, to obtain more comprehensive and accurate information.

Authors' Contributions

Authors contributed equally to this article.

Declaration

In order to correct and improve the academic writing of our paper, we have used the language model ChatGPT.

Transparency Statement

Data are available for research purposes upon reasonable request to the corresponding author.

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Declaration of Interest

The authors report no conflict of interest.

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Ethical Considerations

The study protocol adhered to the principles outlined in the Helsinki Declaration, which provides guidelines for ethical research involving human participants.

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