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Fatigue and Quality of Life Among Patients With Multiple Sclerosis: The Mediating Role of Depression and the Moderating Role of Psychological Resilience

Enkhzul. Batbayar[1], Anika. Venter[2*], Mariana. Téllez[3]

[1] Department of Psychology, National University of Mongolia, Ulaanbaatar, Mongolia
[2] Department of Developmental Psychology, University of Johannesburg, Johannesburg, South Africa
[3] Department of Psychology, National Autonomous University of Nicaragua, Managua, Nicaragua

*** Corresponding author email address**: aventer@uj.ac.za

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ABSTRACT

Objective: This study aimed to examine the relationship between fatigue and health-related quality of life among patients with multiple sclerosis in South Africa by testing the mediating role of depression and the moderating role of psychological resilience.

Methods and Materials: This descriptive-correlational cross-sectional study was conducted using a moderated mediation design. The study population consisted of adult patients with multiple sclerosis receiving care from neurology clinics, rehabilitation centers, and multiple sclerosis support organizations in South Africa. A total of 312 patients were selected through purposive convenience sampling. Data were collected using a demographic and clinical information form, the Modified Fatigue Impact Scale, the Multiple Sclerosis Quality of Life-54 questionnaire, the Beck Depression Inventory-II, and the Connor-Davidson Resilience Scale. Data were analyzed using descriptive statistics, Pearson correlation coefficients, regression-based mediation analysis, moderation analysis, and bootstrap procedures with 5,000 resamples. Statistical significance was considered at $p < .05$.

Findings: Inferential findings showed that fatigue was positively associated with depression and negatively associated with physical, mental, and overall health-related quality of life. Depression was negatively associated with overall quality of life, while psychological resilience was positively associated with quality of life. Fatigue significantly predicted depression ($B = 0.408$, $\beta = .61$, $p < .001$) and overall quality of life ($B = -0.442$, $\beta = -.40$, $p < .001$). Depression significantly mediated the relationship between fatigue and overall quality of life, with a significant indirect effect of -0.290 and a 95% confidence interval of [-0.386, -0.211]. Psychological resilience significantly moderated the association between depression and quality of life ($B = 0.014$, $\beta = .16$, $p = .001$), and the index of moderated mediation was significant (0.006, 95% CI [0.002, 0.010]).

Conclusion: The findings indicate that fatigue reduces quality of life among patients with multiple sclerosis both directly and indirectly through depression, while psychological resilience buffers the negative effect of depression on quality of life.

Keywords: *Multiple sclerosis; fatigue; quality of life; depression; psychological resilience; moderated mediation; South Africa.*

1. Introduction

Multiple sclerosis is a chronic immune-mediated neurological condition that affects not only physical functioning but also emotional adjustment, cognitive performance, social participation, and long-term quality of life. Although disease-modifying therapies have altered the clinical course of multiple sclerosis for many patients, the lived burden of the disease remains multidimensional and persistent. Contemporary models of MS care increasingly emphasize that neurological management alone is insufficient, because symptom control, psychological adaptation, rehabilitation, self-management, social participation, and patient-centered outcomes are all central to effective care (Giovannoni et al., 2024). Among the wide range of symptoms experienced by people with multiple sclerosis, fatigue is one of the most common, disabling, and difficult-to-manage complaints. It may occur independently of physical exertion, fluctuate across the day, interfere with occupational and family roles, and reduce the patient's perceived ability to participate in meaningful activities. Recent work on movement reserve and daily activity patterns in multiple sclerosis has further highlighted that observable functional capacity and fatigue-related limitations cannot be understood only through conventional neurological disability indices, because fatigue may restrict activity even when measurable motor ability is partly preserved (Niyogi et al., 2026). Similarly, longitudinal evidence indicates that disability, cognition, and quality of life are closely connected in patients with multiple sclerosis, suggesting that quality of life reflects the combined burden of neurological, cognitive, emotional, and behavioral factors rather than disease status alone (Niino et al., 2026).

Quality of life has therefore become a major outcome in multiple sclerosis research and care. It reflects how patients evaluate the impact of the disease on their physical health, emotional well-being, social life, cognitive functioning, independence, self-concept, and ability to maintain valued roles. Studies focused on quality of life in multiple sclerosis have shown that patient-reported outcomes often capture dimensions of illness burden that are not fully explained by clinical disability measures. For example, path analytic work on the priorities of people with multiple sclerosis has shown that quality of life is shaped by functional capacity, access to support, employment-related concerns, health needs, and psychosocial resources (Li et al., 2022). Research comparing multiple sclerosis with other progressive neurological conditions has also shown that fatigue and rapid disease progression can interfere with psychosocial adjustment and perceived quality of life, demonstrating that the subjective burden of the disease may remain high even when patients attempt to adapt to long-term illness demands (Balz et al., 2025). In younger populations, quality of life is likewise affected by disease symptoms, developmental needs, family functioning, and school or peer participation, showing that MS-related quality-of-life impairment is relevant across the life span (Mrosková et al., 2021). Educational and coping-based interventions among children with multiple sclerosis further indicate that quality of life is not a fixed consequence of diagnosis but can be influenced by beliefs, coping patterns, knowledge, and adaptive self-management behaviors (Ali et al., 2022).

Fatigue is particularly important because it may affect quality of life through several overlapping pathways. Physically, fatigue reduces energy, endurance, mobility, and participation in daily activities. Cognitively, it can impair attention, concentration, information processing, and decision-making. Psychologically, it may increase frustration, helplessness, perceived loss of control, and emotional distress. In clinical samples, fatigue has been strongly associated with depression and anxiety among ambulatory patients with multiple sclerosis, suggesting that fatigue is not merely a physical symptom but is embedded in broader affective and psychological functioning (AlSaeed et al., 2022). The assessment of mental fatigue is also becoming more refined, with recent research distinguishing objective and subjective aspects of fatigue detection and emphasizing the importance of recognizing mental fatigue as a measurable and clinically meaningful phenomenon (Yoshikawa et al., 2025). In early relapsing-remitting multiple sclerosis, the prediction of quality of life appears to depend on both clinical burden and emotional balance, which reinforces the need to examine fatigue and emotional symptoms together rather than as separate domains (Pérez et al., 2025). This integrated view is especially important because fatigue may reduce quality of life directly by restricting functioning and indirectly by increasing psychological distress.

Depression is one of the most clinically relevant psychological problems among people with multiple sclerosis. It may arise from neurobiological changes associated with the disease, inflammatory processes, uncertainty about disease progression, functional loss, social limitations, unemployment, stigma, fatigue, and reduced self-efficacy. Patient and provider perspectives have emphasized that multiple sclerosis has a substantial impact on mental health, and that depression, anxiety, adjustment difficulties, identity disruption, and emotional burden are often central to patients' experience of the disease (Davis et al., 2021). Cross-sectional evidence comparing patients receiving different disease-modifying treatments has also shown that depression and anxiety are meaningfully related to MSQOL-54 outcomes, indicating that emotional symptoms are closely tied to both mental and physical quality-of-life dimensions (Özbek et al., 2025). Because depression affects motivation, sleep, social engagement, cognitive appraisal, treatment adherence, and perceived control, it is theoretically plausible that depression may mediate the relationship between fatigue and quality of life. In other words, fatigue may lower quality of life partly because it increases depressive symptoms, which then further undermine emotional functioning, role performance, and life satisfaction.

The mediating role of psychological mechanisms in multiple sclerosis has received increasing attention. Evidence suggests that quality of life is not determined only by disease severity but also by how patients interpret, regulate, and respond to illness-related challenges. Psychological flexibility has been identified as an important process linking resilience with distress and quality of life in people with multiple sclerosis, indicating that the capacity to remain open, adaptive, and values-directed may explain why some patients maintain better outcomes despite disease-related adversity (Pakenham & Landi, 2023). Pilot intervention research on online acceptance and commitment therapy resilience training has also suggested that psychological interventions targeting resilience and adaptive coping may be feasible for people with multiple sclerosis and may contribute to improved adjustment (Pakenham et al., 2023). Online psychological interventions more broadly have been reviewed as promising approaches for improving symptoms in multiple sclerosis, particularly because they can reduce access barriers and provide support for patients whose fatigue, mobility limitations, or geographic location may interfere with in-person care (Montañés-Masias et al., 2022). These findings support a model in which psychological variables are not peripheral outcomes but central explanatory mechanisms in the relationship between MS symptoms and quality of life.

Psychological resilience is especially relevant in this context because it refers to the capacity to adapt positively in the face of stress, uncertainty, disability, and chronic illness demands. In multiple sclerosis, resilience may help patients maintain emotional balance, preserve engagement in valued roles, use adaptive coping strategies, seek social support, and reinterpret illness-related challenges in less threatening ways. Empirical studies have shown that resilience is associated with coping style, personality characteristics, and adjustment in patients with multiple sclerosis (Katani et al., 2021). Resilience has also been examined alongside self-compassion, hope, psychological well-being, maladaptive schemas, and social support in women with multiple sclerosis, suggesting that resilience belongs to a broader network of protective psychological resources (Hassani et al., 2021). Character strengths have been found to make a unique contribution to quality of life in people with multiple sclerosis, further supporting the idea that positive psychological capacities may protect well-being even when disease burden is substantial (Smedema & Bhattarai, 2021). Related work on grit, social functioning, and emotional adjustment also indicates that perseverance and adaptive personal resources may be important for understanding how patients respond to diagnosis and illness-related disruption (Klappa et al., 2022).

Recent studies have directly connected resilience with quality of life in multiple sclerosis. Psychological resilience has been reported to mediate the relationship between perceived neuropsychological impairment and quality of life, suggesting that cognitive concerns may affect quality of life partly through their influence on the patient's perceived capacity to cope (Broche-Pérez, Jiménez-Morales, Monasterio-Ramos, Vázquez-Gómez, et al., 2022). Resilience has also been shown to mediate the relationship between fear of relapse and quality of life, indicating that patients who fear future disease activity may experience poorer quality of life when resilience is low or weakened (Broche-Pérez, Jiménez-Morales, Monasterio-Ramos, & Bauer, 2022). More recently, psychological resilience has been examined as a mediator between depression and quality of life in relapsing-remitting multiple sclerosis, reinforcing the central role of resilience in the connection between emotional distress and patient-reported outcomes (Broche-Pérez & Jiménez-Morales, 2024). These findings provide strong theoretical and empirical justification for examining resilience not only as an independent predictor of quality of life but also as a moderating factor that may alter the strength of the association between depression and quality of life. If resilience buffers the harmful effect of depression, then patients with higher resilience may experience less severe quality-of-life impairment even when depressive symptoms are present.

The broader literature on mind-body, psychosocial, and rehabilitation-based approaches also supports the protective role of adaptive psychological and behavioral resources. Mind-body movement interventions have been reviewed as approaches for symptom management in people with multiple sclerosis, reflecting the growing recognition that movement, body awareness, self-regulation, and psychological engagement may contribute to symptom relief and improved functioning (Buttolph et al., 2026). Mindfulness-based interventions have also been systematically reviewed and meta-analyzed in relation to quality of life among people with multiple sclerosis, with findings suggesting that interventions targeting attention, acceptance, and emotional regulation may improve patient-reported outcomes (Simpson, Posa, Bruno, et al., 2022). Compassion in MS care has similarly been conceptualized as a meaningful component of patient experience and clinical interaction, suggesting that compassionate care may influence emotional adjustment, self-management, and perceived support (Simpson, Posa, Langer, et al., 2022). More recent work on body compassion has extended this perspective by validating a measure of body compassion in multiple sclerosis, which is important because many patients experience changes in mobility, appearance, bodily trust, and functional identity (Mistretta et al., 2025). These studies collectively indicate that psychological resources and supportive care processes may influence how symptoms are experienced and how quality of life is preserved.

Self-efficacy, mastery, and identity-related processes are also important in understanding adaptation to multiple sclerosis. The validation of self-efficacy measures for people with multiple sclerosis underscores the importance of assessing patients' perceived capacity to manage disease-related challenges and maintain functioning (Seebacher et al., 2021). Recent evidence indicates that self-mastery may buffer the association between stressful life events, mental quality of life, and fatigue in people living with multiple sclerosis, suggesting that perceived control may reduce the psychological impact of stress and fatigue on well-being (Yu et al., 2026). Narrative work on stigma, psychological well-being, and identity in multiple sclerosis has further shown that social perceptions and illness identity may influence psychological adjustment and quality of life (Montesano et al., 2025). Interventions designed through bio-psycho-social and co-created frameworks also highlight the importance of addressing young adults' psychological, social, and lifestyle needs in MS care (Donisi et al., 2021). Outdoor adventure programs for persons with multiple sclerosis similarly suggest that structured participation in meaningful, confidence-building activities may support adjustment, social connection, and psychological resilience (Herring et al., 2021).

Although the present study focuses specifically on multiple sclerosis, the relevance of quality of life, resilience, fatigue, and psychological adaptation is also evident across chronic illness and rehabilitation research more broadly. For example, studies in chronic kidney disease have emphasized the impact of chronic illness on both patients and caregivers, reinforcing the importance of patient-centered outcomes beyond biomedical markers (Pereira et al., 2023). Research in pediatric transplant populations has shown that rehabilitation approaches can target physical impairment and functional decline, which is conceptually relevant to fatigue and activity limitation in chronic disease contexts (Hager et al., 2023). In Parkinson's disease, virtual rehabilitation approaches involving patients and care partners have demonstrated the growing importance of innovative, participatory interventions in neurological populations (Sadek et al., 2024). Systematic review evidence from cardiac surgery has also emphasized quality of life as a critical comparative outcome when evaluating treatment approaches, reflecting a broader movement in health sciences toward outcomes that capture patients' lived recovery and well-being (Marinescu et al., 2025). While these conditions differ from multiple sclerosis in etiology and clinical trajectory, they support the same general principle: chronic disease research must examine not only survival, symptoms, or clinical progression but also the psychological and functional conditions under which patients maintain quality of life.

Despite the growing literature on fatigue, depression, resilience, and quality of life in multiple sclerosis, several gaps remain. First, many studies have examined direct associations among fatigue, depression, and quality of life, but fewer have tested integrated models that specify depression as a mediator of the fatigue–quality-of-life relationship. Second, although resilience has been identified as a protective factor, it has often been studied as a predictor or mediator rather than as a moderator that may change the strength of the association between depression and quality of life. Third, existing evidence suggests that clinical burden and emotional balance jointly influence quality of life, but there remains a need for models that clarify how symptom burden, emotional distress, and protective psychological resources operate together. A moderated mediation framework is well suited to this need because it can determine whether fatigue is associated with poorer quality of life through depression and whether this indirect effect varies according to psychological resilience. Such a model can contribute to both theory and practice by identifying patients who may be especially vulnerable to fatigue-related quality-of-life impairment and by highlighting resilience as a potential target for psychological and rehabilitation interventions.

Therefore, the aim of this study was to examine the relationship between fatigue and health-related quality of life among patients with multiple sclerosis in South Africa by testing the mediating role of depression and the moderating role of psychological resilience.

2. Methods and Materials

2.1. Study Design and Participants

This study was conducted using a descriptive-correlational, cross-sectional design with a moderated mediation approach. The aim was to examine the relationship between fatigue and health-related quality of life among patients with multiple sclerosis and to determine whether depression mediated this relationship and whether psychological resilience moderated the indirect or conditional effects of fatigue on quality of life. The statistical population consisted of adult patients diagnosed with multiple sclerosis who were receiving care from neurology clinics, rehabilitation centers, and multiple sclerosis support organizations in South Africa. Participants were recruited from clinical and community-based settings in Johannesburg, Pretoria, Cape Town, and Durban. The final sample included 312 patients with multiple sclerosis, selected through purposive convenience sampling based on eligibility criteria and willingness to participate. Inclusion criteria were age 18 years or older, confirmed diagnosis of multiple sclerosis by a neurologist according to accepted clinical diagnostic criteria, at least six months elapsed since diagnosis, ability to read and understand English, and physical and cognitive capacity to complete the questionnaires independently or with minimal assistance. Exclusion criteria included diagnosis of another severe neurological disorder, acute relapse during the data collection period, severe psychiatric disorder other than depressive symptoms, hospitalization at the time of recruitment, and incomplete questionnaire responses exceeding 10% of the total items. Before data collection, all participants received information about the purpose of the study, confidentiality of responses, voluntary participation, and their right to withdraw at any stage without any effect on their treatment or support services. Written informed consent was obtained from all participants. Ethical principles related to anonymity, confidentiality, informed consent, and non-maleficence were observed throughout the study.

2.2. Measures

Demographic and clinical information was collected using a researcher-developed questionnaire designed to obtain background characteristics relevant to multiple sclerosis and quality of life. This form included age, gender, marital status, educational level, employment status, place of residence, duration of illness, type of multiple sclerosis, time since diagnosis, current treatment status, history of relapse during the previous year, and use of rehabilitation or psychological services. The information obtained from this form was used to describe the study sample and to identify potential covariates that could influence fatigue, depression, resilience, and health-related quality of life.

Fatigue was measured using the Modified Fatigue Impact Scale. The Modified Fatigue Impact Scale is a widely used self-report instrument developed to assess the perceived impact of fatigue on daily functioning, particularly among individuals with multiple sclerosis. The scale contains 21 items and evaluates fatigue across three dimensions: physical functioning, cognitive functioning, and psychosocial functioning. Items are scored on a five-point Likert scale ranging from 0, indicating never, to 4, indicating almost always. The total score ranges from 0 to 84, with higher scores indicating a greater impact of fatigue on the individual’s daily life. The physical subscale reflects the effect of fatigue on mobility, energy, and physical activities; the cognitive subscale assesses the effect of fatigue on attention, concentration, memory, and thinking; and the psychosocial subscale evaluates the influence of fatigue on social participation and emotional functioning. The Modified Fatigue Impact Scale has been extensively used in studies involving patients with multiple sclerosis, and its validity and reliability have been confirmed in previous research.

Health-related quality of life was assessed using the Multiple Sclerosis Quality of Life-54 questionnaire. This instrument was developed specifically for patients with multiple sclerosis and combines general health-related quality-of-life domains with multiple sclerosis-specific items. The questionnaire contains 54 items and covers several domains, including physical function, role limitations due to physical problems, role limitations due to emotional problems, pain, emotional well-being, energy, health perceptions, social function, cognitive function, health distress, sexual function, change in health, and overall quality of life. The instrument produces two major composite scores: the Physical Health Composite and the Mental Health Composite. Scores are transformed to a 0 to 100 scale, with higher scores indicating better perceived health-related quality of life. The Multiple Sclerosis Quality of Life-54 is considered appropriate for examining the multidimensional impact of multiple sclerosis on patients' physical, emotional, cognitive, and social functioning. Its psychometric properties, including internal consistency, construct validity, and clinical applicability, have been confirmed in previous studies among patients with multiple sclerosis.

Depression was measured using the Beck Depression Inventory-II. The Beck Depression Inventory-II, developed by Beck, Steer, and Brown in 1996, is a 21-item self-report questionnaire designed to assess the severity of depressive symptoms during the previous two weeks. Each item is scored from 0 to 3 according to symptom severity, and the total score ranges from 0 to 63. Higher scores indicate more severe depressive symptoms. The scale assesses affective, cognitive, motivational, and somatic symptoms of depression, including sadness, pessimism, loss of pleasure, guilt, self-critical thoughts, crying, agitation, loss of interest, indecisiveness, changes in sleep, fatigue, appetite changes, and concentration difficulties. In the present study, depression was considered the mediating variable explaining the pathway through which fatigue may reduce health-related quality of life. The Beck Depression Inventory-II has been widely used in clinical and health psychology research, and its validity and reliability have been supported in different patient populations, including individuals with chronic neurological conditions.

Psychological resilience was assessed using the Connor-Davidson Resilience Scale. The Connor-Davidson Resilience Scale was developed by Connor and Davidson in 2003 to measure the ability to cope with stress, adapt to adversity, and recover from difficult life circumstances. The 25-item version was used in this study. Items are scored on a five-point Likert scale ranging from 0, meaning not true at all, to 4, meaning true nearly all the time. The total score ranges from 0 to 100, with higher scores indicating greater psychological resilience. The scale reflects characteristics such as personal competence, tolerance of negative affect, acceptance of change, secure relationships, control, persistence, adaptability, and spiritual or existential strength. In the present study, resilience was examined as a moderating variable that could weaken or strengthen the association between depression and quality of life among patients with multiple sclerosis. The Connor-Davidson Resilience Scale has demonstrated acceptable validity and reliability in previous studies and has been widely applied in research on chronic illness, psychological adjustment, and health-related quality of life.

2.3. *Data Analysis*

Data were analyzed using SPSS and AMOS statistical software. Before conducting the main analyses, all questionnaires were screened for missing data, response errors, and outliers. Cases with excessive missing responses were excluded from the final analysis, while limited missing values were managed using appropriate statistical procedures. Descriptive statistics, including mean, standard deviation, frequency, and percentage, were used to describe demographic and clinical characteristics of the participants and the distribution of the main research variables. The normality of the data was examined through skewness and kurtosis indices, histogram inspection, and the Kolmogorov-Smirnov test. Internal consistency of the measurement tools was assessed using Cronbach's alpha coefficient. Pearson correlation analysis was used to examine the bivariate relationships among fatigue, depression, psychological resilience, and health-related quality of life.

To test the hypothesized mediating role of depression, path analysis was conducted to determine whether fatigue predicted depression and whether depression, in turn, predicted health-related quality of life. The indirect effect of fatigue on quality of life through depression was examined using the bootstrap method with 5,000 resamples and 95% confidence intervals. The mediation effect was considered statistically significant when the confidence interval for the indirect effect did not include zero. To examine the moderating role of psychological resilience, an interaction term was created after mean-centering the relevant predictor variables. The moderating effect of resilience was tested by examining whether the interaction between depression and resilience significantly predicted health-related quality of life. In addition, conditional indirect effects were evaluated to determine whether the mediating effect of depression differed at low, moderate, and high levels of psychological resilience. Age, gender, illness duration, type of multiple sclerosis, and relapse history were entered as control variables when necessary. Model fit was evaluated using standard fit indices, including the chi-square to degrees of freedom ratio, Comparative Fit Index, Tucker-Lewis Index, Root Mean Square Error of Approximation, and Standardized Root Mean Square Residual. Statistical significance was set at $p < .05$ for all analyses.

3. Findings and Results

The final analysis was conducted on data obtained from 312 patients with multiple sclerosis in South Africa. The mean age of the participants was 38.74 years with a standard deviation of 10.62, and the age range was from 18 to 67 years. Of the total sample, 218 participants were female and 94 were male, representing 69.9% and 30.1% of the sample, respectively. Regarding marital status, 176 participants were married, 82 were single, and 54 were divorced, separated, or widowed. In terms of educational level, 61 participants had completed secondary education, 139 had diploma or undergraduate-level education, and 112 had postgraduate education. With respect to employment status, 133 participants were employed, 71 were unemployed, 49 were students, and 59 were retired or unable to work because of illness-related limitations. The participants were recruited from clinical and community-based multiple sclerosis settings in Johannesburg, Pretoria, Cape Town, and Durban. In relation to clinical characteristics, 213 participants had relapsing-remitting multiple sclerosis, 63 had secondary progressive multiple sclerosis, and 36 had primary progressive multiple sclerosis. The mean duration of illness was 7.86 years with a standard deviation of 5.21. In addition, 128 participants reported at least one relapse during the previous year, while 184 participants reported no relapse during that period. Overall, the demographic and clinical characteristics of the sample indicated that the study included a heterogeneous group of patients with multiple sclerosis in terms of age, gender, disease course, illness duration, and functional impact of the disease.

Table 1

Descriptive Statistics, Internal Consistency, and Correlations Among the Main Study Variables

Variable	Mean	SD	Observed Range	Cronbach's Alpha	1	2	3	4	5	6
Fatigue	49.36	15.21	12–82	.92	1					
Depression	21.84	10.16	1–52	.90	.61***	1				
Psychological resilience	57.42	16.38	16–96	.89	-.43***	-.51***	1			
Physical health-related quality of life	48.27	18.63	11.25–91.40	.91	-.66***	-.58***	.46***	1		
Mental health-related quality of life	51.08	17.94	8.70–92.65	.90	-.63***	-.71***	.60***	.70***	1	
Overall health-related quality of life	49.68	16.74	12.42–90.18	.93	-.70***	-.69***	.58***	.88***	.91***	1

As shown in Table 1, the participants reported a relatively high level of fatigue, with a mean score of 49.36, suggesting that fatigue had a considerable impact on their daily physical, cognitive, and psychosocial functioning. The mean depression score was 21.84, indicating that, on average, participants experienced depressive symptoms within the moderate range. The mean resilience score was 57.42, suggesting a moderate level of psychological resilience among the patients. The mean scores for physical, mental, and overall health-related quality of life were 48.27, 51.08, and 49.68, respectively, indicating that quality of life was noticeably affected in both physical and psychological domains. The reliability coefficients for all study instruments were satisfactory, with Cronbach's alpha values ranging from .89 to .93, confirming acceptable internal consistency of the measures in the present sample. The correlation results showed that fatigue had a strong positive relationship with depression and strong negative relationships with physical, mental, and overall health-related quality of life. This means that patients who reported greater fatigue also tended to report more depressive symptoms and poorer quality of life. Depression was also negatively and strongly associated with all dimensions of quality of life, especially mental health-related quality of life. Psychological resilience was negatively associated with fatigue and depression and positively associated with all quality-of-life indicators. These findings provide preliminary support for the proposed model, suggesting that fatigue may be related to reduced quality of life both directly and indirectly through depression, while resilience may function as a protective psychological factor.

Table 2

Direct Effects of Fatigue, Depression, Psychological Resilience, and the Interaction Term on Overall Health-Related Quality of Life

Outcome variable	Predictor	B	SE	β	t	p	95% CI
Depression	Fatigue	.408	.031	.61	13.21	< .001	.347, .469
Depression	Age	.036	.041	.04	.88	.381	-.045, .117
Depression	Gender	.742	1.018	.03	.73	.467	-1.261, 2.745
Depression	Illness duration	.091	.083	.05	1.10	.273	-.072, .254
Depression	Relapse during previous year	2.164	.946	.10	2.29	.023	.302, 4.026
Overall quality of life	Fatigue	-.442	.049	-.40	-8.97	< .001	-.539, -.345
Overall quality of life	Depression	-.609	.079	-.37	-7.70	< .001	-.765, -.453
Overall quality of life	Psychological resilience	.279	.048	.27	5.82	< .001	.185, .373
Overall quality of life	Depression × psychological resilience	.014	.004	.16	3.43	.001	.006, .022
Overall quality of life	Age	-.067	.077	-.04	-.87	.383	-.219, .085
Overall quality of life	Gender	.924	1.667	.03	.55	.580	-2.357, 4.205
Overall quality of life	Illness duration	-.153	.123	-.05	-1.25	.214	-.395, .089
Overall quality of life	Relapse during previous year	-3.186	1.382	-.09	-2.31	.022	-5.907, -.465

Table 2 presents the direct effects among the main study variables while controlling for selected demographic and clinical covariates. Fatigue significantly and positively predicted depression, indicating that higher fatigue was associated with more severe depressive symptoms among patients with multiple sclerosis. Among the control variables, relapse during the previous year was also a significant positive predictor of depression, suggesting that patients who had experienced a recent relapse tended to report higher depressive symptoms. In the model predicting overall health-related quality of life, fatigue remained a significant negative predictor after depression, resilience, and covariates were entered into the model. This finding indicates that fatigue had a direct detrimental effect on quality of life beyond its association with depressive symptoms. Depression also significantly and negatively predicted overall quality of life, showing that patients with higher depressive symptoms experienced poorer perceived quality of life. Psychological resilience significantly and positively predicted overall quality of life, meaning that patients with higher resilience reported better quality of life. Importantly, the interaction between depression and psychological resilience was statistically significant, indicating that the effect of depression on quality of life differed according to the level of resilience. The positive coefficient of the interaction term shows that resilience weakened the negative association between depression and quality of life. Therefore, the harmful effect of depression on quality of life was stronger among patients with low resilience and weaker among patients with high resilience.

Table 3

Bootstrap Analysis of the Mediating Role of Depression in the Relationship Between Fatigue and Overall Health-Related Quality of Life

Effect	Path	B	SE	β	p	Bootstrapped 95% CI
Total effect	Fatigue → Overall quality of life	-.770	.045	-.70	< .001	-.858, -.681
Path a	Fatigue → Depression	.408	.031	.61	< .001	.347, .469
Path b	Depression → Overall quality of life	-.711	.067	-.43	< .001	-.843, -.579
Direct effect	Fatigue → Overall quality of life after entering depression	-.480	.053	-.43	< .001	-.584, -.376
Indirect effect	Fatigue → Depression → Overall quality of life	-.290	.045	—	< .001	-.386, -.211
Proportion mediated	Indirect effect divided by total effect	37.66%	—	—	—	—

Table 3 shows the results of the mediation analysis examining whether depression explained the relationship between fatigue and overall health-related quality of life. The total effect of fatigue on quality of life was significant and negative, indicating that greater fatigue was associated with lower quality of life before depression was included as a mediator. Fatigue also significantly predicted depression, confirming that patients with higher fatigue experienced higher levels of depressive symptoms. Depression, in turn, significantly predicted lower overall quality of life after controlling for fatigue. When depression was included in the model, the direct effect of fatigue on overall quality of life decreased from -.770 to -.480 but remained statistically significant. This reduction indicates partial mediation rather than full mediation. The bootstrapped indirect effect was -.290, and the 95% confidence interval did not include zero, confirming that depression significantly mediated the relationship between fatigue and quality of life. The proportion mediated was 37.66%, meaning that more than one-third of the negative association between fatigue and overall quality of life could be explained through depressive symptoms. These findings suggest that fatigue reduces quality of life not only through its direct physical and functional burden but also by increasing depressive symptoms, which further impair patients' emotional, cognitive, and social functioning.

Table 4

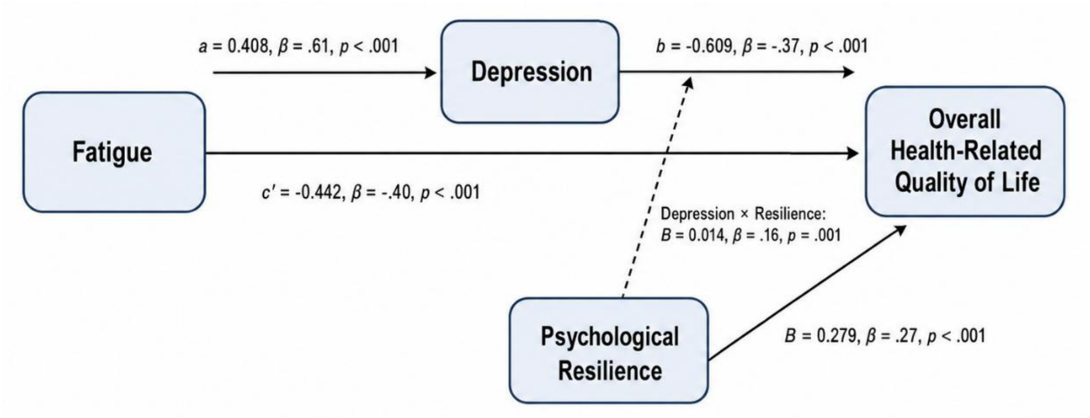
Conditional Effects of Depression on Overall Health-Related Quality of Life and Conditional Indirect Effects at Different Levels of Psychological Resilience

Level of psychological resilience	Resilience score	Effect of depression on overall quality of life B	SE	t	p	Bootstrapped conditional indirect effect	Boot SE	Bootstrapped 95% CI
Low resilience	41.04	-.838	.091	-9.21	< .001	-.342	.060	-.466, -.231
Moderate resilience	57.42	-.609	.079	-7.70	< .001	-.248	.046	-.344, -.167
High resilience	73.80	-.380	.099	-3.84	< .001	-.155	.049	-.263, -.068
Index of moderated mediation	—	—	—	—	—	.006	.002	.002, .010

Table 4 presents the conditional effects of depression on overall health-related quality of life at low, moderate, and high levels of psychological resilience. The results show that depression significantly predicted lower quality of life at all three levels of resilience; however, the magnitude of this effect decreased as resilience increased. Among patients with low resilience, the effect of depression on quality of life was strongest, indicating that depressive symptoms were particularly damaging for quality of life when patients had limited psychological resources for coping with illness-related stress. At moderate levels of resilience, the negative effect of depression remained significant but was weaker. Among patients with high resilience, depression still had a significant negative association with quality of life, but the strength of this association was substantially reduced. The conditional indirect effects also followed the same pattern. The indirect effect of fatigue on quality of life through depression was strongest among patients with low resilience, weaker among those with moderate resilience, and weakest among those with high resilience. The significant index of moderated mediation confirmed that the mediating effect of depression was conditioned by the level of psychological resilience. These results indicate that resilience buffered the psychological pathway through which fatigue impaired quality of life. In other words, while fatigue increased depressive symptoms and depressive symptoms reduced quality of life, this indirect negative process was less severe among patients who reported higher resilience.

Figure 1

Final Model



The model summarized in Figure 1 indicates that fatigue had both a direct and an indirect association with overall health-related quality of life among patients with multiple sclerosis. The indirect pathway operated through depression, such that higher fatigue predicted higher depressive symptoms, and higher depressive symptoms predicted lower quality of life. Psychological resilience moderated the second stage of the mediation pathway by reducing the strength of the negative association between depression and quality of life. The overall pattern of results supports a partial moderated mediation model. This means that fatigue remained an important independent predictor of poorer quality of life, but part of its effect occurred through depression, and the severity of this indirect effect depended on the patient's level of resilience. Patients with low resilience were more vulnerable to the negative psychological consequences of fatigue, whereas patients with high resilience appeared to be better able to maintain quality of life despite depressive symptoms. Therefore, the findings highlight depression as a key psychological mechanism and resilience as a protective factor in explaining quality of life among patients with multiple sclerosis.

4. Discussion

The present study examined fatigue and health-related quality of life among patients with multiple sclerosis in South Africa by testing depression as a mediating mechanism and psychological resilience as a moderating protective factor. The findings showed that fatigue was strongly and negatively associated with physical, mental, and overall health-related quality of life, and strongly and positively associated with depression. Depression was also negatively associated with all quality-of-life indicators, while psychological resilience was positively associated with quality of life and negatively associated with both fatigue and depression. The mediation analysis demonstrated that depression partially mediated the relationship between fatigue and overall health-related quality of life, indicating that fatigue reduced quality of life both directly and indirectly through depressive symptoms. In addition, the moderation analysis showed that psychological resilience weakened the negative association between depression and quality of life. The conditional indirect effects further confirmed a moderated mediation pattern: the indirect effect of fatigue on quality of life through depression was strongest among patients with low resilience and weakest among those with high resilience. These results support an integrated bio-psycho-social interpretation of multiple sclerosis, in which symptom burden, emotional distress, and adaptive psychological resources jointly shape patients' perceived quality of life.

The strong negative association between fatigue and quality of life is consistent with the broader multiple sclerosis literature, which identifies fatigue as one of the most disabling and quality-of-life-reducing symptoms of the disease. Fatigue can restrict physical activity, reduce social participation, impair cognitive performance, and undermine occupational functioning, even when neurological disability is not severe. The present findings are aligned with evidence showing that clinical burden and emotional balance jointly predict quality of life in relapsing-remitting multiple sclerosis (Pérez et al., 2025). They are also consistent with longitudinal evidence demonstrating that disability, cognition, and quality of life are interrelated, suggesting that patient-reported well-being reflects more than neurological impairment alone (Niino et al., 2026). The finding that fatigue was strongly related to poorer quality of life also supports research emphasizing that movement reserve, activity patterns, and functional capacity in multiple sclerosis require attention beyond conventional disability measures (Niyogi et al., 2026). Similarly, studies comparing multiple sclerosis with other neurological conditions have shown that fatigue can interfere with psychosocial adjustment and reduce patients' ability to maintain quality of life during disease progression (Balz et al., 2025). Therefore, the present results reinforce the view that fatigue is not simply a secondary symptom but a core determinant of illness burden and subjective well-being in multiple sclerosis.

The positive association between fatigue and depression observed in this study is also theoretically and empirically meaningful. Patients who reported greater fatigue tended to report more severe depressive symptoms, indicating that fatigue may function as both a physical and psychological stressor. This finding is consistent with research showing that fatigue, depression, and anxiety frequently co-occur among ambulatory patients with multiple sclerosis (AlSaeed et al., 2022). It also aligns with narrative evidence showing that multiple sclerosis has a substantial impact on mental health, including depressive symptoms, emotional distress, identity-related disruption, uncertainty, and reduced psychological well-being (Davis et al., 2021). Fatigue may contribute to depression by limiting participation in meaningful activities, reducing perceived autonomy, increasing dependency, disrupting sleep, and creating a sense of unpredictability in daily functioning. At the same time, depression may intensify the subjective experience of fatigue through reduced motivation, negative cognitive appraisal, diminished activity initiation, and hopelessness. Recent work on mental fatigue assessment supports the importance of distinguishing and measuring subjective fatigue as a clinically meaningful experience rather than treating it only as a physical complaint (Yoshikawa et al., 2025). The present finding therefore supports the need to assess fatigue and depression together in clinical and research settings.

The mediation results indicated that depression partially explained the relationship between fatigue and quality of life. Specifically, fatigue predicted higher depression, and depression predicted lower overall health-related quality of life. The indirect effect was significant, accounting for a substantial proportion of the total effect, while the direct effect of fatigue remained significant after depression was included in the model. This pattern suggests that fatigue affects quality of life through at least two pathways. The first is a direct pathway, in which fatigue reduces physical activity, role functioning, cognitive efficiency, and social engagement. The second is an indirect psychological pathway, in which fatigue increases depressive symptoms, and depressive symptoms further reduce quality of life. This result is consistent with studies showing that emotional symptoms are closely related to MSQOL-54 outcomes and that depression and anxiety are important correlates of quality of life in patients with relapsing-remitting multiple sclerosis (Özbek et al., 2025). It also aligns with evidence that psychological flexibility mediates associations between resilience, distress, and quality of life, demonstrating that psychological processes can explain how illness-related burden translates into patient-reported outcomes (Pakenham & Landi, 2023). The partial nature of the mediation is important because it indicates that depression is a key mechanism, but not the only mechanism, through which fatigue impairs quality of life.

The significant positive association between psychological resilience and quality of life supports the growing evidence that adaptive psychological resources are central to adjustment in multiple sclerosis. Resilience may help patients manage uncertainty, regulate emotional responses, maintain hope, use problem-focused coping strategies, and preserve participation in valued activities despite disease-related limitations. The present findings are consistent with research showing that resilience is related to coping styles, personality traits, and adjustment among patients with multiple sclerosis (Katani et al., 2021). They also align with evidence linking resilience with self-compassion, hope, psychological well-being, social support, and reduced maladaptive psychological patterns among women with multiple sclerosis (Hassani et al., 2021). The role of personal strengths is further supported by research showing that character strengths uniquely contribute to quality of life in persons with multiple sclerosis (Smedema & Bhattarai, 2021). Related evidence on grit, social adjustment, and emotional experience after diagnosis also supports the interpretation that perseverance and adaptive personal resources may help individuals maintain quality of life in the presence of chronic neurological illness (Klappa et al., 2022). Thus, the present results add to a growing body of work showing that quality of life in multiple sclerosis depends not only on symptom severity but also on the patient’s psychological resources.

The moderation finding is one of the most important results of this study. Psychological resilience significantly moderated the relationship between depression and overall quality of life, such that the negative effect of depression was strongest among patients with low resilience and weakest among patients with high resilience. This finding suggests that resilience may buffer the harmful effect of depressive symptoms on quality of life. Even when depressive symptoms are present, resilient patients may be better able to maintain adaptive routines, seek support, regulate negative emotions, and preserve meaning in daily life. This result is compatible with recent evidence indicating that psychological resilience mediates the relationship between depression and quality of life in relapsing-remitting multiple sclerosis (Broche-Pérez & Jiménez-Morales, 2024). It is also consistent with findings showing that resilience mediates the relationship between perceived neuropsychological impairment and quality of life, indicating that resilience can reduce the quality-of-life consequences of perceived cognitive difficulties (Broche-Pérez, Jiménez-Morales, Monasterio-Ramos, Vázquez-Gómez, et al., 2022). In addition, research on fear of relapse has shown that resilience can explain how illness-related fear affects quality of life, further supporting the protective role of resilience in the psychological adjustment process (Broche-Pérez, Jiménez-Morales, Monasterio-Ramos, & Bauer, 2022). The present study extends this literature by positioning resilience as a moderator, showing that it may not only explain quality-of-life outcomes but also alter the strength of the depression–quality-of-life relationship.

The moderated mediation results further clarify the conditional psychological pathway linking fatigue to quality of life. The indirect effect of fatigue on quality of life through depression was strongest at low levels of resilience and weakest at high levels of resilience. This means that fatigue was most likely to impair quality of life through depressive symptoms when patients had fewer adaptive psychological resources. Conversely, higher resilience reduced the severity of this indirect pathway. This finding is aligned with research showing that self-mastery can buffer associations between stressful life events, mental quality of life, and fatigue among people living with multiple sclerosis (Yu et al., 2026). It also corresponds with the broader literature on self-efficacy, which emphasizes patients' perceived capacity to manage MS-related challenges as an important psychological resource (Seebacher et al., 2021). Intervention studies and reviews also support the possibility that resilience-related capacities can be strengthened. Online acceptance and commitment therapy resilience training has been explored as a feasible approach for people with multiple sclerosis (Pakenham et al., 2023), while online psychological interventions have been reviewed as accessible methods for improving symptoms and psychological adjustment in this population (Montañés-Masias et al., 2022). These findings support the clinical relevance of the present model because they suggest that resilience may be a modifiable target rather than a fixed personal trait.

The present findings also correspond with contemporary holistic approaches to multiple sclerosis care. Integrated MS care increasingly emphasizes advanced therapies together with rehabilitation, psychological support, lifestyle management, and patient-centered outcomes (Giovannoni et al., 2024). Mind-body movement interventions have also been reviewed as potentially useful approaches for symptom management in multiple sclerosis, suggesting that interventions combining physical activity, self-regulation, and psychological engagement may help address complex symptoms such as fatigue (Buttolph et al., 2026). Mindfulness-based interventions have shown relevance for quality of life among people with multiple sclerosis by targeting attention, acceptance, and emotional regulation (Simpson, Posa, Bruno, et al., 2022). Compassion-oriented care may also influence adjustment by improving emotional support, patient-provider relationships, and the experience of being understood within healthcare contexts (Simpson, Posa, Langer, et al., 2022). More recent work on body compassion in multiple sclerosis has further emphasized that patients' relationship with their bodies may be an important aspect of adaptation, particularly when symptoms alter mobility, energy, appearance, or bodily trust (Mistretta et al., 2025). The current findings support these approaches by showing that emotional and psychological resources are closely tied to quality-of-life outcomes.

The results may also be understood within a broader framework of identity, social functioning, and rehabilitation. Stigma, psychological well-being, and illness identity are increasingly recognized as important components of the MS experience, particularly because chronic neurological symptoms can influence how patients view themselves and how they participate in social life (Montesano et al., 2025). Bio-psycho-social, co-created interventions for young adults with multiple sclerosis further support the need to design care models that integrate physical, psychological, and social dimensions of illness (Donisi et al., 2021). Outdoor adventure programs and other structured activity-based interventions may contribute to social connection, confidence, and adaptive coping among persons with multiple sclerosis (Herring et al., 2021). Evidence from children and adolescents with multiple sclerosis also shows that quality of life is affected by developmental, emotional, and social factors, and that educational interventions based on coping and health beliefs may improve adaptation (Ali et al., 2022; Mrosková et al., 2021). Although the present sample consisted of adults, these findings reinforce the importance of addressing quality of life across the illness trajectory and across age groups.

5. Conclusion

Finally, the interpretation of the present results is supported by the wider chronic illness and rehabilitation literature. Studies in chronic kidney disease show that chronic illness affects both patients and caregivers and that quality of life is a central outcome beyond biomedical indicators (Pereira et al., 2023). Rehabilitation research in pediatric transplant populations highlights the importance of addressing physical decline and functional limitations, which conceptually parallels the need to address fatigue and reduced activity in multiple sclerosis (Hager et al., 2023). Virtual rehabilitation approaches in Parkinson's disease demonstrate the value of innovative, participatory interventions for neurological populations and their care partners (Sadek et al., 2024). Similarly, quality-of-life outcomes have become central in evaluating treatment approaches in other medical fields, including cardiac surgery, where patient-centered recovery is considered a meaningful endpoint (Marinescu et al., 2025). Although these populations differ from multiple sclerosis, they support the same broader conclusion: chronic illness outcomes must be understood through the interaction of physical symptoms, psychological distress, coping resources, and quality of life.

6. Limitations & Suggestions

The present study has several limitations. First, the cross-sectional design prevents causal interpretation of the relationships among fatigue, depression, resilience, and quality of life. Although the proposed moderated mediation model was theoretically grounded, the temporal sequence of the variables cannot be confirmed without longitudinal data. Second, all variables were measured using self-report questionnaires, which may increase the risk of response bias, shared method variance, and subjective over- or under-reporting of symptoms. Third, the sample was recruited from selected clinical and community-based settings in South Africa, and therefore the findings may not be fully generalizable to all patients with multiple sclerosis, particularly those with severe disability, limited access to care, low literacy, or different cultural and linguistic backgrounds. Fourth, the study did not include objective neurological measures such as Expanded Disability Status Scale scores, MRI indicators, inflammatory markers, or clinician-rated cognitive assessments, which could have provided a more comprehensive picture of disease burden.

Future research should examine the proposed model using longitudinal and prospective designs to clarify the direction and stability of the relationships among fatigue, depression, resilience, and quality of life over time. Studies should also test whether changes in fatigue predict later changes in depression and whether resilience protects patients from long-term quality-of-life decline. Future work may benefit from combining self-report measures with objective clinical, cognitive, and activity-based assessments. In addition, larger and more diverse samples should be recruited across different regions, socioeconomic groups, disease subtypes, and levels of disability. Comparative studies across countries may also clarify how cultural, healthcare, and social support factors influence the role of resilience in multiple sclerosis. Finally, intervention studies are needed to determine whether resilience-focused psychological programs can reduce the indirect effect of fatigue on quality of life by decreasing depression or improving adaptive coping.

The findings have several implications for clinical practice. Routine assessment of fatigue in patients with multiple sclerosis should be accompanied by screening for depression and evaluation of psychological resilience. Patients with high fatigue and low resilience may represent a particularly vulnerable group requiring early psychological and rehabilitative support. Interventions should not focus only on symptom control but should also address emotional regulation, coping skills, self-efficacy, acceptance, social support, and meaningful activity engagement. Multidisciplinary care teams should include neurologists, psychologists, rehabilitation specialists, nurses, and social workers to provide integrated care. Resilience-building strategies, psychoeducation, fatigue management, counseling, mindfulness-based approaches, and supportive rehabilitation may help patients preserve quality of life despite ongoing disease burden. By identifying depression as a key mechanism and resilience as a protective factor, the present findings support a more personalized and psychologically informed approach to multiple sclerosis care.

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Declaration of Interest

The authors of this article declared no conflict of interest.

Ethical Considerations

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

Transparency of Data

In accordance with the principles of transparency and open research, we declare that all data and materials used in this study are available upon request.

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Authors' Contributions

All authors equally contributed to this article.

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