Journal of Psychosomatic Research 170 (2023) 111375

Contents lists available at ScienceDirect

Journal of Psychosomatic Research

journal homepage: www.elsevier.com/locate/jpsychores

The bidirectional effect of stress and functionality in multiple sclerosis and the interaction role of anxiety, coping and social support

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ARTICLE INFO

Keywords:
Anxiety
Coping
Functionality
Multiple sclerosis
Social support
Stress

ABSTRACT

Objective: The present study aims to analyse the bidirectional hypothesis between stress and multiple sclerosis with several measures of stress, impairment and functionality, considering also the interaction role of stress-related psychosocial factors such as anxiety, coping and social support.

Methods: A one-year follow-up was conducted with 26 people with multiple sclerosis. Participants reported i) at baseline, anxiety (State-Trait Anxiety Inventory), and social support (Multidimensional Scale of Perceived Social Support); ii) daily, Ecological Momentary Assessment through self-reported diaries of stressful events and coping strategies; iii) monthly, the perceived stress (Perceived Stress Scale), iv) trimonthly, the self-reported functionality (Functionality Assessment in multiple sclerosis) and v) at baseline and at the end, neurologist rated impairment (Expanded Disability Status Scale). Mixed-effect regression models were conducted.

Results: The bidirectional hypothesis was confirmed with perceived stress and self-reported functionality, which were negatively related in both directions. Coping and anxiety showed an interaction effect: active coping increased functionality only with high levels of stress, and high-trait anxiety showed lower functionality whereas low-trait anxiety showed higher functionality but only with low stress levels.

Conclusion: People with multiple sclerosis may benefit from different types of psychological therapies, from gold-standard therapies like Cognitive Behavioural Therapy to third-waves therapies like Dialectical Behaviour Therapy or mindfulness, that focus on dealing with stress and affective symptoms, adjusting to the disease, and to improving their overall quality of life. More research is needed in this field under the biopsychosocial model.

1. Introduction

Multiple Sclerosis (MS) is an autoimmune neurological disease that affects 2.8 million people worldwide. According to the Atlas of MS in 2020, the global median prevalence has increased to 35.9 per 100.000 inhabitants, with 30% more cases than in 2013. It is more prevalent in women than men, with a ratio of 2:1 or higher [1]. There are two main types of MS: relapsing-remitting and progressive forms, but 85% of people with Multiple Sclerosis (pwMS) start with the first one [2]. The clinical symptoms are very varied and depend on the location of the lesions and the inflammatory processes [3]. The most frequent symptoms are motor and sensory alterations, loss of strength in the extremities, paraesthesia, vision problems, and disorders in coordination and balance. Also, it is common to experience fatigue, pain, affective disorders, cognitive deficits like alterations in attention or memory, and lower quality of life [3–5]. There is no definite cure for MS.

The diagnosis of the disease is usually made by a neurologist according to the McDonald Criteria [6] which is based on a complex interaction of different factors (biological, clinical). Thus, the worsening of the disease may be evaluated through several measures [7]. First, at a

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https://doi.org/10.1016/j.jpsychores.2023.111375
Received 3 January 2023; Received in revised form 27 March 2023; Accepted 10 May 2023
Available online 12 May 2023
0022-3999/

biological level, inflammation and new lesions in the brain can be measured through Magnetic Resonance Imaging scan (MRI). Second, at a clinical level, relapses, symptoms, functionality and impairment levels can be rated by a neurologist (i.e., Expanded Disability Status Scale; EDSS) or self-reported by the patient (i.e., functionality). However, to understand and analyse the daily life with pwMS the most suitable assessments are symptoms, functionality, and impairment. Relapses may occur occasionally, and lesions and inflammation observed via MRI may not be directly correlated with clinical symptoms or disability.

Psychological stress is believed to have an impact on the progression of MS [8,9], and it is commonly observed that pwMS experience high levels of stress [10,11]. Stress may be defined as any stimulus that disrupts or threatens homeostasis. The stress response aims to restore homeostatic processes through a complex interaction between the Hypothalamic-Pituitary-Adrenal (HPA) axis, and the nervous and immune systems [12]. If this response lasts, there is immune deregulation, altering or amplifying cytokine production through stress-triggered neuroendocrine hormones, which may affect autoimmune diseases like MS [13,14]. Studies assessing stress as a trigger factor for disease progression in MS yielded disparate results, but most showed an association [15–18]. Psychological stress has been found to be associated with the exacerbation of MS symptoms and with new brain lesions on MRI [16,19]. At the same time, worsening of the disease has been related to higher levels of stress [20–22]. As MS progresses, new symptoms can emerge that may have a significant impact on daily life and cause psychological difficulties and stress, resulting in a process of continual adaptation [23]. The bidirectional hypothesis has been confirmed in several studies, giving rise to a complex interplay between psychological stress and the course of the disease, [20,21,24] and highlighting the importance for pwMS to manage stressful situations [25].

One of the most challenging issues in the study of psychological stress is its evaluation. According to Lazarus [26], stress is a complex phenomenon that is considered a process involving many variables and moderating factors associated with appraisal and coping. As a dynamic process, it needs to be assessed repeatedly over time. Studies addressing the relationship between stress and MS have mainly used self-administered questionnaires [20,21,25,27,28] or weekly self-reported diaries [29,30]. However, most of them measured stress only once, and only a few considered stress-related factors (for a review, see Briones-Buixassa et al., 2015) [8]. Ecological Momentary Assessment (EMA) is a set of methods that used repeated collection of real-time data on subjects' behaviour and experience in their natural environments to improve ecological validity [31]. In the study of psychological stress, EMA measures have been widely used [32,33]. However, in the study of MS, few studies have used EMA measures to track stress [29,30] and the data recorded by participants may have recall bias because it is collected once a week.

Another crucial issue in the study of stress on disease progression is the interaction effect of other stress-related factors. Some of these factors were identified in a previous systematic review [8] and were tested in a case-control study, where the most relevant were coping, anxiety and social support [34]. These results together highlight the importance of studying the role of these specific factors when analysing the relationship between stress and disease progression.

Based on the literature review, this study aims to a) test the bidirectional hypothesis between stress, functionality, and impairment using several methods (EMA, self-reported questionnaires, and objective measures of impairment) in a cohort of pwMS during 1-year follow-up, and b) analyse the interaction role of coping, anxiety and social support on this relationship. This knowledge may help us better understand the relationship between stress and MS, and develop and test more accurate psychotherapeutic interventions for pwMS.

2. Method

2.1. Participants

Twenty-six adult volunteers with MS participated in the study from May 2014 to September 2015. Participants were recruited from Vic University Hospital in Catalonia, Spain. After screening possible individuals with MS with a neurologist through the clinical history, we contacted eligible participants. Inclusion criteria were a) age over 18, b) diagnosed with MS by a neurologist, c) EDSS score of ≤7. Exclusion criteria were a) pregnancy, b) current abuse of alcohol or drugs, c) diagnosis of other neurologic or psychopathological disorders. All adult volunteers had clinically definite relapsing remitting MS. All participants gave written informed consent. A consort flow diagram of the participants' recruitment process is shown in Fig. 1.

2.2. Study design and procedure

It is an observational, one-year follow-up study nested within the project "PsychoMSS Study: Stress and Psychosocial Factors in Multiple Sclerosis". Each participant received a total of 5 individual interviews by a trained psychologist at Vic University Hospital: one at baseline and every three months at 3, 6, 9 and 12 months. In the first interview, the psychologist asked for socio-demographic and lifestyle data, administered standardised questionnaires for functionality and for psychosocial factors of anxiety and social support, and provided instructions and material to complete the self-reported measures of stress and coping. In the subsequent interviews, data about stress (EMA and questionnaire) and functionality were collected. At the beginning and end of the study, data on impairment (EDSS) was neurologist rated.

The study was approved by the local ethics committee, Fores Foundation (23 July 2013, register number 2013841-PR71), and conducted according to the Declaration of Helsinki [35].

2.3. Measures

2.3.1. Socio-demographic, lifestyle, and medical record data

Information about age, gender, marital status, and educational level

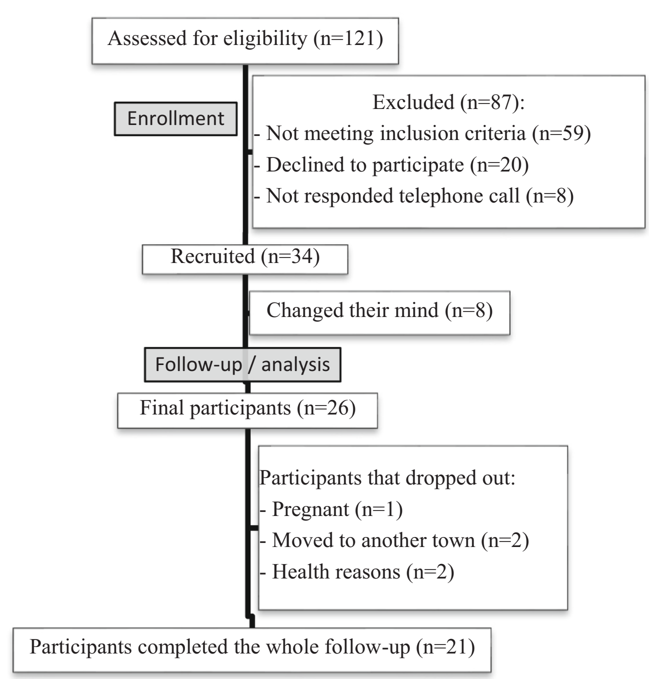

Fig. 1. Participants consort flow diagram.

was obtained in the first interview. Year of diagnosis, type of MS, EDSS score, and MS medication were obtained through medical record.

2.3.2. Stress

Stress was assessed using two self-reported measures: an EMA diary and the Perceived Stress Scale (PSS) questionnaire (monthly).

The EMA diary used a combination of event-based and time-based sampling schemes [31], where participants were instructed to record any stressful event that occurred to them at any time, as well as at least once a day (even if they did not experience any stressful situation). Participants were also given the freedom to decide what constituted a stressful situation, as it was considered a subjective experience. Thus, every person completed a register every day and each time they had a stressful event, along with the coping strategy used to deal with it. This information was compiled for each week of the 1-year follow-up period (52 weeks), with the total number of stressful events for every week being calculated.

The Spanish version of PSS [36] is a self-reported questionnaire comprising 14 items that measure perceived stress over the last month. It was completed every 4 weeks during the 1-year follow-up period, for a total of 13 times. To facilitate completion, a period of 4 weeks was considered as “a month”. The score ranged from 0 to 56, with a higher score indicating higher perceived stress.

2.3.3. Psychosocial factors

Coping strategies were assessed through the EMA self-reported diaries (as mentioned above), which provided the strategy used with every stressful event. Coping strategies were categorised as active (i.e., dealing with the problem, seeking social support) or passive (i.e., avoidance) according to the axis of the Strategic Approach to Coping Scale of Hobfoll (SACS) [37], and then the median was calculated to see the more prevalent strategy.

Trait anxiety was assessed by the State-Trait Anxiety Inventory (STAI) [38]. The total score ranged from 0 to 60 points, with a higher score indicating higher levels of anxiety. High trait anxiety was considered to be $\geq$28 in men and $\geq$ 31 in women (above the 75th percentile adjusted for age and gender in standardised Spanish population tables).

Perceived social support was assessed by the Multidimensional Scale of Perceived Social Support (MSPSS) [39], which assessed 3 sources of social support: from family, friends, and relevant persons. The total score ranged from 12 to 84 points, with a higher score indicating higher levels of perceived social support.

2.3.4. Impairment and functionality

Impairment was objectively measured through EDSS, and functionality through the self-reported Functional Assessment of MS (FAMS) questionnaire.

The EDSS score was rated at the beginning and at the end of the follow-up by a neurologist. EDSS is the most widely used scale to measure impairment in MS [40]. It ranges from 0 (no impairment) to 10 (death from MS complications). A score of 7 and above means daily life support is required.

The FAMS questionnaire [41] was administered at baseline (T0) and every three months at times T3, T6, T9 and T12. FAMS measures 7 subscales of different symptoms: mobility, symptoms (i.e., pain), emotional state, life satisfaction, mental activity and fatigue, family and social environment, and other preoccupations (i.e., incontinence). The score ranges from 0 to 236, with a higher score indicating higher functionality and fewer symptoms. It was evaluated every three months in order to observe substantial changes.

2.4. Statistical analysis

The data were analysed using IBM SPSS Statistics for Windows, version 23. To present descriptive data, means and standard deviations were used for continuous variables and absolute frequencies and percentages for categorical variables. The normality of the data was tested using the Shapiro-Wilk and Kolmogorov-Smirnov tests.

To test the bidirectional hypothesis, several steps were taken. First, the data on stress and disease parameters were temporally matched by calculating the mean of the times T3, T6, T9, and T12 for all measures except EDSS. Second, bivariate correlations were conducted to assess the relationship between stress measures (number of stressful events and PSS), and disease parameters of impairment and functionality. Third, four mixed-effect regression models were estimated to test the statistically significant correlations. The variable “time” was considered a distributing variable, and the data were transformed into long format. It means that the distribution of data changes from a row to a column, meaning that each person has several data rows, and each row represents one time point (T0 or baseline, T3, T6, T9 and T12). Four separate regression models were estimated for each direction of the bidirectional hypothesis, regressing the outcome at the current time (t) point on the predictor assessed at the previous time point (−t). The models tested were perceived stress and functionality, stressful events (number) and functionality, in both directions, considering all variables as predictors and outcomes. In step 1, age and gender were entered as covariates. In step 2, the main predictor was introduced. In step 3, the different psychosocial stress-related variables were added individually to assess their main effects. Finally, in step 4, the interaction effect between the predictor and each psychosocial variable was tested. Coping style was categorised as active or passive, anxiety was categorised as high or low trait anxiety, and social support was treated as a continuous variable. The significance level was set at 5% ($p \leq .05$). Fig. 2 presents a diagram of the models tested.

3. Results

Socio-demographic data, clinical data, and psychosocial factors of the participants are presented in Table 1. The participants were mainly female (73%), married (85%) and with higher educational levels (69%). The summary of descriptive statistics for stress measures, impairment, and functionality assessments at different time points is presented in Table 2.

Table 3 summarizes the bivariate correlations. Impairment (EDDS) did not show any significant correlation and was not entered into the models. Functionality (FAMS) was inversely correlated with both stress measures (events through EMA and perceived stress through PSS), indicating that higher stress scores were related to lower functionality and higher symptomatology. FAMS showed low negative correlations with stressful events (−0.30 to −0.50) and moderate (−50 to-0.70) and

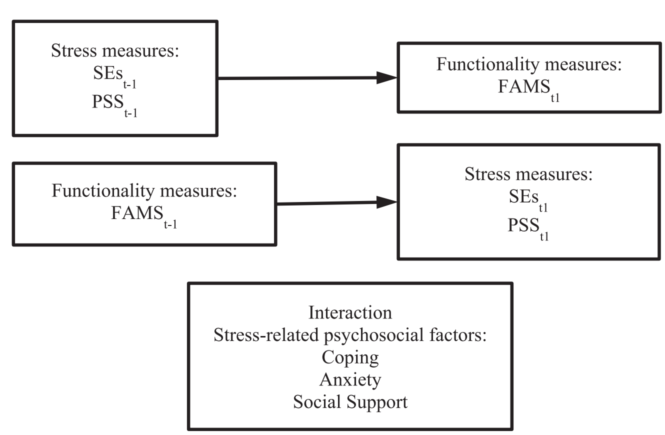

Fig. 2. Diagram of the models tested.
Note: FAMS=Functional Assessment of Multiple Sclerosis; PSS=Perceived Stress Scale; SEs = Stressful Events; t = current time point; t-1 = previous time point.

Table 1
Sociodemographic data, clinical data and psychosocial factors of PwMS.

	PwMS (n = 26)
Female n (%)	19 (73%)
Age y M (SD; range)	47.1 (11.9; 25–67)
MS age diagnosis M (SD; range)	34.4 (10.6; 12–51)
MS duration y M (SD; range)	13.8 (7.5; 4–29)
EDSS baseline M (SD); Median (range)	1.96 (1.84); 1.5 (0–6)
EDSS final M (SD); Median (range)	2.17 (1.92); 2 (0–6)
Marital status n (%)	
Single	4 (15%)
Married	22 (85%)
Educational level n (%)	
Elementary	5 (19%)
Secondary	3 (12%)
FP or equivalent	8 (31%)
University	10 (39%)
Medication n (%)	
No medication	17 (65%)
Glatiramer acetate (Copaxone)	4 (15%)
Beta interferon 1b (Betaferon, Rebif 44)	3 (12%)
Beta interferon 1a (Avonex)	2 (8%)
Psychosocial factors	
Social support (MSPSS) M (SD; range)	70.23 (14.57; 29–84)
Trait Anxiety (STAI-T) M (SD; range)	23.08 (11.32; 3–42)
Coping (more prevalent) n (%)	
Active coping	13 (50%)
Passive coping	13 (50%)

Note: MS = multiple sclerosis; M = mean; SD = standard deviation; EDSS = Expanded Disability Status Scale; y = years; STAI-T = State Trait Anxiety Inventory – Trait; MSPSS = Multidimensional Scale of Perceived Social Support.

Table 2
Summary of descriptive statistics for all the measures at different time points.

Mean(SD)	T0-Baseline	T3	T6	T9	T12	Total/M
Predictors						
SEs	–	8.69 (3.27)	6.74 (4.02)	6.90 (3.96)	9.30 (5.26)	27.50 (15.23)
PSS	–	26.55 (10.02)	27.20 (9.34)	24.90 (9.37)	27.59 (10.18)	26.53 (8.61)
Outcomes						
EDSS	1.96 (1.84)	–	–	–	2.17 (1.92)	2.07 (1.85)
FAMS	153.88 (42.07)	156.62 (40.88)	156.57 (42.90)	157.19 (40.48)	152.58 (43.80)	157.19 (41.40)

Note: SEs = Stressful Events; PSS=Perceived Stress Scale; EDSS = Expanded Disability Status Scale; FAMS=Functional Assessment of MS; Mean for each trimester period: T3 = 3 months; T6 = 6 months; T9 = 9 months; T12 = 12 months; M = Mean; SD=Standard Deviation.

high (−0.70 to −0.90) negative correlations with perceived stress through all the PSS scores (criteria in Mukaka, 2012) [42].

Table 4 presents the results of the mixed-effect regression models. The first model used perceived stress (PSS) as a predictor and functionality (FAMS) as an outcome. After adjusting for age and gender, an inverse relationship was observed between perceived stress and functionality, indicating that higher levels of perceived stress were associated with lower levels of functionality and increased symptomatology. Coping style (passive/active) and social support did not show any significant relationship with functionality, but the interaction between perceived stress and coping was significant. With low levels of stress, active coping was related to decreased functionality, but with high levels of stress, active coping was associated with increased functionality. Anxiety (STAI) showed a significant positive main effect, indicating that low anxiety was related to higher levels of functionality. There was also a significant interaction effect between anxiety and perceived stress. Low-anxious individuals appeared to have better functionality without stress, but with higher levels of stress, functionality decreased at almost the same level as the whole sample. Perceived social support (MSPSS) did not show any effect (see Model 1).

Table 3
Bivariate Correlations (confidence intervals) for stress, functionality, and impairment variables.

	EDSS (baseline and final)	FAMS (baseline and total)	FAMS (T3, T6, T9 & T12)
PSS T3	**EDSS baseline**0 .09 (−0.31 to 0.46)	**FAMS baseline**− 0.70*** (−0.86 to −0.43)	**FAMS T3**− 0.74*** (−0.87 to −0.49)
PSS T6	–	–	**FAMS T6**− 0.56** (−0.80 to −0.16)
PSS T9	–	–	**FAMS T9**− 0.70*** (−0.87 to −0.38)
PSS T12	**EDSS final**0 .04 (−0.41 to 0.48)	–	**FAMS T12**0 .84*** (−0.94 to −0.62)
PSS total	**EDSS final**0 .09 (−0.31 to 0.46)	**FAMS total**− 0.75*** (−0.88 to −0.51)	–
SEs_T3	**EDSS baseline**− 0.03 (−0.41 to 0.37)	**FAMS baseline**− 0.40* (−0.68 to −0.01)	**FAMS T3**− 0.27 (−0.60 to 0.13)
SEs_T6	–	–	**FAMS T6**− 0.36 (−0.69 to 0.08)
SEs_T9	–	–	**FAMS T9**− 0.43 (−0.73 to 0.00)
SEs_T12	**EDSS final**− 0.04 (−0.47 to 0.41)	–	**FAMS T12**0 .49* (−0.77 to −0.05)
SEs_total	**EDSS final**0 .06 (−0.33 to 0.44)	**FAMS total**− 0.42* (−0.69 to −0.04)	–

Note: PSS=Perceived Stress Scale; SEs = Stressful Events; EDSS = Expanded Disability Status Scale; FAMS=Functional Assessment of MS; Mean for each trimester period: T3 = 3 months; T6 = 6 months; T9 = 9 months; T12 = 12 months; base = baseline. Significance (two-tailed) = $*p < .05$, $**p < .01$, $***p < .001$.

The second model used functionality as the predictor and perceived stress as the outcome, showing an inverse relationship between them. An increase in the functionality score was related to a decrease in the perceived stress score. Coping and social support did not show any relationship. However, anxiety showed a negative main effect, meaning that low-anxious people were related to lower levels of perceived stress (see Model 2).

The third model used stressful events (SEs) as the predictor and functionality as the outcome. This model showed no significant relationships (data not shown).

The fourth model used functionality as the predictor and stressful events as the outcome, showing an inverse relationship between them. An increase in the functionality score was related to a decrease in the number of stressful events. Coping did not show any relationship. Perceived social support and anxiety showed a negative main effect, meaning that higher levels of perceived social support and low-anxious people were related to a decrease in stressful events (see Model 3).

4. Discussion

To our knowledge, this is the first prospective study to test the bidirectional hypothesis using different methods and measures of stress, impairment, and functionality, and to consider the interaction role of psychosocial stress-related factors such as anxiety, coping, and social support. The bidirectional hypothesis was only confirmed with self-reported measures of perceived stress and functionality. Coping and anxiety showed an interaction effect with stress and functionality. Active coping seemed to be adaptive with high levels of stress, but not with low levels, while low-anxiety individuals showed higher levels of functionality compared to the whole sample. However, as stress

Table 4
Mixed-effect regression models to test the bidirectional hypothesis and the interaction of psychosocial stress-related factors.

Model 1	Outcome: FAMS			Model 2	Outcome: PSS			Model 3	Outcome: SEs		
Predictor: PSS	βi (CI)	AIC	*p* value	**Predictor: FAMS**	βi (CI)	AIC	*p* value	**Predictor: FAMS**	βi (CI)	AIC	*p* value
Step 1 Age Gender	−17.86 (−118.71 to 82.99) −1.30 (−3.61 to 1.01)	798.36	0.730 .27	**Step 1** Age Gender	−1.33 (−9.99 to 7.34) 0.03 (−0.31 to 0.37)	609.04	0.760 .86	**Step 1** Age Gender	1.59 (−1.38 to 4.57) 0.04 (−0.07 to 0.16)	493.29	0.280 .44
Step 2 PSS	−1.38 (−2.21 to 0.56)	790.35	0.002**	**Step 2** FAMS	−0.18 (−0.22 to −0.13)	568.26	<0.001***	**Step 2** FAMS	−0.03 (−0.05 to −0.00)	476.28	0.04*
Step 3a Coping	3.59 (−2.01 to 9.18)	746.72	0.19	**Step 3a** Coping	−1.59 (−4.29 to 1.11)	521.72	0.24	**Step 3a** Coping	1.23 (−0.18 to 2.65)	423.98	0.09
Step 3b MSPSS	0.62 (−0.17 to 1.40)	808.71	0.12	**Step 3b** MSPSS	−0.24 (−0.67 to 0.19)	670.22	0.28	**Step 3b** MSPSS	−0.09 (−0.16 to −0.02)	495.49	0.02*
Step 3c STAI	31.75 (12.55 to 50.95)	812.91	0.01*	**Step 3c** STAI	−4.27 (−8.44 to −0.10)	557.15	0.05*	**Step 3c** STAI	−4.06 (−6.84 to −1.27)	470.68	0.004**
Step 4a PSS x Coping	0.96 (0.19 to 1.72)	739.57	0.01*	**Step 4a** FAMS x Coping	−0.01 (−0.08 to 0.05)	526.63	0.70	**Step 4a** FAMS x Coping	0.02 (−0.2 to 0.05)	429.35	0.35
Step 4b PSS x MSPSS	−0.20 (−1.22 to 0.83)	1049.63	0.71	**Step 4b** FAMS x MSPSS	0.002 (−0.07 to 0.08)	876.42	0.97	**Step 4b** FAMS x MSPSS	4.78 (−0.002 to 0.002)	520.71	0.96
Step 4c PSS x STAI	−1.60 (−2.90 to −0.29)	738.18	0.01*	**Step 4c** FAMS x STAI	0.03 (−0.05 to 0.12)	793.60	0.41	**Step 4c** FAMS x STAI	0.02 (−0.03 to 0.08)	715.16	0.36

Note: PSS=Perceived Stress Scale; SEs = Stressful Events; FAMS=Functional Assessment of MS; MSPSS = Multidimensional Scale of Perceived Social Support; STAI=State-Trait Anxiety Inventory. Significance (two-tailed) = *p < .05, **p < .01, ***p < .001.

increased, differences in functionality decreased. Individuals with high-trait anxiety also showed lower levels of functionality. Finally, less social support was related to more stressful events.

Previous studies have shown that stress is negatively associated with some disease parameters [29,43], and a meta-analysis [17] found that stress was associated with exacerbations of disease (more relapses, symptoms or brain lesions) with an effect size of $d = 0.53$ (95% CI 0.40 to 0.65), $p < .0001$. These exacerbations usually occur several weeks after the onset of the stressor, and after the stressful situation has ended [20,21,29]. One explanation for this is the resolution hypothesis, which suggests that the dissipation of stress, accompanied by a decrease in cortisol levels, facilitates the development of active inflammation and increases the risk of exacerbation a few weeks after the onset of stress [7,44]. Furthermore, a study by Mohr et al. (2012) [18] tested an individual training program in stress management strategies for 24 weeks, which was associated with a significant decrease in the number of new lesions seen on MRI compared to a waiting list control group. Moreover, a higher percentage of patients remained lesion-free during the intervention period, although the effects disappeared at the end of the intervention [18].

Only a few studies have tested the bidirectional hypothesis (i.e., it maybe that exacerbation results in greater stress rather than the other way around). Schwartz et al., (1999) [24] found that there was almost twice the risk of stress following physical deterioration compared to the risk of functional deterioration given a particular level of self-reported stress. Otherwise, Brown et al. (2006) [20,21] found that the strength of the stress-relapse relationship was similar to the strength of the relapse-stress relationship, for both acute and chronic stressors.

In the present study, the bidirectional hypothesis was tested using different stress assessments (perceived stress and stressful events) and disease measures (neurologist-rated impairment and self-reported functionality). Only perceived stress and self-reported functionality supported the bidirectional hypothesis. Worsening functionality was related to an increase in both perceived stress and the occurrence of more stressful events. These findings suggest that perceived stress may provide more reliable information than the number of stressful events to understand self-reported functionality and day-to-day symptoms in MS. This may be because perceived stress and self-reported functionality may share much of the variance; people who perceive or self-report more stress may also report more symptoms and functional problems related to stress, even if they think they are related to MS. Moreover, more symptoms and functional problems may, in turn, increase the perception of stress. These results highlight the difference in results when using different parameters for measuring disease progression. The EDSS provides a general perception of the disease stage, and it only changes after significant deterioration. However, symptoms such as fatigue, cognitive deficits, or bladder dysfunction are common and often more disabling in the daily life of pwMS. For this reason, self-reported measures of symptoms and functionality may be more useful in determining the immediate effect of stress and other stress-related psychosocial factors in the daily life of pwMS.

In this regard, anxiety also appears to be a significant factor in MS. It has been identified as one of the main factors associated with MS, with a higher prevalence (between 22,1-34,2%) than in the general population (13%) [34,45]. In the present study, anxiety was found to be related to higher levels of stress (both perceived and number of stressful events) and lower levels of functionality. The high prevalence of anxiety in pwMS may be due to the disease diagnosis, but additional precipitating factors such as fatigue, insomnia, cognitive dysfunction, spasticity, neurogenic bladder, pain, and sexual dysfunction [45] could also contribute to it. However, it is worth noting that some patients reported experiencing higher levels of anxiety many years before the diagnosis or had a high trait anxiety throughout their lives, indicating a potential biological link between MS and anxiety. Future studies could investigate this link through various approaches, such as a) exploring the potential connection with the serotonin transporter gen (5-HTT), which is associated with anxiety [46]; b) studying the brain structures involved in anxiety (e.g., amygdala or pre-frontal cortex) [47]; or c) analysing the link with physiological measures of anxiety (e.g., startle reflex, electrodermal activity, heart rate) as done by Ackerman et al. (2003) [28].

Furthermore, therapies aimed at managing stress and anxiety, particularly those utilizing Cognitive Behavioural Therapy (CBT) and relaxation techniques, have demonstrated positive impacts on biological outcomes of the disease [18], mental health symptoms [48], better adjustment to the disease [49], and improved quality of life [50]. Therefore, it appears reasonable to continue investigating psychotherapeutic interventions that focus on improving the adjustment to MS, daily living with the disease, and the treatment of associated mental health symptoms and disorders.

In previous studies, coping has been shown to interact with the relationship between stress and MS inflammation [7,51]. Problem-focused coping has been associated with better adjustment [52] and lower levels of depression in pwMS [53]. In the present study, active coping was found to be associated with better self-reported functionality with high perceived stress but not with low levels of stress. A possible explanation is that although active coping can give a sense of control and empowerment, especially when it successfully solves the problem, it may require effort that can result in increased short-term stress perception. It would be interesting to investigate whether active coping is advisable in all situations in a chronic and unpredictable disease like MS, especially in the relapse phase, progressive forms, or with greater levels of disability where some forms of passive coping (e.g., acceptance) may be more appropriate [54]. Third-wave therapies like Mindfulness or Dialectic-Behavioural Therapy (DBT) have shown to be useful in improving emotion regulation, distress tolerance, self-acceptance, validation of experience, and non-judgment, which can improve symptoms of stress, depression, anxiety, and overall quality of life. However, evidence for these therapies in pwMS is still limited (for a scoping review, see Zaroti et al., 2022) [55].

4.1. Strengths and limitations

The strengths of this study are the design and the methods used. It is a prospective study where data were collected during a 1-year follow-up at various times using different methods. Moreover, the use of EMA ensures more ecological validity as repeated data were collected in the real-time and natural context of individuals.

The main limitation is the small sample size. The number of tasks required, and the duration of the study (1 year) may have excluded those participants who were unable to commit to the follow-up. Another limitation is that most participants were female. Despite the male-to-female ratio in MS being approximately 1:2, it may be difficult to generalise the results to the entire MS population. Similarly, a control group would have been useful to compare the bidirectional relationship with healthy volunteers. However, the outcome variables were focused on MS symptoms, functionality and impairment, and therefore would not have been appropriate for people without MS. Finally, some parameters of the disease worsening (e.g., EDSS) would have needed more time to observe reliable results.

5. Conclusions and future directions

In summary, the results supported the bidirectional hypothesis with self-reported measures of perceived stress and functionality, although we must be cautious due to the small sample size. Considering the association between stress, anxiety and functionality, and the fact that active coping might be counterproductive with low levels of stress, pwMS may benefit from psychotherapeutic interventions to reduce stress and anxiety and to increase acceptance, compassion, and emotional regulation, to prevent a possible potential deteriorating cycle. Focusing on these aspects, more research is needed in both psychological gold standard therapies like CBT as well as third-wave therapies (e.g., Mindfulness or DBT) that may be useful for pwMS to deal with stress and affective symptoms, adjust to the disease, and improve their overall quality of life. Moreover, as results were collected before the COVID-19 pandemic, some stressors may have changed, and future studies should consider how these new stressors (e.g., lockdowns) may affect pwMS.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical approval

The study was approved by the local ethics committee, Fores Foundation (23 July 2013, register number 2013841-PR71), and conducted according to the Declaration of Helsinki (World Medical Association, 2013).

Informed consent

All the participants gave written informed consent before being included to the study.

Declaration of Competing Interest

The authors have no competing interests to report.

Data availability

The datasets generated during and/or analysed during the present study are available from the corresponding author on reasonable request.

Acknowledgments

A special thanks to all the participants for helping us to carry out the study.

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