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Predictors of Anxiety in Multiple Sclerosis

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Abstract

Purpose/Objectives—The aims of this study were to (1) Identify the predictors of symptoms of anxiety, and (2) Evaluate the differential association of somatic and non-somatic symptoms of depression on anxiety over time in persons with multiple sclerosis (MS).

Methods/Design—Participants were 513 persons with MS who previously enrolled in a study exploring the experience of living with MS and completed a 4-month follow-up survey. The main outcome measure used was the Hospital Anxiety and Depression Scale-Anxiety (HADS-A). Demographic, disease-associated variables (time since onset of MS, EDSS, pain and fatigue), and time 1 psychological variables (somatic and non-somatic symptoms of depression) were entered into a hierarchical regression model to examine predictors at baseline for anxiety symptoms at time 2.

Results—Of the 513 participants in this study a large portion of the sample was white (92%), female (82%), and had relapsing-remitting MS (57%). After adjusting for demographic and disease related variables, anxiety (β <.001), employment (β =.07) and non-somatic depressive symptoms (β =.10) at baseline significantly predicted anxiety at time 2, *p*s<.05. Interactions revealed significant effects for time since onset of MS and somatic symptoms as well as time since onset and non-somatic symptoms, *p*s<.05. Non-somatic symptoms were more linked to anxiety early in the disease and somatic symptoms were more prominently linked to anxiety later in the disease.

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Conclusions—Findings suggest that non-somatic symptoms of depression and employment predict anxiety in MS. The relationship between different aspects of depression and anxiety may change over the course of the disease.

Keywords

Multiple Sclerosis; Anxiety; Depression

Multiple sclerosis (MS) is a chronic neurologic condition that impacts as many as 2.3 million individuals worldwide ("Atlas of MS Database," 2013). The disease course and symptom profile varies significantly between individuals and usually progressively worsens over time. Typically, patients experience multiple symptoms resulting in physical, cognitive and psychological difficulties. Although a wealth of research has focused on depression and its treatments in MS, little is known about symptoms of anxiety and risk factors for its development in MS. Hence, currently there exists no unified theoretical conceptualization of the experience of anxiety in MS and how that may change over time. This is a surprising gap in the literature, especially given that prevalence of anxiety disorders in MS ranges from 14% to 45% (Korostil & Feinstein, 2007; Wood et al., 2013) and may result in poorer medication adherence (Turner, Williams, Sloan, & Haselkorn, 2009), higher pain intensity and pain interference with health- related quality of life (Bruce & Arnett, 2009; Kalia & O'Connor, 2005), lower quality of life (Garfield & Lincoln, 2012), and suicidal intent (Korostil & Feinstein, 2007).

Identification of risk factors for anxiety in MS would lay a critical foundation for developing an advanced conceptualization of the experience of anxiety in MS over time. This holds tremendous practical implications in that such a theoretical advancement would enhance clinical efforts directed towards the prevention, screening, and treatment of anxiety and concomitant secondary symptoms. In the absence of prior risk factor research for anxiety in MS, it is informative to consider if the cross-sectional variables associated with anxiety in MS may also be predictive of symptoms over time. Higher anxiety has been associated with female gender (Jones et al., 2012), younger age (Wood et al., 2013), a diagnosis of relapsing-remitting MS (Jones et al., 2012), longer time since onset of MS (though results are mixed; Feinstein, O'Connor, Gray, & Feinstein, 1999; Janssens et al., 2006), greater MS-related disability (Jones et al., 2012), higher levels of fatigue (Beiske et al., 2008), MS exacerbations (rapid onset or an increase in symptoms; Burns, Nawacki, Siddique, Pelletier, & Mohr, 2013; Feinstein et al., 1999), and depression (Garfield & Lincoln, 2012; Wood et al., 2013). Investigation is needed to identify if these cross-sectional correlates may represent predictive risk factors that have an extended impact on the development, maintenance, or exacerbation of anxiety symptoms over time.

A challenge for identifying risk factors of anxiety is the high comorbidity between anxiety and depression (Almeida et al., 2012; Burns, Siddique, Fokuo, & Mohr, 2010). Evidence suggests that individuals with a history of depression may be at a higher risk of experiencing anxiety over time (Korostil & Feinstein, 2007). A further challenge is that anxiety, depression, and MS include overlapping somatic symptoms (e.g., sleep disturbance, fatigue, concentration difficulties). Similarly, reports of 'numbness and tingling,' 'feeling unsteady,'

and 'wobbliness in legs' might be attributed to anxiousness or the MS disease process (Feinstein et al., 1999). A number of studies have discussed the importance of removing somatic symptoms from both depression and anxiety scales to avoid this confound (Benedict, Fishman, McClellan, Bakshi, & Weinstock-Guttman, 2003; Donnchadha et al., 2013). Recommendations include utilizing an outcome measure comprised only of non-somatic items (i.e., excessive worry, fear of losing control, unable to relax, etc.) of anxiety (Donnchadha et al., 2013; Zigmond & Snaith, 1983) or utilizing a two-factor model of somatic vs. non-somatic depression symptoms (Richardson & Richards, 2008).

The present study sought to extend the literature on anxiety in MS by conducting a evaluation of current demographic, disease-related characteristics and psychological factors that contribute to anxiety symptom severity at a 4-month follow-up. In the absence of prior longitudinal research on anxiety among the MS population, we hypothesized that variables cross-sectionally associated with anxiety would also remain predictors during 4-month follow-up: age, level of disability, time since onset, and depression. To account for the concerns of somatic overlap, we utilized an anxiety measure that focuses on cognitions (and excludes somatic items), and a two-factor measure of depression that differentiates somatic and non-somatic symptoms. We hypothesized that the non-somatic depression symptoms would be associated with anxiety symptom severity due to the substantial overlap between the affective/cognitive symptoms of anxiety and depression derived from the shared distress and negative affect (Kendler et al., 1995; Watson & Clark, 1984; Watson, Clark, & Carey, 1988). Finally, since there is considerable reason to believe that *both* depression and anxiety may be influenced by age (Janssens et al., 2006; Jones et al., 2012; Mattioli, Bellomi, Stampatori, Parrinello, & Capra, 2011; Williams et al., 2005; Wood et al., 2013), time since onset (Chwastiak et al., 2002; Forman & Lincoln, 2010; Janssens et al., 2006; Korostil & Feinstein, 2007; Williams et al., 2005), and disability (Beiske et al., 2008; Mattioli et al., 2011; Moore et al., 2012), we explored the potential synergistic (i.e., interaction) effect between depression and age, time since onset, and disability on anxiety over time to determine if a differential pattern of association would emerge between these factors.

Methods

Recruitment and Procedures

Participants were individuals enrolled in a large study examining the experience of living with MS who completed a series of self-report questionnaires (described below). The data for the present analysis represent two time points, 4-months apart. Detailed information on recruitment is reported elsewhere (Amtmann et al., 2012). Briefly, participants were recruited from the Greater Northwest chapter of the National Multiple Sclerosis Society. Of the 1,628 who were mailed invitations, 1,367 met eligibility criteria (age 18 years or older with self-reported MS) and were mailed a paper survey or a link to the online survey. Of the 1,270 individuals who completed this baseline assessment, 562 randomly selected participants were invited to continue participating in the survey. A total of 513 individuals (93% response rate) completed the four-month follow-up survey either online (n=119) or on paper (n=394). All participants provided informed consent and received $25 per completed

survey. Procedures were approved by the Human Subjects Division of the primary research institution.

Measures

Demographics—Participants provided demographic and basic medical information, including age, sex, race/ethnicity, education, employment, and time since onset of MS.

Disability Status—Participants completed the self-reported Expanded Disability Status Scale Mobility (EDSS-Mobility; (Bowen, Gibbons, Gianas, & Kraft, 2001). A continuous score (range 1–9) was used for all analyses. For descriptive purposes, participants were divided into three categories: no mobility aid (≤ 4, minimal severity), bilateral or unilateral mobility aid (4.5–6.5, intermediate severity), and use of a wheelchair for mobility (≥ 7, advanced severity).

Pain—The Numeric Rating Scale (NRS) assessed pain severity, with participants rating the intensity of their pain over the past week from 0 (no pain) to 10 (highest pain imaginable). This single item NRS is widely utilized and is well validated (Jensen & Karoly, 2011).

Fatigue—The Fatigue Severity Scale (FSS) was utilized to measure the severity and impact of fatigue. The FSS includes nine items ranging from 1 (no symptoms) to 7 (severe fatigue), with higher scores indicating greater levels of fatigue. The FSS has high sensitivity and good internal consistency (Cronbach's α = .88; Krupp, LaRocca, Muir-Nash, & Steinberg, 1989).

Anxiety—The Hospital Anxiety and Depression Scale-Anxiety (HADS-A) is a 7-item measure of anxiety symptom severity. Items are rated on a 4-point Likert scale, with higher scores indicating greater anxiety symptoms (Zigmond & Snaith, 1983). The HADS-A has been validated for use in identifying anxiety in individuals with MS (Honarmand & Feinstein, 2009).

Depression—The Patient Health Questionnaire – 9-item (PHQ-9) is a measure of depression symptom severity developed in parallel with the diagnosis of Major Depressive Disorder in the DSM-IV (Spitzer, Kroenke, & Williams, 1999). Items are rated according to how persistent the symptom has been in the past two weeks: 0 (not at all), 1 (several days), 2 (more than half the days), or 3 (nearly every day). The PHQ-9 demonstrates good internal consistency (Cronbach's α = .89) and test-retest reliability (r =. 84; Kroenke, Spitzer, & Williams, 2001).

A two-factor structure consisting of non-somatic and somatic items was used to comprise the two-dimensional construct (Richardson & Richards, 2008). Reliability analysis confirmed that the two constructs had sufficient internal consistency (Cronbach's α = .81 for non-somatic scale and Cronbach's α = .74 for somatic scale). Since the two subscales indicated acceptable reliability (Cronbach's α of .70 or higher cutoff; Nunnally, 1978) we used the composite scores to form the two-dimensional scales in the current study.

Data Analytic Strategy

Statistical assumptions of the data were examined, including evaluation of descriptive statistics and histograms to assess normality and linearity. Collinearity diagnostics were conducted to help identify multicollinearity among predictors. A correlation matrix of all predictor variables are included in Table 1. Correlations among the variables were examined and Tolerance values and Variance Inflation Factor (VIF=1/T) were used to measure the impact of collinearity in the regression model. All Tolerance and VIF values were within an acceptable range (acceptable range: 0.2<T<2 and VIF < 10; (Belsley, Kuh, & Welsch, 2005). All predictors for the interaction were centered to reduce nonessential multicollinearity. Centered predictor variables were used for linear by linear interaction (Aiken & West, 1991).

A hierarchical regression analysis was used to test the study hypotheses, with the model including time 1 variables as predictors and the time 2 variable (anxiety, at time 2) as the outcome. The model tested whether the participant's "current" subset of biopsychosocial variables (time 1), predicted anxiety four months later (time 2). The predictors represented the "current" (time 1) set of variables for the participant. The first step included anxiety (time 1) to identify the extent to which current anxiety predicted future anxiety. Including anxiety at time 1 also allowed for identifying whether the step 2 variables contributed to the severity of anxiety at time 2 beyond what could be attributed to anxiety at time 1. The step 2 variables entered into the regression model included a selection of important biopsychosocial factors: demographic variables (age, sex, race, education, employment), disease-related characteristics (time since onset, disability, pain, fatigue) and psychological variables (somatic and non-somatic symptoms of depression). The third step in the specified regression model tested for interaction effects and determined how these interaction effects may predict worsening of anxiety symptoms. In step 3, the following *a priori* selected interaction terms were entered: age X somatic symptoms, age X non-somatic symptoms, time since MS onset X somatic symptoms, time since MS onset X non-somatic symptoms, disability X somatic symptoms, and disability X non-somatic symptoms.

For graphical representations of the significant interaction effects for time since onset of MS and somatic or non-somatic symptoms of depression on anxiety, groups were created reflecting three different categories of time since onset of disease (Aiken & West, 1991): (1) < −1 standard deviation (*SD*; <3.8 years) below the mean; (2) between −1 *SD* (>3.8 years) and +1 *SD* (<23.2 years); and (3) > +1 *SD* (> 23.2 years) above the mean. All statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS), 20th edition.

Results

Sample Characteristics

Participants were 513 individuals with a self-reported diagnosis of MS. Consistent with the MS population at large ("Atlas of MS Database," 2013) the sample was predominantly non-Hispanic white (92%) and female (82%). The average participant was 51 years old with mean time since onset of MS of 13.5 years (SD = 9.77; range=1–60). Relapsing-remitting

MS was most common (57%) followed by secondary-progressive, primary-progressive, and progressive-relapsing MS (see Table 2).

Risk Factors for Anxiety Symptom Severity

The multiple regression analysis assessing the relationship of risk factors with anxiety indicated that the predictors accounted for 63% variance in the final model (R^2 = .63, $F(18, 459) = 42.58$, $p<.001$; see Table 3 for all model parameters). As expected, there was a significant main effect for anxiety at time 1 (β=.70, $p<.001$) such that greater anxiety at time 1 was associated with greater anxiety at time 2. There were no significant main effects for age, time since MS onset, and EDSS; however, results indicated that employment status at time 1 significantly predicted anxiety symptoms at time 2, with participants who were employed reporting higher anxiety (β=.07, p=.03). Non-somatic symptoms of depression also significantly predicted anxiety (β=.10, p=.02); greater levels of non-somatic depressive symptoms at time 1 were associated with greater anxiety at time 2. There were no other significant main effects in the model.

Analysis revealed significant interaction effects for time since onset of MS and non-somatic depressive symptoms (β=−.10, p=.03; see Figure 1). Participants with the shortest time since onset of MS experienced significantly more anxiety with more non-somatic depressive symptoms (see Figure 1). An interaction effect was also found with time since MS onset and somatic symptoms of depression (β=.10, p=.02; see Figure 2). Participants with the longest time since onset experienced significantly more anxiety with more somatic depressive symptoms (see Figure 2).

Discussion

This study identified several risk factors for anxiety symptoms in MS at a short-term follow-up. Results partially supported our hypothesis, such that non-somatic symptoms of depression (time 1) were associated with higher levels of anxiety symptoms (time 2). Additionally, employment status unexpectedly emerged as a significant predictor of anxiety symptoms. Surprisingly, many variables cross-sectionally associated with anxiety in the literature were not associated with worsening anxiety symptoms when examined during the short-term follow-up. Exploratory analyses revealed two important interaction effects. Specifically, results indicated that in the early stages after a MS diagnosis, individuals experience greater severity of non-somatic symptoms of depression and this appears to exert a negative, synergistic effect that leads to worsening anxiety. However, over time (i.e., as time since MS diagnosis increases), there is a shift in reported coping associated with MS such that the somatic symptoms of depression emerge as more predominant, and this corresponds with heightened risk for anxiety symptoms.

The premise of the present study was the identification of variables at one time point that signal risk for anxiety symptoms worsening by a second time point, so future research could focus on developing clinical assessments and treatments focused on intervening early with at risk patients. As expected, the individual's level of anxiety (time 1) was a significant predictor of anxiety at the second time point (Janssens et al., 2006). However, beyond initial level of anxiety, the individual's current non-somatic symptoms of depression and

employment status were also risk factors for higher anxiety symptom severity at 4-month follow-up. These findings serve an important purpose from a clinical assessment perspective: while the presence of anxiety might be an obvious reason to be concerned about future anxiety, clinicians might also pay attention to the presence of non-somatic depressive symptoms and employment status.

The current findings are only a first step towards clinical interventions; important future research is needed to understand *why* these risk factors are important. For example, one might consider whether the impact of non-somatic symptoms of depression on anxiety symptoms is due to a shared mechanism and/or the exacerbating effects of having anxiety and depression simultaneously. Similarly, we cannot determine why employment is impactful from these findings. However, we might speculate the involvement of several factors: practical concerns (e.g., finances), emotional concerns (e.g., feeling overwhelmed with demands at work in the context of worsening MS symptoms), and/or social concerns (e.g., the human interaction that is built in to many workplaces; Busche, Fisk, Murray, & Metz, 2003; Jellie, Sweetland, Riazi, Cano, & Playford, 2014). By understanding why these variables are important, intervention research can then focus on the value of intervening on specific factors that impact anxiety and, more importantly, on early intervention on these factors in an effort to decrease the presence and severity of anxiety symptoms.

We were equally intrigued that there were no significant findings for the predictive nature of biomedical variables to anxiety symptom severity. The examined relationships of MS disease course, time since diagnosis (Feinstein et al., 1999; Forman & Lincoln, 2010; Janssens et al., 2006; Korostil & Feinstein, 2007), and MS symptoms (Kalia & O'Connor, 2005) to anxiety symptom severity were all non-significant. Perhaps the most probable explanation for these unexpected findings are (a) while the nature of MS (e.g., uncertainty and uncontrollability; Janssens et al., 2003; Kroencke, Denney, & Lynch, 2001) may contribute to anxiety, it may not impact variability in anxiety symptom severity over time; and/or (b) disease-related factors did not change significantly in the span of the study hence their capacity to influence anxiety over time may have been methodologically limited. More research is needed to understand the contribution of MS-specific variables to anxiety.

In our close examination of the relationship of depression with anxiety symptoms, we found a significant relationship of non-somatic symptoms of depression with symptoms of anxiety. The association of non-somatic symptoms suggests a shared cognitive and affective overlap, whereby a person with more depressive cognitions may be at greater risk for also having more anxious cognitions. This was particularly notable in participants with a more recent diagnosis of MS, such that participants with the shortest time since onset of MS experienced significantly more anxiety with more non-somatic depressive symptoms. The association of non-somatic depressive and anxious symptoms should be a focus for future research, as it carries important clinical implications. Specifically, it may be important clinically to determine if these are the same cognitions observed through different lenses (i.e., a single cognition that at times is observed as depressive, but at other times is observed as anxious) or whether these are unique cognitions but these individuals are more predisposed to maladaptive thought patterns. Having a shared cognition manifesting differently over time would suggest the importance of developing trans-diagnostic interventions targeting those

shared cognitions, rather than intervening on “anxiety” or “depression.” Findings indicate the relationship between symptoms of depression and anxiety may change over the MS disease course in another way: Individuals seem to report a stronger link between somatic symptoms of depression with symptoms of anxiety later in the disease. Possibly, somatically experienced depression symptoms contribute to the symptoms of anxiety associated with the overall burden of MS, and as the disease burden increases over time, so does the importance of these symptoms. Overall these findings highlight how the correlation between depression and anxiety may change over time such that early in the disease process they are linked by cognitive appraisal, and late in the disease they are linked by somatic experiences. This has interesting clinical implications, as psychologists treating people with MS can expect that at first individuals will be worried and sad as they grapple with the uncertainty of what might happen to them. Later in the disease they are worried and sad as they come to terms with what is happening to them. This process is less a function of maturity (age) or actual disability (EDSS) as it is the amount of time the person has had to live with the disease.

Study Limitations

We acknowledge several limitations to the present study. First, the sample includes individuals with MS who voluntarily participated in a broad study of life with MS. Results may be subject to selection and response bias and may not generalize to other populations of individuals with MS. The favorable response rate (92.9%) and large sample size (N = 513) partially mitigates these concerns. Additionally, the complex relationship that may exist between age and time since onset of MS requires a systematic and comprehensive analysis to determine whether one or both of these variables may add unique variance to the prediction of anxiety symptoms. While our findings do support some association between the interaction of time since MS onset, depression and anxiety, this relationship cannot be uniquely parceled out from the effect of aging. Finally, it is important to consider that this study describes anxiety symptom severity, but not anxiety disorders, as the HADS-A is not a diagnostic measure. An exploration of risk factors for anxiety disorders, as well as differences between types of anxiety disorders, is worthy of future research.

CONCLUSIONS

The present study provides important, novel information on predictors of anxiety in individuals with MS. Whereas previous research identified variables that are associated with anxiety cross-sectionally, the present study identified variables that may signal a heightened risk of worsening anxiety symptoms over time. These identified risk factors serve an important clinical purpose, highlighting areas that are worth extra scrutiny, much as how certain laboratory values or blood pressure might indicate increased scrutiny for certain medical conditions (Almeida et al., 2012). Finally, this study serves as a starting point for future research on interventions for anxiety in MS. In particular, research is needed to better understand *why* the present variables are important and how intervening on these variables could alter an individual’s prognosis regarding future anxiety and coping with MS over time.

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Impact

- The present study extends beyond existing cross-sectional research by identifying predictors associated with heightened risk of anxiety symptoms in MS.
- Although future research is needed to confirm these findings, this study preliminarily identified three risk factors (anxiety symptoms, depression symptoms and employment status) that may be highly associated with worsening anxiety symptoms in individuals with MS.
- This study also highlights how the correlation between depression and anxiety may change over time such that early in the disease process they are linked by cognitive appraisal, and late in the disease they are linked by somatic experiences.

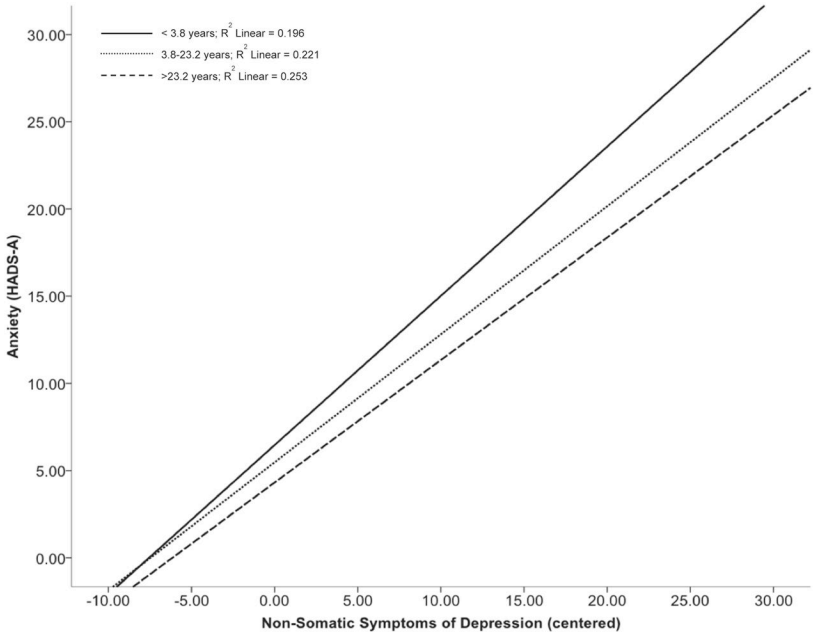

Figure 1.

Effects of time since onset of MS and non-somatic symptoms of depression on Anxiety overtime. Figure presented are based on the final model (model 3).

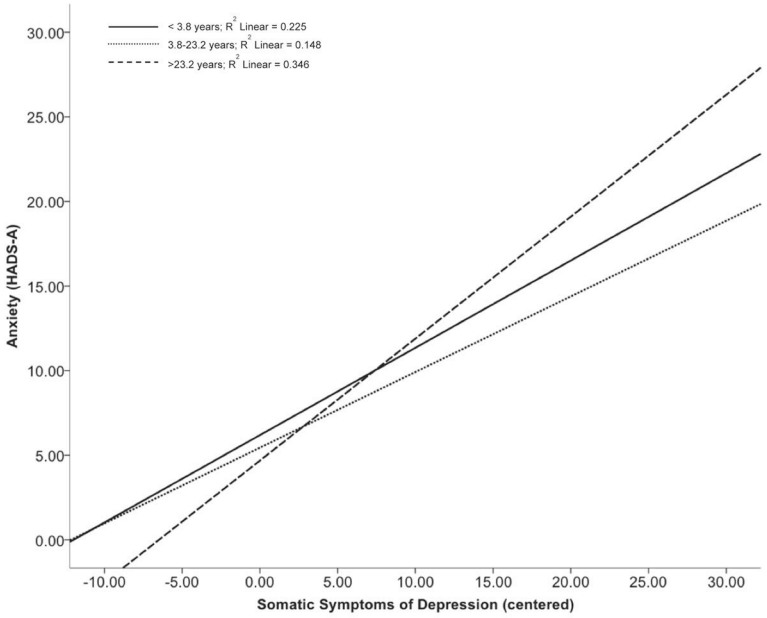

Figure 2.

Effects of time since onset of MS and somatic symptoms of depression on Anxiety overtime. Figure presented are based on the final model (model 3).

Table 1

Correlation coefficients, means and SD for study variables

	Anxiety	Non-Somatic Symptoms	Somatic Symptoms	Time since onset	EDSS	Age	Fatigue	Pain	Employment	*M*	SD
1. Anxiety at Time 1	-									5.58	3.95
2. Non-Somatic Sx of Depression	.541***	-								2.39	2.58
3. Somatic Sx of Depression	.519***	.639***	-							4.98	3.40
4. Time since onset of MS	−.142***	−.035	−.078	-						13.45	9.77
5. EDSS	.019	.206***	.235***	.379***	-					4.18	2.81
6. Age	−.178***	−.053	−.059	.522***	.354***	-				51.41	10.98
7. Fatigue	.250***	.393***	.523***	.063	.425***	.130**	-			5.14	1.47
8. Pain	.326***	.377***	.540***	−.010	.177***	−.010	.354***	-		2.83	2.73
9. Employment	.015	−.138***	−.147***	−.376***	−.494***	−.386***	−.309***	−.131**	-	0.40	0.49

Note. Total Depression score measured by Patient Health Questionnaire-9 (PHQ-9) Mean= 7.38 and SD=5.42. Anxiety measured by the Hospital Anxiety and Depression Scale-Anxiety (HADS-A) with scores Range (0–20). Abbreviations: EDSS, Expanded Disability Status Scale Mobility

* $p < .05$;

** $p < .01$;

*** $p < .001$.

Table 2

Participant characteristics

	N (%)
Total sample	513
Sex	
Male	93 (18.2)
Female	417 (81.8)
Ethnicity	
Non-Hispanic white	468 (91.8)
Other ethnicity	42 (8.2)
Education	
≤ High School	115 (22.5)
College and above	392 (76.9)
Employment	
Yes	306 (60)
No	201 (39.4)
MS Type	
Relapsing-remitting	284 (55.7)
Secondary-progressive	103 (20.2)
Primary-progressive	64 (12.5)
Progressive-relapsing	49 (9.6)
Not known	10 (2.0)
EDSS	
≤ 4.0	169 (32.9)
4.5–6.5	247 (48.1)
≥7.0	97 (18.9)
	M (SD)
Age	51.4 (10.9)
Time since onset of MS	13.5 (9.8)

Note. Participant characteristic of the entire sample. Values Are expressed as mean (SD) for continues variables and total N (%) for all categorical variables. Abbreviations: EDSS, Expanded Disability Status Scale Mobility

Table 3

Regression coefficients

	B	SE B	β	*p*
Block 1				
Anxiety at time 1	.71	.04	.70	<.001
Block 2				
Age	.01	.01	.03	.47
Race	.34	.42	.02	.42
Sex	.47	.31	.04	.14
Employment	.60	.28	.07	.03
Education	.09	.28	.07	.75
Pain	.09	.05	.06	.09
Fatigue	.06	.10	.02	.57
Time since onset	−.003	.01	−.01	.86
EDSS	−.07	.05	−.05	.17
Depression- Somatic	.001	.05	.001	.99
Depression- Non-somatic	.16	.06	.10	.01
Block 3				
Age x Depression-Somatic	−.001	.01	−.01	.92
Age x Depression-Non-somatic	<.001	.01	.001	.99
EDSS x Depression-Somatic	−.02	.02	−.04	.27
EDSS x Depression-Non-somatic	−.01	.02	−.02	.70
Time since onset x Depression-Somatic	.01	.01	.10	.02
Time since onset x Depression-Non-somatic	−.02	.01	−.10	.03

Note. N=478. Abbreviation: EDSS, Expanded Disability Status Scale Mobility. All coefficients presented in table are from the final model (model 3).