

ORIGINAL RESEARCH

Relative Importance of Baseline Pain, Fatigue, Sleep, and Physical Activity: Predicting Change in Depression in Adults With Multiple Sclerosis



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Abstract

Objective: To determine whether baseline levels of pain, fatigue, sleep disturbance, and physical activity measured at the initial assessment predicted the development of or improvement of depression 3.5 years later, while controlling for sex, age, and disease severity.

Design: Observational, longitudinal survey study.

Setting: A community-based population sample.

Participants: Adults with multiple sclerosis (MS) (N=489).

Interventions: Not applicable.

Main Outcome Measure: Primary outcome was classification of depression group measured using a Patient Health Questionnaire-9 cutoff score ≥ 10 , indicating probable major depression.

Results: Fatigue severity (odds ratio, 1.19; 95% confidence interval, 1.12–1.26; $P < .0001$) and sleep disturbance (odds ratio, 1.06; 95% confidence interval, 1.02–1.10; $P = .001$) predicted probable major depression 3.5 years later among those not depressed at the initial assessment. An effect of age (odds ratio, .96; 95% confidence interval, .92–.99; $P = .008$) was found among those who developed depression, indicating that younger adults were more likely to develop depression. Pain, fatigue, sleep, and physical activity at baseline were not significantly associated with recovery from depression among those depressed at the initial assessment.

Conclusions: Fatigue and sleep may contribute to the development of depression. Clinical trial research targeting these variables to determine their influence on depression is warranted.

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In people with multiple sclerosis (MS), depression is associated with poorer adherence to medical treatments,¹ reduced quality of life,² and increased mortality rate.³ The 1-year prevalence of major depression in MS is about 25%,⁴ which is substantially higher than the 5% to 7% prevalence rate in the general U.S. population.⁵ Depression in MS has complex relationships with multiple factors, including cognitive impairment, brain pathology, immunologic factors, high levels of stress, decreased social

support, and maladaptive coping strategies.³ To inform treatment and prevention efforts, longitudinal research is needed to identify modifiable factors that predict the subsequent development or remission of depression in persons with MS.

Findings from previous research⁶⁻⁹ indicate that potentially modifiable risk factors for the development of depression in MS include physical inactivity, pain, poor sleep, and fatigue. For example, studies have shown that low levels of physical activity or exercise are related to higher depression severity^{7,10} and that improved physical activity alone can reduce subsequent depressive symptoms.¹¹⁻¹⁴ Pain and depression frequently co-occur in MS,^{15,16} and individuals with MS and chronic pain may be 5 times more likely to meet criteria for a major depressive episode than those who do not have pain.^{6,17,18} In regards to sleep quality, sleep disturbances were 3 times more likely to occur in individuals with

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MS as compared with healthy controls,¹⁹ and disrupted sleep is a risk factor for depression.²⁰⁻²⁴ Lastly, fatigue is among the most common symptoms associated with MS, ranging in prevalence from 50% to 93%.⁹ Fatigue and depression also frequently co-occur as supported by multiple studies,^{8,25,26} and while fatigue is a symptom of major depression, it also can be directly attributable to MS.³ Despite the availability of research describing the impact of pain, sleep, activity, and fatigue on mood in persons with MS, many of these studies have been limited by the use of cross-sectional and unifactorial designs along with a reliance on depression measures with weak diagnostic validity. Similarly, many of these predictors have been examined in isolation rather than in the context of other unmodifiable factors, including age.²⁷⁻³¹ Age has been shown to have an intricate relationship with depression among those with MS. Previous studies have mixed findings, with some indicating that depression is worse among younger individuals, because of poorer coping skills than older adults,^{29,31} and others indicating that age does not have an effect on depression.^{32,33}

To address these limitations in the literature, the current study sought to better understand physical activity, pain, quality of sleep, and fatigue as predictors of clinically significant change in depression status over a period of 3.5 years in a large sample of adults with MS, while accounting for the effects of important contextual factors. Given the existing literature, we hypothesized that pain intensity and fatigue severity, along with poor sleep and physical inactivity, measured at the initial assessment, would be risk factors for developing probable major depression (among those who are not depressed at the initial assessment) and for persistent depression (among those who are depressed at the initial assessment). Conversely, we hypothesized that lower levels of pain and fatigue, along with better sleep and engagement in physical activity, measured at the initial assessment, would be identified as protective factors for developing probable major depression (among those who are not depressed at the initial assessment) or for improving depression (among those who are depressed at the initial assessment) 3.5 years later. In tests of both hypotheses, we controlled for the effects of disease course as well as participant nonmodifiable factors (age, sex). In addition to testing these primary study hypotheses, we planned to explore the extent to which age at the initial assessment period, while controlling for disease course and sex, moderated the associations between the study predictors and subsequent change in depression status.

Methods

Participants

Participants were enrolled in an ongoing U.S. national longitudinal survey study examining secondary health conditions in individuals aging with 1 of 4 physical disabilities (MS, spinal cord

injury, muscular dystrophy, postpolio syndrome). These data have been described elsewhere.³⁴⁻³⁶ This study is the first to address change in depression status among the MS disability group (N=489) in this dataset. Inclusion criteria required that participants be ≥ 18 years, able to read and write English, and self-report a physician's diagnosis of MS.

Procedures

Participants were recruited from multiple sources including a registry of adults involved in past research at the University of Washington (n=329), through web and print advertisements at national MS organizations (n=279), and by word of mouth (n=32). Individuals were screened over the phone by research staff; eligible participants were mailed a consent form with the first survey that they could return in a prepaid postage envelope. The first survey was mailed between June 2009 and March 2010 (baseline). Two more surveys were mailed over the next 2 years; however, these surveys did not contain any measures examined in the current study. The final survey was sent 3.5 years later between August 2012 and March 2013. Participants who did not return their surveys received reminder letters 4 weeks after each mailing and were called by staff if the survey was not received within 6 weeks of mailing. Missing data were collected over the phone by research staff, and a \$25 thank you payment was sent for each completed survey. All study procedures were approved by the Human Subjects Division at the University of Washington.

Measures

Demographic variables included self-report birth date, sex, race, marital status, and education level. Age was calculated from the reported birth date. Disease course was assessed via a self-report measure that provided pictorial representations of 4 MS disease courses (relapsing remitting, primary progressive, secondary progressive, progressive relapsing). Duration was calculated from the reported year of diagnosis. MS disability status and disease severity were measured using a self-report version of the Expanded Disability Status Scale (EDSS), shown to be highly correlated with standard physician-administered outcomes.³⁷⁻³⁹ The Patient Health Questionnaire-9 (PHQ-9) assessed depressive symptom severity, and a cutoff of 10 was used to assess probable major depression, which has 95% sensitivity and 86% specificity in identifying a *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* major depressive episode in individuals with MS.⁴⁰⁻⁴² The 3-item Godin Leisure-Time Exercise Questionnaire assessed physical activity, an 11-point numeric rating scale assessed average pain intensity, the 8-item Patient-Reported Outcomes Measurement Information System (PROMIS) Sleep Disturbance Short-Form (version 1) assessed level of sleep disturbance, and the PROMIS Fatigue Short-Form assessed severity of fatigue. All of these measures have demonstrated validity in MS populations.⁴³⁻⁴⁸ The internal consistencies (Cronbach α values) for the multi-item measures used in the study were .84 (PHQ-9), .93 (PROMIS Sleep Disturbance Short-Form), and .85 (PROMIS Fatigue Short-Form), indicating good to excellent reliability for these measures in the current sample.

Data analysis

For descriptive purposes, we computed means and percentages of the descriptive and MS disease variables. Assumptions testing for

List of abbreviations:

CBT	cognitive-behavioral therapy
EDSS	Expanded Disability Status Scale
MS	multiple sclerosis
PHQ-9	Patient Health Questionnaire-9
PROMIS	Patient-Reported Outcomes Measurement Information System

planned regression analyses included estimates of skew, kurtosis, and multicollinearity.⁴⁹

To test the effect of baseline predictors on change in being classified as having probable major depression, we formed 4 groups of participants, based on a PHQ-9 cutoff of ≥ 10 . These were (1) participants who did not meet the PHQ-9 cutoff (ie, score < 10) at both the baseline and final assessment (ie, no evidence of depression); (2) participants who were below the PHQ-9 cutoff at baseline but exceeded it at the final assessment (ie, they developed depression); (3) participants who exceeded the PHQ-9 cutoff for probable major depression at baseline but were below this cutoff at the final assessment (ie, their depression improved); and (4) participants who met the PHQ-9 cutoff at the baseline and final assessment (ie, they remained depressed at both assessments).

We then performed a series of 2 logistic regression analyses to test the study hypotheses. The first logistic regression looked at individuals who did not meet criteria for probable major depression at baseline, and tested which predictor variables could differentiate those who develop depression from those who did not show evidence of depression at the final assessment. The second logistic regression focused only on individuals who did meet criteria for probable major depression at baseline, and tested which predictor variables could differentiate those who remained depressed from those whose depression improved at the final assessment. To examine the extent to which the study factors and depression classification were moderated by age, we also included interaction terms in our analysis. Variables used in the interaction terms were centered. Control variables (entered in block 1) included age, sex, and disability level (EDSS). We then entered the study predictors (measures of pain intensity, fatigue, sleep quality, and physical activity) in block 2, and age moderation terms (age \times pain intensity, age \times fatigue, age \times sleep disturbance, and age \times physical activity) in block 3.

Results

Participant characteristics

The first survey was mailed to 640 eligible participants and completed by 584 (91.3%). Between the first and second survey, 12 participants withdrew from the study. The second survey was sent to 572 participants and returned by 511 (89.3%); 489 (85.4%) had complete data and were used for the current analyses. Demographic and MS descriptive information for the study sample can be found in table 1. The baseline prevalence of probable major depression within our sample, 26% (n=128), matches the prevalence of probable major depression in a nationally representative sample of Canadians with MS.⁵⁰ Among the total sample, from baseline to the final assessment, 15% (n=68) remained depressed, 13% (n=60) had depression that improved, 66% (n=335) did not meet the criteria for depression at either time point, and 6% (n=26) developed depression. Descriptive statistics of the individuals classified into each depression trajectory are presented in table 2.

Testing physical activity, pain, fatigue, and sleep quality as predictors of developing and improving depression

There was no evidence of significant skew, kurtosis, or outliers noted with any of the study variables. We also assessed

Table 1 Description of study sample

Measure	N	Mean \pm SD or %
Age (y)	489	54.27 \pm 10.43
Sex		
Male	87	18
Female	402	82
MS disease duration (y)	489	17.85 \pm 9.62
MS disease course		
Relapsing remitting	259	53
Primary progressive	79	16
Secondary progressive	109	22
Progressive relapsing	42	9
Education level*		
<High school	5	1
High school/Tech school	287	16
Some college	127	26
College graduate	163	33
Professional/Graduate school	115	24
Ethnicity/Race*		
Black/African American	12	2.5
Asian	13	0.2
White/Caucasian	458	93.7
Hispanic/Chicano	7	1.4
Native American/Alaska Native	1	0.2
More than 1 race	9	1.8
Other/Unknown	2	0.4
Annual household income* (\$)		
<25,000	91	19
25,000–55,000	120	25
56,000–85,000	82	17
>86,000	127	26
Marital status		
Married	317	65
Divorced/Separated	90	20
Living with significant other	25	5
Never married	26	5
Widowed	31	6

* Does not add to 489 because of missing data/no response.

multicollinearity across all predictor variables, and none of the correlation coefficients met the cutoff score of $r \geq .70$.⁴⁹ To control for multicollinearity within the interaction terms, all variables were centered before analyses were performed.

In the first model, we selected only individuals who did not meet criteria for probable major depression at baseline (ie, PHQ-9 < 10). We then predicted which of these individuals would go on to report probable major depression 3.5 years later. The results of these analyses are presented in table 3. The full model was statistically significant (χ^2_{11} [n=361]=149.75; $P < .001$) and accounted for an estimated 30% of the variance in the outcome (Cox & Snell $R^2 = .295$). Of the control variables, only age contributed significantly to the model, suggesting that younger age was associated with greater risk of probable major depression 3.5 years later (odds ratio=.95, Wald=7.1, $P = .008$). After controlling for age, sex, and disease course, both fatigue (odds ratio=.119, Wald=36.1, $P < .0001$) and sleep disturbance (odds ratio=.106, Wald=10.6, $P < .01$) predicted probable major depression 3.5 years later. Neither physical activity nor pain intensity was significantly associated with probable major

Table 2 Basic descriptive information for each depression status group

Depression Status Group	n or n (%)	Mean Age (y)	EDSS at Time 1	PHQ-9 Score at Time 1	PHQ-9 Score at Time 2
Group 1: Nondepressed at initial assessment	361	55.12	3.99±2.75	4.43±2.55	4.21±3.78
Nondepressed → Nondepressed	335 (66)	55.69	4.09±2.76	4.27±2.52	3.46±2.57
Nondepressed → Depressed	26 (6)	47.85	2.73±2.36	6.5±2.01	13.81±3.80
Group 2: Depressed at initial assessment	128	51.87	4.65±2.38	14.48±4.04	10.44±5.83
Depressed → Depressed	68 (15)	50.96	4.76±2.28	15.68±4.34	14.72±4.32
Depressed → Nondepressed	60 (13)	52.90	4.52±2.50	13.13±3.22	5.58±2.61

NOTE. Values are mean ± SD or as otherwise indicated.

depression 3.5 years later after adjusting for control variables and for the effects of fatigue and sleep disturbance. None of the interaction terms were significant, indicating that age did not moderate the associations between any of the study predictors and change in depression.

In the second model, we selected only individuals who met criteria for probable major depression at baseline. We then predicted which of these individuals would maintain, versus improve, in terms of probable major depression 3.5 years later. The results of the regression analyses are presented in table 4. The full model was not statistically significant (χ^2_{11} [n=128]=14.754, P =not significant) and accounted for an estimated 11% of the variance in the outcome (Cox & Snell R^2 =.109). Moreover, none of the predictors, nor their interaction with age, made a significant contribution to the prediction of depression (all P values >.11).

Discussion

The key findings from this study are that (1) in individuals with MS who were not depressed at the initial assessment, fatigue and sleep disturbance significantly predicted the development of depression 3.5 years later; and (2) in individuals who were depressed at the initial assessment, none of the study predictors predicted recovery from depression. Importantly, these findings took into account and controlled for differences in age, sex, and disease course. The findings provide only partial support for the study hypotheses, which stated that increased pain, fatigue, and

poor sleep along with physical inactivity would predict the development of depression, and that decreased pain and fatigue along with better sleep and physical activity would predict recovery from depression. These findings have important clinical and research implications.

Predicting development of depression

Our findings indicating that fatigue and sleep disturbance predict development of depression 3.5 years later are consistent with previous research^{21,25,51} showing concurrent associations among these variables. This study extends past research by using a longitudinal design, which provides stronger support for—but does not yet prove—a causal influence of fatigue and sleep disturbance on depression. It is also possible that fatigue and sleep are markers for other changes that contribute to depression, such as neurologic or immunologic changes. Future research examining not only psychosocial predictors but also immunologic and neurologic changes (eg, lesion volume in frontal and temporal regions, brain atrophy, cognitive impairment) is needed to understand the complex interplay among these systems.

Unexpectedly, neither pain nor physical activity level assessed at the initial assessment was a significant predictor of depression 3.5 years later in participants who were not initially depressed. These findings add to the controversy regarding whether pain and physical inactivity represent risk factors for development of depression,^{6,7,11,14,15} especially when examined in combination

Table 3 Results of binary regression analyses predicting development of depression for those who were not initially depressed

Step and Variable	β	SE	Wald	DF	P	Exp(B)	95% CI for Exp(B) Lower	95% CI for Exp(B) Upper
Step 1: Control variables								
Age	-.05	.02	7.06	1	.008	0.95	0.92	0.99
Sex	-.40	.41	0.95	1	.330	0.67	0.30	1.50
EDSS	-.06	.07	0.79	1	.374	0.94	0.83	1.07
Step 2: Predictors								
Physical activity	-.01	.01	0.70	1	.401	0.99	0.98	1.01
Pain intensity	.09	.07	1.70	1	.193	1.09	0.96	1.25
Sleep disturbance	.06	.01	10.57	1	.001	1.06	1.02	1.10
Fatigue	.17	.03	36.14	1	<.001	1.19	1.12	1.26
Step 3: Age interaction terms								
Age × Physical activity	.00	.00	0.01	1	.937	1.00	1.00	1.00
Age × Pain intensity	.00	.01	0.05	1	.822	1.00	0.99	1.02
Age × Sleep disturbance	.00	.00	0.08	1	.776	1.00	1.00	1.00
Age × Fatigue	.00	.00	0.05	1	.832	1.00	1.00	1.00

Abbreviations: CI, confidence interval; DF, degrees of freedom; Exp(B), exponentiation of B coefficient or odds ratio.

Table 4 Results of binary regression analyses predicting recovery from depression for those who were initially depressed

Predicting Improvement From Depression	β	SE	Wald	DF	<i>P</i>	Exp(B)	95% CI for Exp(B) Lower	95% CI for Exp(B) Upper
Step 1: Control variables								
Age	.02	0.04	0.16	1	.688	1.02	0.93	1.11
Sex	-.83	0.52	2.57	1	.109	0.43	0.16	1.21
EDSS	-.02	1.00	0.05	1	.832	0.98	0.81	1.18
Step 2: Predictors								
Physical activity	.00	0.01	0.01	1	.925	1.00	0.98	1.03
Pain intensity	.08	0.09	0.92	1	.339	1.09	0.92	1.28
Sleep disturbance	-.02	0.02	0.68	1	.411	0.98	0.94	1.03
Fatigue	-.05	0.04	1.53	1	.216	0.95	0.87	1.03
Step 3: Age interaction terms								
Age \times Physical activity	.00	0.00	0.28	1	.599	1.00	1.00	1.00
Age \times Pain intensity	.02	0.01	2.52	1	.112	1.02	1.00	1.04
Age \times Sleep disturbance	.00	0.00	0.86	1	.353	1.00	0.99	1.00
Age \times Fatigue	.00	0.00	0.12	1	.733	1.00	0.99	1.00

Abbreviations: CI, confidence interval; DF, degrees of freedom; Exp(B), exponentiation of B coefficient or odds ratio.

with other modifiable factors. The results of this study suggest that perhaps interventions that target symptoms such as fatigue^{52,53} and sleep disturbance^{54,55} may represent more promising approaches to preventing depression 3.5 years later than interventions that target pain or physical activity. The extent to which these relationships hold true for shorter periods is not known and in need of future research.

In other health conditions, a range of behavioral interventions are available to treat fatigue and sleep disturbances including cognitive-behavioral therapy (CBT), mindfulness meditation, and, in MS samples, fatigue self-management interventions.⁵⁶⁻⁵⁸ A meta-analysis⁵⁶ focused on the effects of internet-based CBT on comorbid anxiety and depression in the general population and found it successful in reducing sleep disturbances as well as depressive and anxiety symptoms. Another meta-analysis⁵⁸ examining differing interventions for fatigue in individuals with MS found that fatigue self-management and educational interventions were more successful in reducing fatigue severity than pharmacologic interventions (ie, medications). This suggests that CBT, mindfulness meditation, and fatigue management interventions may provide individuals with MS strategies for managing fatigue and sleep problems and, as supported by our findings, may also help prevent the development of future depression.

Predicting improvement from depression

Inconsistent with the study hypotheses, physical activity, pain, fatigue, or sleep disturbance at the initial assessment did not predict depression improvement among those with probable major depression at baseline. As summarized previously, prior cross-sectional research^{10,12,18,19,51} has found significant cross-sectional associations among pain, fatigue, sleep disturbance, and lack of activity and depression. However, the findings from this study suggest that while these factors may be related to depression, they do not necessarily predict prospectively who later improves from depression 3.5 years later. Therefore, it may be that these factors may not influence long-term improvement from depression, although it remains possible that they may play a role in predicting depression improvement using different (eg, shorter or longer) longitudinal time frames.

Nonmodifiable factors that might influence depression

With respect to the nonmodifiable factors examined here, we found a significant age effect among individuals who were classified as not depressed at the initial assessment. That is, among those who were not depressed at the initial assessment, younger individuals were more likely than older individuals to become depressed 3.5 years later.⁵⁹ This finding is consistent with some previous research,^{24,60,61} indicating that older individuals may have decreased emotional reactivity and better coping mechanisms than younger individuals. In any case, the findings suggest the possibility that younger individuals with MS may be particularly vulnerable to develop depression, and so might benefit from treatments, such as those mentioned above, to minimize the chances that they might later develop depression. Lastly, the current study explored the extent to which age might moderate the relationship between the study predictors and depression. The findings indicated that age was not a significant moderator, suggesting that the importance of the role of the modifiable factors examined in this study on depression does not vary as a function of age.

Study limitations

This study has several limitations that should be considered when interpreting the results. First, our study sample was primarily white (94%) and women (82%). While these demographic characteristics may be fairly representative of the population of individuals with MS as a whole, the extent to which these findings generalize to minorities or men with MS is not clear. Another limitation was the use of a mail survey (as opposed to in-person or telephone interviews) for data collection, which may have limited the participants' continued participation in this longitudinal study. This may have introduced additional selection bias into the study (eg, highly depressed individuals might have been less willing to participate). Again, replication of the study in additional populations with higher levels of baseline depression would help determine the reliability and generalizability of our findings. Third, the measure of activity level used in the study, the Godin Leisure-Time Exercise Questionnaire, may have limited validity as a measure of exertion

in individuals with high levels of physical disability. For example, individuals with an EDSS score ≥ 4 report having difficulty walking three tenths of a mile or less without stopping to rest. However, the Godin classifies “easy cycling and swimming” as moderate exercises that are “not exhaustive”; for those who have difficulty walking, such activities may require more intense and exhaustive effort. As a result, strenuous exercise for people who are more disabled may be achieved through activities that might be considered mild or moderate for individuals who are less disabled. Further research should explore other physical activity measures that may represent more valid assessments of true physical exertion in populations such as those studied here. These might include, for example, an assessment of the actual exertion associated with different activities for individual participants (eg, by assessing heart rate during the activity), and classifying exercise as mild, moderate, or strenuous based on such a tailored approach. Finally, our method of depression classification and assessment timing may not reflect a meaningful change in clinical depression. We used scores above and below valid PHQ-9 cut-points as an indication of change in depression rather than basing the classification on a criterion standard diagnostic assessment such as the Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*.⁶² We assessed participants only twice in a 3.5-year period when the median length of a depressive episode is only 20 weeks.⁶³ Future research should use diagnostic interviews and assess participants more frequently to gain a better sense of true change in clinical depression status over time.

Conclusions

We identified fatigue and sleep quality (but not pain or activity level) as factors that may contribute to the development of depression among individuals with MS who were not depressed at the initial assessment. None of these factors were significantly associated with recovery from depression among those who were depressed at the initial assessment. Although there are many factors that could potentially affect the development of depression over time, our findings indicate that further research is needed to evaluate the potential causal impact of fatigue and sleep problems on the development of subsequent depression or as potential markers of depression incidence. Research is also needed to identify other modifiable factors not examined here and further explore them as causal agents in true experiments and clinical trials. Importantly, the findings also indicate that the factors that may contribute to the development of depression 3.5 years later may not be the same as those that contribute to the recovery from depression. Therefore, further investigation of these findings should be pursued in order to be better able to improve the quality of life among those living with MS.

Keywords

Chronic pain; Depression; Fatigue; Multiple sclerosis; Rehabilitation; Sleep

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