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Predictors of Fatigue Impact in Persons with Longstanding Multiple Sclerosis

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Abstract

Background—Fatigue is a common experience among persons diagnosed with multiple sclerosis (MS). Fatigue negatively influences quality of life, interferes with activities of daily living, and impairs the ability to maintain gainful employment (Amato et al., 2001; Julian, Vella, Vollmer, Hadjimichael, & Mohr, 2008; Smith & Arnett, 2005). Mechanisms underlying the pathophysiologic determinants of fatigue in MS are poorly understood and effective treatments to manage fatigue present a challenge (Krupp, Christodoulou, & Serafin, 2010). While the use of pharmacologic therapies (e.g., Modafinil) is recommended to treat symptomatic fatigue, under-treatment of fatigue is common (Hatzakis et al., 2005; Brichetto, Messmer, Mancarki & Solaro, 2003). Better long-term management and symptomatic relief may be provided by the use of non-pharmacologic treatments such as increased physical activity, energy conservation, and cognitive behavioral therapy (Motl, McAuley & Snook, 2005; van Kessel et al., 2008; McCullagh, Fitzgerald, Murphy, & Cooke, 2008).

Methods—The purpose of this study was to explore the physical, cognitive and psychosocial dimensions of fatigue impact among persons with longstanding MS - defined here as having been diagnosed with MS for 17 years or more. A sample of 331 participants with MS completed surveys measuring fatigue impact, MS-related functional limitation, depressive symptoms, barriers to health promotion, personal resources, and health promoting behaviors.

Results—MS-related functional limitation and depressive symptoms were the strongest predictors of fatigue impact. MS-related functional limitation explained the greatest amount of variance in models predicting physical and psychosocial fatigue impact while depressive symptoms explained the most variance in models predicting total and cognitive fatigue impact. Barriers to health promotion explained the least amount of variance among the models. Personal resources and health promoting behaviors were not significant predictors of fatigue impact in this study.

Conclusion—Interventions aimed at reducing MS-related functional limitations, depressive symptoms, and barriers to health promotion may have beneficial influences on fatigue impact

while actions designed to promote personal resource adequacy as well as engagement in health promoting behaviors may not translate into improvements in fatigue impact in persons with MS.

Background

MS is the most common neurological disease of young adults affecting 2.3 million persons worldwide and approximately 140 per 100,000 in North America (Multiple Sclerosis International Federation, 2013). Fatigue related to MS is the most frequently reported and arguably among the most disabling symptoms of the disease. The majority of persons with MS experience significant fatigue on a daily basis (Fisk, Pontefract, Ritvo, Archibald, & Murray, 1994). In a nationally representative sample of over 4000 individuals with MS, more respondents cited fatigue (83%) as a current symptom than difficulties with ambulation (67%), spasticity (63%) or cognitive problems (56%) (Minden et al., 2006). Fatigue negatively impacts social, emotional, cognitive and physical functioning in those with MS and is related to lower health-related quality of life and unemployment (Krupp, 2003). Despite MS-related fatigue being so prevalent, its pathophysiology is not well understood and therapeutic regimens lack robust effects (Kluger, Krupp, & Enoka, 2013).

While fatigue is a ubiquitous human experience, MS-related fatigue is a uniquely complex, multi-factorial phenomenon that for the purposes of this paper is defined as, “a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities” (Multiple Sclerosis Council for Clinical Practice Guidelines, 1998). Appraisal of fatigue in MS presents unique challenges as fatigue is hypothesized to be derived from primary sources directly related to MS pathology (e.g., lesions in the central nervous system, hypothalamus-pituitary-adrenal axis dysfunction) as well as secondary sources related to coexisting features of MS such as depression and physical deconditioning (Induruwa, Constantinescu, & Gran, 2012; Krupp et al., 2010). Strategies to assess fatigue include both self-report and performance-based measures. Self-report measures such as the Modified Fatigue Impact Scale (Fisk, Ritvo, et al., 1994), aim to capture perceptions of fatigue impact on a variety of daily activities, while others, like the Fatigue Severity Scale (Krupp, LaRocca, Muir-Nash, & Steinberg, 1989), depict fatigue intensity (Krupp & Christodoulou, 2001).

While much has been reported on the experience of fatigue in persons with MS, scant attention has been focused on individuals living with the disease for extended periods of time. The current study examined individuals who have all been diagnosed with MS for over 17 years. The study sample has a mean disease duration of 26.5 years $\pm$ 6.5. The authors define this phenomenon as longstanding MS. Little is known of factors that covary with and, therefore, may be predictive of fatigue among persons with longstanding MS. A better understanding of factors predictive of fatigue in persons with longstanding MS can inform intervention studies designed to reduce the impact of fatigue in persons living with MS. The aims of this study were to (a) evaluate the impact of fatigue among persons with longstanding MS; (b) assess relationships among dimensions of fatigue impact and age, disease duration, MS-related functional limitation, depressive symptoms, barriers to health promotion, personal resources, and health promoting behaviors; as well as (c) to evaluate the

amount of variance explained by those variables significantly ($p < .05$) related to fatigue impact.

Purpose

Dimensions of fatigue impact – total, physical, cognitive, and psychosocial - among persons with longstanding MS are the focus of this paper. The purpose of this study was to investigate relationships among self-reported ratings of fatigue impact, age, MS duration, MS-related functional limitations, personal resources, depressive symptoms, health promoting behaviors and barriers to health promotion. Two research questions were addressed using Pearson's correlations and multiple regression analyses:

1. What relationships exist among measures of fatigue impact, age, MS duration, MS-related functional limitations, personal resources, depressive symptoms, health promoting behaviors and barriers to health promotion in this sample of persons with longstanding MS?
2. What amount of variance in fatigue impact, measured by the Modified Fatigue Impact Scale, can be explained by significantly related variables among persons with longstanding MS?

Methods

Participants and Procedures

For the current study, data were derived from the 17th year of a longitudinal survey study of persons with MS residing in the community. In 1999, after approval from the university's institutional review board respondents from a 1991 cross-sectional study who expressed interest in continuing to participate in a longitudinal descriptive study were consented. The original study was recruited through selected chapters of the National MS Society and announcements in several rural southwestern newspapers (Stuijbergen & Roberts, 1997). Participants in the longitudinal study are mailed a survey each year through the U.S. Postal Service that contains selected self-report measures of health promoting behaviors, MS-related functional limitations, barriers to health promotion, personal resources, depressive symptoms and quality of life. A measure of fatigue impact was included in the 2013 survey. The current analysis examined responses to selected variables for the 331 individuals responding to the 2013 survey.

The sample for this study is well educated (75% have 12+ years of formal education), married or living with a significant other (68%), and mostly female (87%). These demographic characteristics are common among MS studies. Participants ranged in age from 35 to 89 years with an average of 62.9 years $\pm$ 9.3. Average MS duration was 26.5 years $\pm$ 6.5. Responses to questions about employment indicate that 30% were unemployed due to disability and 38% were retired, while 16% were employed either full or part-time. (See Table 1)

Measures

Demographic data—Background demographic characteristics were collected in the third and seventh years of the longitudinal study regarding age, gender, year diagnosed with MS, race, ethnicity, and education. Employment and marital status data are reported from the current 2013 survey.

Fatigue—The Modified Fatigue Impact Scale (MFIS) is a 21-item form of the Fatigue Impact Scale (Fisk, Ritvo, et al., 1994) derived from interviews with 105 MS patients by the Consortium of MS Centers Health Services Research Subcommittee (1997). The MFIS assesses the impact of fatigue on the lives of persons with MS over the previous four weeks yielding a total (21-item) score and three subscale scores: physical (9 items), cognitive (10 items) and psychosocial (2 items). Responses use a 5-point scale from 0 (never) to 4 (almost always) with higher scores reflecting greater impairment attributed to fatigue. Total scale scores range from 0 to 84. Internal consistency reliability for total and subscale scores range from 0.85 to 0.97 in this sample.

MS Functional Limitation—Kurtzke's Incapacity Status Scale (MS-ISS) was used to assess functional limitation related to MS in this study (Kurtzke, 1981). The MS-ISS was developed for individuals with MS and validated by the International Federation of Multiple Sclerosis Societies (Wingerchuk, Noseworthy, & Weishenker, 1997) and subsequently adapted for use as a self-report survey by Stuijbergen and Roberts (1997). The MS-ISS is a 16-item inventory of functional limitations for role performance and activities of daily living that uses a 5-point scale to rate sixteen domains of personal functioning (e.g., ambulation, self-care, and sensory function). A response of 0 indicates no impairment in function and a response of 4 reflects pronounced or total inability to perform the function. Total scale scores range from 0 to 64 with higher scores reflecting greater functional limitation. Cronbach's alpha reliability for the MS-ISS in this sample was 0.87.

Depressive Symptoms—The Center for Epidemiologic Studies Depression Scale (CES-D) 10-item short form was used to measure depressive symptoms (Radloff, 1977). The CES-D, which was not developed for use as a diagnostic tool, has been used extensively in epidemiologic studies of healthy and diseased populations. Validity and reliability properties of the CES-D have been established among numerous underserved populations including persons with MS (Verdier-Taillefer, Gourlet, Fuhrer, & Alperovitch, 2001). The short 10-item form of the CES-D has been supported for screening purposes in persons with MS (Kim et al., 2012). The short-form CES-D uses a 5-point scale from 1 (never) to 4 (routinely) to assess depressive symptoms. Total scores range from 10 to 40 with higher scores indicating more depressive symptoms. A cut-point of 16 is considered indicative of significant depressive symptomology (Graziano, Calandri, Borghi, & Bonino, 2014). Internal consistency reliability for the 10-item CES-D was 0.86 in this sample.

Barriers—The Barriers to Health Promoting Activities for Disabled Persons Scale was developed by Becker, Stuijbergen, & Sands (1991) to assess how often specific barriers keep respondents from attending to their health. The 18-item scale incorporates interpersonal, intrapersonal and environmental barriers (e.g., concern about safety, lack of money).

Responses are scaled from 1 (never) to 4 (routinely). Higher scores indicate greater perceived barriers. Internal consistency reliability for this sample was 0.89.

Personal Resources—The Personal Resource Questionnaire (PRQ-85 Part 2) (Weinert & Brandt, 1987) was used to measure perceived social support among the respondents. The PRQ includes 25 items that are rated from 1 (strongly disagree) to 7 (strongly agree). Higher scores indicate greater perceived support. Content, construct, and criterion-related validity have been supported in the literature (Weinert & Brandt, 1987). Internal consistency reliability for this sample was 0.93.

Health Promoting Behaviors—The Health Promoting Lifestyle Profile II (HPLP II) was used to assess health-promoting behaviors among the respondents (Walker, Sechrist, & Pender, 1987). The HPLP II is a 52-item scale that assesses engagement in activities that support health and well being. Responses measure frequency of health promoting behaviors on a 4-point scale (never, sometimes, often, or routinely) with higher scores indicating more frequent practice of health behaviors. Reliability and validity of the HPLP II have been supported in psychometric testing in a large sample of adults (Walker & Hill-Polrecky, 1996). Stuijbergen (1995) demonstrated the use of the HPLP II as a valid measure of health behavior in individuals with chronic disabling conditions including MS. Internal consistency reliability for the HPLP II total score in this sample was 0.95.

Data Analysis

Statistical analyses were performed using Statistical Package for Social Science (SPSS), version 20.0.0 after being proofed for accuracy by research staff (IBM Corp., Armonk, NY). Participants with missing data were excluded from the correlation analysis using pairwise deletion whereas listwise deletion was used for the regression analyses. Participant characteristics were summarized using descriptive statistics including frequencies, means, and standard deviations. Pearson product-moment correlations were conducted between age, disease duration, fatigue impact (total, physical, cognitive, and psychosocial), MS-related functional limitation, depressive symptoms, barriers, personal resources, and health promoting behaviors. Four separate standard multiple regression analyses were conducted to predict fatigue impact as conceptualized and operationalized by the MFIS (total, physical, cognitive, and psychosocial fatigue impact). In each analysis, the predictor variables significantly correlated to fatigue (MS-related functional limitation, depressive symptoms, barriers, personal resources, and health promoting behaviors) were entered in one step.

Results

Descriptive statistics (means, standard deviations, and percentiles) were computed for this sample of 331 individuals with longstanding MS (See Table 2). Internal consistency reliability for each of the summated scales exceeded 0.85.

Pearson's bivariate correlations denoted that age and MS duration were not significantly ($p > .05$) related to fatigue impact (See Table 3). Moderate to strong positive, linear relationships existed among the fatigue impact measures and MS functional limitation (range: $r = .41$ to $r = .58$, $p < .01$), depressive symptoms (range: $r = .58$ to $r = .63$, $p < .01$)

and barriers (range: $r = .55$ to $r = .63$, $p < .01$). Moderate inverse linear relationships existed among the fatigue impact measures and personal resources (range: $r = -.40$ to $r = -.50$, $p < .01$) and health promoting behaviors (range: $r = -.34$ to $r = -.44$, $p < .01$).

Separate multiple linear regression analyses were performed to predict variation in total, physical, cognitive and psychosocial fatigue impact. Variables significantly related to fatigue impact were entered simultaneously: MS functional limitation, depressive symptoms, barriers to health promotion, personal resources, and health promoting behaviors. Results showed that all variables in the model, when considered together, explained 54.9% of the variance in total fatigue impact, 52.0% of the variance in physical fatigue impact, 51.7% of the variance in psychosocial fatigue impact and 41.8% of the variance in cognitive fatigue impact scores (See Table 4). MS functional limitation (MS-ISS) was the strongest predictor in the models for physical fatigue impact ($\beta = .368$, $p < .01$) and psychosocial fatigue impact ($\beta = .308$, $p < .01$) while depressive symptoms (CES-D) was the strongest predictor in the models for total fatigue impact ($\beta = .368$, $p < .01$), and cognitive fatigue impact ($\beta = .360$, $p < .01$). Personal resources and health promoting behaviors were not significant predictors of variation for any of the fatigue impact variables.

Discussion

This study was designed to explore relationships among dimensions of fatigue impact in persons with longstanding MS and measures of age, MS duration, MS functional limitation, personal resources, depressive symptoms, barriers to health promoting activities, and health promoting behaviors. Age and MS duration were found to be linearly unrelated to fatigue in this sample. Similarly, Flachenecker et al. (2002) reported that age and disease duration were not related to fatigue measured using either the Modified MS Fatigue Impact Scale (Fisk, Ritvo, et al., 1994) or the Fatigue Severity Scale (Krupp, LaRocca, Muir-Nash, & Steinberg, 1989) in a much younger sample of persons with MS (mean age = 39.0 years $\pm$ 9.3) with shorter disease duration (9.9 years $\pm$ 6.7) than the current sample of persons with longstanding MS. This suggests that fatigue may be experienced throughout the disease course irrespective of age or duration of illness.

The models best predicting each of the four dimensions of fatigue impact in the current study included MS-related functional limitation, depressive symptoms, and barriers to health promoting activities. MS functional limitation was found to be the strongest predictor of physical and psychosocial fatigue impact while depressive symptoms was the strongest predictor of total and cognitive fatigue impact in this sample of persons with longstanding MS. Kroencke, Lynch, and Denney (2000) reported that depressed mood and MS disability were significant predictors of fatigue using different instruments (Self-Rating Depression Scale, Expanded Disability Status Scale, and Fatigue Severity Scale) in a younger (mean age = 45.0 + 11.5) sample with shorter duration (8.7 years + 8.2) of MS (Zung, 1965; Kurtzke, 1983; Krupp et al., 1989). These results uphold the importance of nurses assessing and monitoring depressive symptoms, functional status as well as dimensions of fatigue at each opportunity.

Barriers to health promoting activities was the weakest predictor of total, physical and psychosocial fatigue impact while functional impairment was the weakest predictor of cognitive fatigue impact. This variation in the relationships between predictors and dimensions of fatigue impact may elucidate modifiable factors for nurses to target in interventions to manage fatigue. Conceptually, it makes sense that MS functional incapacity is predictive of physical and psychosocial fatigue impact. Similarly, it is plausible that depressive symptoms predict cognitive as well as total fatigue impact.

These findings suggest that MS functional impairment, depressive symptoms, and barriers to health promoting activities are associated with fatigue impact in individuals with longstanding MS. While a positive relationship between functional impairments (e.g. mobility, cognitive) and fatigue in MS has been described in a number of studies including a large (n= 9077) North American registry sample; the mechanisms of the relationship have yet to be explicated (Bol, Duits, Hupperts, Vlaeyen, & Verhey, 2009; Hadjimichael, Vollmer, and Oleen-Burkey, 2008, Kos, Kerckhofs, Nagels, D'hooghe, & Ilsbroukx, 2008). Significant associations between depression and fatigue in persons with MS have also been reported (Bol et al., 2009; Kroencke et al., 2000). The relationship between fatigue and depression is quite complex, has numerous symptoms in common (e.g., sleep disturbances, low motivation), with causality yet to be explained (Kos et al., 2008). Becker and Stuifbergen (2004) described fatigue and impairment as the most commonly cited barriers to health promoting activities among a sample of persons with MS. Future intervention studies designed to improve management of fatigue should include content related to identification and management of depressive symptoms as well as strategies to address barriers to health promoting activities.

Limitations of this study include a lack of demographic diversity in this predominantly well-educated, white, married, female sample with longstanding MS. The cross-sectional design and correlational analyses prohibit attributing causal means to the findings. In addition, participants are “survivors” in a 17-year longitudinal study and may differ in unknown ways from other groups of persons with longstanding MS. To our knowledge, this is the first study published on fatigue impact where the entire sample is known to have longstanding MS (MS diagnosis for more than 17 years).

MS functional impairment, depressive symptoms, and barriers to health promoting activities may be significant sources of fatigue among persons with longstanding MS. Functional impairment related to pathophysiologic changes in the central nervous system (inflammation and axonal loss) may underlie fatigue in MS but the exact mechanisms are unclear (Kos et al., 2008; Krupp et al., 2010). Assessment and treatment of depression has potential to lessen the impact of fatigue in persons with MS (Krupp, 2003). Additional research is needed to explore if interventions to enhance management of depressive symptoms and barriers to health promoting activities would result in lower fatigue impact in persons with longstanding MS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1
Participant Demographic Characteristics (N = 331)

<i>Variable</i>	M	SD	Range
Age	62.9	9.3	35-89
Disease Duration (years)	26.5	6.5	17-56
	n	%	
Gender			
Female	288	87	
Male	43	13	
Marital Status			
Married or living with Significant Other	226	68	
Ethnicity/Race			
Non-Hispanic White	298	90	
Years of Education			
12 or less	82	25	
13 to 16	186	56	
More than 16	63	19	
Employment			
Working (Full or Part-Time)	52	16	
Unemployed Due to Disability	98	30	
Retired	127	38	

Table 2
Descriptive Statistics for Persons with Longstanding MS (N=330)

	Mean	SD	Range
MS-ISS (16-items)	18.2	10.0	1-50
CES-D (10-items)	9.2	6.3	0-28
Barriers Scale (18-items)	29.6	8.7	18-60
PRQ (25-items)	141.6	23.4	48-175
HPLP II (52-items)	145.2	24.7	76-204
MFIS total scale (21-items)	37.6	20.9	0-84
MFIS physical subscale (9-items)	19.4	9.5	0-36
MFIS cognitive subscale (10-items)	14.7	10.8	0-40
MFIS psychosocial subscale (2-items)	3.5	2.4	0-8

Note: MS-Incapacity Status Scale (MS-ISS); Center for Epidemiologic Studies Depression Scale (CES-D); Barriers To Health Promoting Activities For Disabled Persons Scale (Barriers); Personal Resource Questionnaire (PRQ); Health Promoting Lifestyle Profile II (HPLP II); Modified Fatigue Impact Scale (MFIS)

Table 3
Correlations Among Personal Characteristics, Disease Related Variables, and Fatigue

Measure	1	2	3	4	5	6	7	8	9	10	11
1. Age	—										
2. MS Duration	.40**	—									
3. MS-ISS	.06	.14*	—								
4. CES-D	-.17**	-.06	.36**	—							
5. Barriers	-.15**	.01	.51**	.63**	—						
6. PRQ	.06	.02	-.35**	-.58**	-.56**	—					
7. HPLP-II	.07	.02	-.37**	-.50**	-.43**	.69**	—				
8. MFIS Total	-.04	.05	.55**	.63**	.63**	-.46**	-.39**	—			
9. MFIS Physical	.00	.06	.58**	.58**	.60**	-.43**	-.36**	.93**	—		
10. MFIS Cognitive	-.08	.03	.41**	.58**	.55**	-.40**	-.34**	.92**	.71**	—	
11. MFIS Psychosocial	-.02	.09	.56**	.58**	.60**	-.50**	-.44**	.85**	.85**	.67**	—

* $p < .05$.

** $p < .01$.

Note: MS-Incapacity Status Scale (MS-ISS); Center for Epidemiologic Studies Depression Scale (CES-D); Barriers To Health Promoting Activities For Disabled Persons Scale (Barriers); Personal Resource Questionnaire (PRQ); Health Promoting Lifestyle Profile II (HPLP II); Modified Fatigue Impact Scale (MFIS)

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Table 4

MFIS Total Regression Analysis

	<i>B</i>	<i>SE B</i>	β	<i>t</i>	<i>p</i>	<i>R</i> ²
(Constant)	-1.49	8.73		-.17	.86	
MS-ISS	.60	.10	.28	6.29	.00	
CES-D	1.23	.17	.37	7.08	.00	
Barriers	.60	.13	.25	4.56	.00	
PRQ	-.03	.05	-.03	-.48	.63	
HPLP II	.02	.05	.02	.42	.68	.55

Note: Modified Fatigue Impact Scale (MFIS); MS-Incapacity Status Scale (MS-ISS); Center for Epidemiologic Studies Depression Scale (CES-D); Barriers To Health Promoting Activities For Disabled Persons Scale (Barriers); Personal Resource Questionnaire (PRQ); Health Promoting Lifestyle Profile II (HPLP II)

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Table 5

MFIS Physical Regression Analysis

	<i>B</i>	<i>SE B</i>	β	<i>t</i>	<i>p</i>	<i>R</i> ²
(Constant)	.12	4.11		.029	.98	
MS-ISS	.35	.04	.37	7.90	.00	
CES-D	.51	.08	.33	6.19	.00	
Barriers	.22	.06	.21	3.65	.00	
PRQ	-.01	.02	-.01	-.24	.81	
HPLP II	.02	.02	.04	.77	.44	.52

Note: Modified Fatigue Impact Scale (MFIS); MS-Incapacity Status Scale (MS-ISS); Center for Epidemiologic Studies Depression Scale (CES-D); Barriers To Health Promoting Activities For Disabled Persons Scale (Barriers); Personal Resource Questionnaire (PRQ); Health Promoting Lifestyle Profile II (HPLP II)

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Table 6

MFIS Cognitive Regression Analysis

	<i>B</i>	<i>SE B</i>	β	<i>t</i>	<i>p</i>	<i>R</i> ²
(Constant)	-2.9	5.1		-.57	.57	
MS-ISS	.17	.06	.16	3.08	.00	
CES-D	.62	.10	.36	6.11	.00	
Barriers	.31	.08	.25	4.06	.00	
PRQ	-.01	.03	-.02	-.36	.72	
HPLP II	.01	.03	.02	.28	.78	.42

Note: Modified Fatigue Impact Scale (MFIS); MS-Incapacity Status Scale (MS-ISS); Center for Epidemiologic Studies Depression Scale (CES-D); Barriers To Health Promoting Activities For Disabled Persons Scale (Barriers); Personal Resource Questionnaire (PRQ); Health Promoting Lifestyle Profile II (HPLP II)

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Table 7

MFIS Psychosocial Regression Analysis

	<i>B</i>	<i>SE B</i>	<i>β</i>	<i>t</i>	<i>p</i>	<i>R</i> ²
(Constant)	1.43	1.03		1.39	.17	
MS-ISS	.07	.01	.31	6.64	.00	
CES-D	.10	.02	.26	4.88	.00	
Barriers	.06	.02	.21	3.80	.00	
PRQ	-.01	.01	-.10	-1.72	.09	
HPLP II	-.00	.01	-.03	-.53	.60	.52

Note: Modified Fatigue Impact Scale (MFIS); MS-Incapacity Status Scale (MS-ISS); Center for Epidemiologic Studies Depression Scale (CES-D); Barriers To Health Promoting Activities For Disabled Persons Scale (Barriers); Personal Resource Questionnaire (PRQ); Health Promoting Lifestyle Profile II (HPLP II)