Characterizing Fatigue by Multiple Sclerosis Subtype and Determining Validity of a Fatigue Scale Specific to Persons With Progressive Multiple Sclerosis

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ABSTRACT

BACKGROUND: Fatigue is a common and debilitating symptom of multiple sclerosis (MS). Prior work suggests that the prevalence of fatigue is higher in progressive MS (PMS) than relapsing MS (RRMS). No patient-reported outcomes of fatigue have been validated specifically for individuals with PMS, despite evidence that they characterize fatigue differently than individuals with RRMS. Therefore, the objective of this study was to characterize fatigue in both the RRMS and PMS subtypes and determine the convergent validity of the Fatigue Symptoms and Impacts Questionnaire (FSIQ) for individuals with PMS.

METHODS: A nationwide survey yielded 806 (637 RRMS, 169 PMS) complete responses. The survey collected demographic information and self-reported disease severity, as well as measures of fatigue, health-related quality of life, and self-reported functioning.

RESULTS: People with PMS reported significantly more severe fatigue than those with RRMS ($P < .001$). The FSIQ subdomains of physical, cognitive/emotional, and coping demonstrated moderate ($r = 0.5$-0.75) to excellent ($r > 0.75$) validity ($P < .001$) with other measures of fatigue.

CONCLUSIONS: More severe fatigue in people with PMS as compared to those with RRMS underscores the importance of using validated tools to capture fatigue in persons with PMS. The FSIQ is a valid and freely available tool to capture the physical, mental, and emotional fatigue of individuals with PMS.

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One of the most common symptoms in multiple sclerosis (MS) is fatigue, with up to 92% of individuals reporting fatigue[1] that manifests as lack of energy, exhaustion, or worsening of MS symptoms and ultimately contributes to increasing disability.[2] Fatigue is common in both the relapsing and progressive phenotypes of MS. Due to the higher prevalence of relapsing-remitting MS (RRMS), the majority of fatigue research has focused on this phenotype. However, it has been recently suggested that fatigue may be more prevalent in progressive forms of the disease (PMS).[3] Currently, there are very few measures of fatigue for patients with PMS. A recent systematic review[4] recommended the following fatigue measures for individuals with MS based on available psychometrics: Fatigue Impact Scale, Fatigue Severity Scale (FSS), Modified Fatigue Impact Scale (MFIS), Neurological Fatigue Index-MS, and Unidimensional Fatigue Impact Scale. However, none of the studies included in the review exclusively examined the psychometrics in PMS; all had mixed samples with more individuals with relapsing than progressive phenotypes. Thus, the psychometric properties of the recommended and most widely used fatigue measurement scales for people with PMS are largely unknown.

Recent work has developed and examined psychometrics of a fatigue scale specifically for persons with RRMS, the Fatigue Symptoms and Impacts Questionnaire (FSIQ).[5] FSIQ development included interviews with individuals with MS to determine fatigue-related symptoms and impacts and cognitive interviews with additional people with RRMS using a draft questionnaire. Next, content confirmation interviews with people with PMS were conducted, followed by item reduction, which resulted in 7 symptom items and 13 impact items. Critically, this comprehensive measure includes physical, mental, and emotional subscales, while many existing measures fail to capture all 3 domains. In a recent qualitative study, individuals with PMS identified physical and mental concepts of fatigue separately and characterized fatigue as occurring daily with negative impacts on quality of life.[6] Concept mapping to existing patient-reported outcome measures supported the FSIQ as

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the most suitable exiting option for assessing fatigue in persons with PMS.[6] The validity and minimal detectable change of this measure and its physical, mental, and emotional subscales in individuals with progressive disease are not known. Further, convergent validity of the FSIQ with other commonly used measures of fatigue (eg, FSS or MFIS) or with common clinical symptoms (ie, depression, anxiety) has not been established for individuals with either RRMS or PMS. Valid measures of fatigue for people with RRMS and people with PMS are critically needed to monitor change over time and with intervention.

Therefore, the objectives of this study were to characterize fatigue in both the RRMS and PMS subtypes and to determine the convergent validity of the FSIQ for people with PMS compared with those with RRMS. Furthermore, we examined the relations between fatigue and other self-reported symptoms (eg, depression, sleep, anxiety, pain, stress, physical activity, cognition, and quality of life) in people with RRMS and PMS.

METHODS

Design and Recruitment

All data were collected and managed using an online survey designed in Research Electronic Data Capture (REDCap). REDCap is a secure, Health Insurance Portability and Accountability Act–compliant, web-based software platform designed to support data capture for research studies hosted at Wayne State University[7,8] and available via a link distributed through the National Multiple Sclerosis Society electronic newsletter. Participants anonymously responded to the survey and did not report identifying or personal health information. Participants were included if they endorsed a diagnosis of RRMS or PMS, were age 18 years or older, and were able to read and write in English. Participants were excluded if they were unable to complete or consent to the survey. All study procedures were approved by the Wayne State University Institutional Review Board. The survey collected demographic information and self-reported disease severity with the Patient-Determined Disease Steps (PDDS) scale, as well as measures of fatigue, health-related quality of life, and self-reported functioning.

Measures of Fatigue

Fatigue was assessed with a battery of self-report questionnaires; in all cases, higher scores indicate greater fatigue.

The FSIQ assesses fatigue-related symptoms, as well as fatigue-related impacts, in physical, cognitive, emotional, and coping domains. The FSIQ has established validity for RRMS.[5]

The FSS is a 9-item scale measuring severity of physical fatigue and its impact on activity and lifestyle. The FSS has moderate test-retest reliability and excellent convergent validity with self-reported walking function on the MS Walking Scale-12 (MSWS-12).[9]

The MFIS is a 21-item scale with physical, cognitive, and psychosocial subscores.[10] The MFIS has excellent test-retest reliability[8] and excellent concurrent validity with the FSS.[11,12]

The Patient-Reported Outcomes Measurement Information System (PROMIS) Fatigue-MS is an 8-question scale examining fatigue frequency and interference with physical functioning in people with MS.[13] The PROMIS Fatigue-MS has excellent test-retest reliability in MS.[14]

The Quality of Life in Neurological Disorders (Neuro-QOL) Fatigue is an 8-item standardized measure of fatigue with established reliability in people with neurologic conditions.[15]

Health-Related Quality of Life

The MS Quality of Life 54 (MSQOL-54) is a 54-item multidimensional health-related quality-of-life measure that combines generic items from the Short Form Health Survey and MS-specific items for scores in both physical and mental health dimensions, with higher scores indicating better quality of life. The MSQOL-54 has established reliability and validity in MS.[16]

Self-Reported Functioning

Self-reported functioning in domains other than fatigue and quality of life was assessed with valid and reliable measures including PROMIS Depression 8a[17]; PROMIS Sleep Disturbance 8a[17]; PROMIS Anxiety 8a[17]; PROMIS Cognitive Function 8a[18]; PROMIS Physical Function 8b[17]; PROMIS Pain Interference 4a and Pain Intensity 3a[17]; National Institutes of Health (NIH) Toolbox Item Bank – Perceived Stress[19]; Godin Leisure-Time Exercise Questionnaire[20,21]; and MSWS-12.[22] *T* scores were used for analyses for all PROMIS and NIH measures. MSWS-12 scores were converted to a 0 to 100 scale.

Statistical Analyses

Data analyses were performed using IBM SPSS Statistics version 28.0.1. Responses were screened for inclusion criteria and analyzed for total and individual MS subtypes. In all analyses, individuals who endorsed having primary progressive MS or secondary progressive MS were combined into a single PMS group. Mann-Whitney *U* tests were used to examine differences in fatigue among people with RRMS and PMS. Spearman correlation was used to assess the convergent validity of the FSIQ with other measures of fatigue in both RRMS and PMS phenotypes. Spearman correlation was also used to assess the divergent validity of the FSIQ with other measures of MS symptoms, including pain, mobility, mood, and quality of life. Correlation coefficients of less than 0.25 were interpreted as little or no relation, greater than or equal to 0.25 to less than or equal to 0.5 as a fair relation, greater than or equal to 0.5 to less than or equal to 0.75 as a moderate to good relation, and greater than or equal to 0.75 as a good to excellent relation.[23] A priori, we set a threshold at r greater than or equal to 0.50 for reporting results.

RESULTS

Of the 1224 responses received, 806 (65.8%) participants consented and completed full demographic information. Of these, 637 (79.0%) self-reported as having RRMS, and 169 (21.0%) self-reported as having a progressive form of MS (109 [13.5%] secondary progressive MS; 60 [7.4%] primary progressive MS). A majority of participants were female (83%) and White (85.2%), with an average age of 50.5 years and a symptom duration of 3.6 years (**TABLE S1**). Participants who reported PMS were, on average, older with a longer average symptom

TABLE 1. Convergent Validity of the FSIQ Domains With Other Measures of Fatigue

FSIQ Physical		
	RRMS	Progressive MS
FSS	.765, <.001[a] (.734-.793)	.630, <.001[b] (.458-.744)
MFIS Physical	.812, <.001[a] (.785-.835)	.762, <.001[a] (.640-.850)
MFIS Cognitive	.631, <.001[b] (.597-.688)	.295, .006 (.059-.510)
MFIS Psychosocial	.734, <.001[b] (.693-.770)	.673, <.001[b] (.532-.778)
MFIS Total	.800, <.001[a] (.770-.828)	.595, <.001[b] (.413-.737)
PROMIS Fatigue	.797, <.001[a] (.766-.828)	.588, <.001[b] (.405-.713)
Neuro-QOL Fatigue	.795, <.001[a] (.761-.831)	.675, <.001[b] (.514-.791)
FSIQ Cognitive/Emotional		
	RRMS	Progressive MS
FSS	.698, <.001[b] (.654-.735)	.566, <.001[b] (.376-.699)
MFIS Physical	.727, <.001[b] (.684-.766)	.588, <.001[b] (.409-.724)
MFIS Cognitive	.810, <.001[a] (.777-.839)	.833, <.001[a] (.748-.890)
MFIS Psychosocial	.701, <.001[b] (.648-.746)	.728, <.001[b] (.617-.814)
MFIS Total	.849, <.001[a] (.827-.869)	.870, <.001[a] (.812-.907)
PROMIS Fatigue	.801, <.001[a] (.770-.827)	.767, <.001[a] (.620-.877)
Neuro-QOL Fatigue	.757, <.001[a] (.719-.789)	.702, <.001[b] (.555-.818)
FSIQ Coping		
	RRMS	Progressive MS
FSS	.806, <.001[a] (.770-.838)	.745, <.001[b] (.645-.822)
MFIS Physical	.827, <.001[a] (.797-.856)	.738, <.001[b] (.625-.819)
MFIS Cognitive	.721, <.001[b] (.670-.770)	.602, <.001[b] (.437-.726)
MFIS Psychosocial	.761, <.001[a] (.715-.803)	.741, <.001[b] (.620-.826)
MFIS Total	.858, <.001[a] (.829-.882)	.782, <.001[a] (.667-.862)
PROMIS Fatigue	.858, <.001[a] (.826-.884)	.787, <.001[a] (.697-.858)
Neuro-QOL Fatigue	.856, <.001[a] (.825-.881)	.802, <.001[a] (.688-.883)
FSIQ Daily		
	RRMS	Progressive MS
FSS	.750, <.001[a] (.703-.793)	.574, <.001[b] (.407-.705)
MFIS Physical	.740, <.001[b] (.700-.779)	.528, <.001[b] (.330-.689)
MFIS Cognitive	.654, <.001[b] (.600-.703)	.568, <.001[b] (.349-.727)
MFIS Psychosocial	.668, <.001[b] (.616-.720)	.533, <.001[b] (.342-.695)
MFIS Total	.770, <.001[a] (.733-.805)	.653, <.001[b] (.476-.792)
PROMIS Fatigue	.810, <.001[a] (.776-.841)	.694, <.001[b] (.542-.804)
Neuro-QOL Fatigue	.814, <.001[a] (.775-.845)	.683, <.001[b] (.542-.804)

FSIQ, Fatigue Symptoms and Impacts Questionnaire; FSS, Fatigue Severity Scale; MFIS, Modified Fatigue Impact Scale; MS, multiple sclerosis; Neuro-QOL, Quality of Life in Neurological Disorders; PROMIS, Patient-Reported Outcomes Measurement Information System; RRMS, relapsing-remitting multiple sclerosis.

Note: All values listed correlation coefficient, *P* (95% CI). All values had significance at *P*<.05

[a]Good to excellent correlation.

[b]Moderate to good correlation.

TABLE 2. Divergent Validity of the FSIQ With Other Measures of MS Symptoms

FSIQ Physical		
	RRMS	Progressive MS
MSQOL Physical	−.837, <.001[a] (−.868 to −.800)	−.739, <.001[b] (−.839 to −.594)
MSQOL Mental	−.670, <.001[b] (−.718 to −.612)	−.435, <.001 (−.602 to −.246)
PROMIS Depression	.559, <.001[b] (.485-.620)	.523, <.001[b] (.338-.687)
PROMIS Sleep	.209, <.001 (.116-.301)	.179, .062 (−.031 to .401)c
PROMIS Cognition	.572, <.001[b] (.507-.634)	.204, .061 (−.006 to .420)c
PROMIS Physical	.761, <.001[a] (.720-.798)	.775, <.001[a] (.647-.864)
GLTEQ Score	−.355, <.001 (−.428 to −.275)	−.493, <.001 (−.646 to −.293)
PROMIS Anxiety	.485, <.001 (.407-.555)	.397, <.001 (.188-.585)
NIH Stress	.360, <.001 (.275-.440)	.305, .005 (.075-.506)
PROMIS Pain	.618, <.001[b] (.553-.680)	.475, <.001 (.283-.635)
MSWS12	.671, <.001[b] (.616-.718)	.677, <.001[b] (.544-.776)
FSIQ Cognitive		
	RRMS	Progressive MS
MSQOL Physical	−.722, <.001[b] (−.765 to −.667)	−.588, <.001[b] (−.723 to −.430)
MSQOL Mental	−.689, <.001[b] (−.736 to −.636)	−.613, <.001[b] (−.741 to −.426)
PROMIS Depression	.532, <.001[b] (.465-.589)	.479, <.001 (.289-.632)
PROMIS Sleep	.212, <.001 (.122-.294)	.094, .387 (−.129 to .311)[c]
PROMIS Cognition	.743, <.001[b] (.700-.782)	.741, <.001[b] (.644-.816)
PROMIS Physical	.569, <.001[b] (.503-.627)	.259, .016 (.024-.467)
GLTEQ Score	−.176, <.001 (−.280 to .081)	−.198, .067 (−.379 to −.013)[c]
PROMIS Anxiety	.521, <.001[b] (.459-.585)	.478, <.001 (.261-.647)
NIH Stress	.421, <.001 (.339-.497)	.387, <.001 (.178-.559)
PROMIS Pain	.558, <.001[b] (.489-.621)	.568, <.001[b] (.383-.720)
MSWS12	.478, <.001 (.407-.546)	.205, .058 (−.027 to .409)[c]
FSIQ Coping		
	RRMS	Progressive MS
MSQOL Physical	−.801, <.001[a] (−.837 to −.759)	−.707, <.001[b] (−.807 to −.561)
MSQOL Mental	−.710, <.001[b] (−.758 to −.650)	−.620, <.001[b] (−.760 to −.421)
PROMIS Depression	.570, <.001[b] (.507-.628)	.582, <.001[b] (.408-.715)
PROMIS Sleep	.188, <.001 (.099-.272)	.179, .097 (−.051 to .404)c
PROMIS Cognition	.628, <.001[b] (.570-.679)	.479, <.001 (.324-.620)
PROMIS Physical	.667, <.001[b] (.619-.711)	.282, .008 (.066-.488)
GLTEQ Score	−.299, <.001 (−.375 to −.221)	-.172, .110 (−.385 to .067)c
PROMIS Anxiety	.529, <.001[b] (.459-.594)	.538, <.001[b] (.343-.687)
NIH Stress	.371, <.001 (.282-.449)	.580, <.001[b] (.408-.716)
PROMIS Pain	.600, <.001[b] (.536-.656)	.623, <.001[b] (.480-.744)
MSWS12	.555, <.001[b] (.495-.614)	.238, .026 (.025-.440)

TABLE 2. Divergent Validity of the FSIQ With Other Measures of MS Symptoms (continued)

FSIQ Daily		
	RRMS	Progressive MS
MSQOL Physical	−.706, <.001[b] (−.758 to −.648)	−.605, <.001[b] (−.742 to −.421)
MSQOL Mental	−.650, <.001[b] (−.699 to −.597)	−.537, <.001[b] (−.686 to −.357)
PROMIS Depression	.511, <.001[b] (.443-.573)	.503, <.001[b] (.328-.637)
PROMIS Sleep	.170, <.001 (.084-.247)	.245, .023 (.016-.434)
PROMIS Cognition	.560, <.001[b] (.494-.618)	.446, <.001 (.197-.652)
PROMIS Physical	.570, <.001[b] (.505-.631)	.306, .004 (.078-.494)
GLTEQ Score	−.237, <.001 (−.323 to −.147)	−.201, .063 (−.406 to .029)c
PROMIS Anxiety	.475, <.001 (.402-.542)	.510, <.001[b] (.316-.661)
NIH Stress	.353, <.001 (.275-.429)	.422, <.001 (.231-. 607)
PROMIS Pain	.600, <.001[b] (.531-.653)	.606, <.001[b] (.450-.723)
MSWS12	.444, <.001 (.370-.511)	.294, .006 (.080-.490)

FSIQ, Fatigue Symptoms and Impacts Questionnaire; GLTEQ, Godin Leisure-Time and Exercise Questionnaire; MS, multiple sclerosis; MSQOL, Multiple Sclerosis Quality of Life; MSWS12, 12-item Multiple Sclerosis Walking Scale; NIH, National Institutes of Health; PROMIS, Patient-Reported Outcomes Measurement Information System; RRMS, relapsing-remitting multiple sclerosis.

Note: All values listed correlation coefficient, *P* (95% CI). Higher scores indicate better function for MSQOL and GLTEQ, whereas lower scores indicate better function for PROMIS scales, NIH Stress scale, and MSWS12.

[a]Good to excellent correlation.

[b]Moderate to good correlation.

[c]All values reached significance at $P < .05$ except these.

duration and reported an increased level of disability compared with those with RRMS (Table S1).

Comparing Fatigue Domains and Severity in RRMS and PMS Subtypes

Compared to people with RRMS, people with progressive forms of MS reported significantly higher scores (ie, more severe fatigue) in all domains of the FSIQ except the cognitive domain (**TABLE S2**). Participants with PMS reported significantly greater fatigue severity on the FSS ($P < .001$), and greater physical and psychosocial impacts of fatigue on the MFIS ($P < .001$). As observed with the cognitive domain of the FSIQ, there was no significant difference in cognitive fatigue on the MFIS between participants with RRMS and PMS. Additionally, participants with PMS self-reported increased symptoms of fatigue through the PROMIS fatigue scale ($P < .001$), and significantly greater impact of fatigue on quality of life in the Neuro-QOL fatigue scale ($P < .001$).

Convergent Validity of the FSIQ

All subsections of the FSIQ demonstrated moderate to excellent convergent validity with the FSS, MFIS Physical, MFIS Cognitive, MFIS Psychosocial, MFIS Total, PROMIS Fatigue, and Neuro-QOL Fatigue in persons with RRMS (**TABLE 1**).

There were significant correlations between the FSIQ Physical and all other measures for both RRMS and PMS (Table 1); however, all correlations were stronger for the RRMS cohort than the PMS cohort. Further, the FSIQ Physical had the weakest correlations with the MFIS Cognitive in both MS types. Together, these findings demonstrate good convergent validity of the FSIQ Physical as a measure of physical fatigue in people with PMS and suggest that there are modest to null associations between physical fatigue and cognitive fatigue in PMS.

The FSIQ Cognitive demonstrated strong and significant correlations with the MFIS Cognitive and good correlations with the MFIS Psychosocial in both RRMS and PMS. There were also good strength correlations between the FSIQ Cognitive with all other measures and the MFIS Physical for both MS phenotype groups (Table 1).

Among people with PMS, the FSIQ Coping demonstrated excellent correlation with the Neuro-QOL fatigue measure, the PROMIS fatigue measure, and the MFIS Total, and good strength correlations with all other measures (Table 1). The weakest association of the FSIQ Coping for people with PMS was with the MFIS Cognitive, but this was also the weakest for people with RRMS. Of note, the correlations for the FSIQ Coping tended to be higher than those for the FSIQ Physical for people with PMS, suggesting that the coping questions may be particularly relevant for assessing the impact of fatigue in PMS (and RRMS). Again, the strength of associations was stronger for the RRMS cohort than the PMS, which may be due to differences in sample size. Nonetheless, all associations were acceptable to excellent for demonstrating convergent validity in PMS.

PRACTICE POINTS

People with multiple sclerosis (MS) commonly experience fatigue that impacts function, and those with progressive MS report more severe fatigue than those with relapsing-remitting MS.

The Fatigue Symptoms and Impacts Questionnaire is a valid tool to capture physical, mental, and emotional fatigue in progressive MS. ■

Finally, the FSIQ Daily also demonstrated good to excellent correlations in RRMS (Table 1) and moderate to good correlations among people with PMS.

The FSIQ and Other Common MS Symptoms

The FSIQ Physical demonstrated a moderate to excellent correlation with health-related quality of life (MSQOL physical), self-reported physical functioning (PROMIS Physical), and self-reported walking function (MSWS-12) in individuals with RRMS and individuals with PMS. The fair relation with sleep and the moderate relation with cognition observed in RRMS were not found in the PMS cohort (**TABLE 2**).

In the PMS group, the FSIQ Cognitive demonstrated a moderate correlation with the MSQOL physical and mental, as well as self-reported depression, cognition, anxiety, and pain, which was similar to the findings for the RRMS group (Table 2).

Finally, both the FSIQ Coping and FSIQ Daily demonstrated moderate correlations with the MSQOL physical and mental, as well as self-reported depression, anxiety, stress, cognition, and pain, which was similar to the findings for the RRMS group (Table 2).

DISCUSSION

Compared with people with RRMS, we found that people with PMS, on average and across all measures, reported more severe fatigue. Considering the different types of fatigue across all included measures, people with PMS reported more severe physical and psychosocial fatigue than people with RRMS. There were no differences between the RRMS and PMS groups in cognitive fatigue measured by either the FSIQ Cognitive/Emotional scale or the MFIS Cognitive scale. This may be because cognitive fatigue was relatively mild in both groups on both cognitive fatigue measures. Indeed, among the different fatigue domains, physical fatigue was the most severe, especially in people with PMS. It has been reported that fatigue is more prevalent in people with progressive forms of MS.[24-27] Our findings suggest that it is not only more prevalent, but it is also more severe and predominantly driven by the subjective experience of physical fatigue. The current findings also suggest that it may be important to rate physical fatigue separately from other types of fatigue. In this regard, the FSIQ and the MFIS, which provide physical and cognitive subscores, may be optimal.

Overall, the FSIQ subdomains (physical fatigue, cognitive fatigue, and coping) demonstrated good to excellent convergent validity with other more established measures of self-reported fatigue in people with PMS (Neuro-QOL fatigue, PROMIS fatigue, MFIS total, FSS), as well as the respective physical and cognitive subdomains of the MFIS. The finding that the FSIQ Physical was least strongly related to cognitive fatigue on the MFIS Cognitive subscale provides further evidence that physical and cognitive/emotional dimensions of fatigue are discrete entities and may need to be measured separately (in both RRMS and PMS). Indeed, when talking spontaneously about fatigue, people with PMS characterize physical and mental aspects of fatigue separately.[6] Thus, instruments that help clinicians differentiate whether perceptions of fatigue and fatigability are associated with physical and/or cognitive/emotional impacts, such as the FSIQ and MFIS, may have greater clinical value over other fatigue measures that generate a single overall fatigue score. The current data provide new evidence that the FSIQ has good to excellent validity in people with PMS.

The FSIQ Coping Impacts subdomain had the strongest convergent validity for people with PMS compared with the other FSIQ subdomains. The exception was that the FSIQ Coping score demonstrated weaker correlations with MFIS Cognitive scores than with the FSIQ Cognitive scores. The high convergent validity of the FSIQ Coping Impacts also suggests that this subdomain may be particularly relevant to evaluating self-reported fatigue in people with PMS. The FSIQ Coping section includes questions that ask about both difficulty (motivation to perform routine daily activities, taking part in social activities) as well as frequency of needing to take a nap, take a break, and rearrange plans. Two of the 5 items of the FSIQ Coping subdomain are also included in the FSIQ Physical fatigue score, which may explain their similarly strong correlations with other existing fatigue measures. However, 4 of 5 items on the FSIQ Physical Activity rate difficulty rather than frequency. It may be the combination of both symptom frequency and its associated difficulty that makes the FSIQ Coping particularly sensitive to detecting fatigue in people with PMS.

The strong relation between the FSIQ Physical and other physical symptom self-rating scales (MSQOL Physical, PROMIS Physical, and MSWS-12) is consistent with prior research that physical fatigue is associated with perceived limitations in physical performance.[6,28] Based on the current data, this appears to be true for both RRMS and PMS. Interestingly, however, despite the perceived link between physical fatigue and physical function, meta-analyses of the effects of exercise interventions on fatigue indicate substantial heterogeneity.[29] That is, improving

physical function or exercise capacity does not consistently result in improved ratings of fatigue. Indeed, treatment of fatigue in MS remains a considerable challenge. This is most likely due to our limited understanding of fatigue mechanisms and because fatigue is a dynamic phenomenon that can vary greatly both among and within individuals.[30] Evaluating fatigue on comprehensive instruments such as the FSIQ may be an important step in guiding person-centered interventions for fatigue.

Although sleep disturbance may appear as a cluster of symptoms that exacerbate fatigue,[31] neither physical fatigue nor cognitive fatigue (FSIQ) had any association with sleep (PROMIS Sleep) in people with PMS and little to no relation in people with RRMS. The statistical significance of the weak relation between FSIQ Physical and FSIQ Cognitive scores and PROMIS Sleep in people with RRMS ($r < 0.22$) is likely due to the large RRMS group sample size and simply indicates that the weak relation has a high probability of being real (ie, very low probability of Type II error), though recent work suggests that subjective reports of sleep may not correlate with fatigue.[32,33] It is possible that subjective reports of sleep disturbance do not adequately capture the relation between sleep and fatigue,[34] necessitating the use of objective measures of sleep that better align with fatigue.[35,36] Whereas FSIQ Cognitive/Emotional fatigue scores did not correlate with physical fatigue scores, they were associated with physical aspects of health-related quality of life, albeit only moderately for people with PMS. Cognitive fatigue was also associated with depression, lower mental health–related quality of life, and self-rated cognitive function. Fatigue arising from depression, anxiety, and pain may decrease the ability to cope with the disease and have an impact on daily living.[37] Our findings suggest that subjective reports of cognitive function may be influenced by depression and fatigue, emphasizing the importance of cognitive, mood, and fatigue screening in routine clinical care.

The key strengths of this study were the large sample sizes for the 2 MS phenotypes, the use of multiple existing patient-reported outcomes, and the comparisons between people with PMS and RRMS. Our study had some limitations. Due to the survey nature of the study, we were not able to capture any functional measures of performance or objective measures of fatigability. The study also assessed fatigue at a single point in time, and it is well known that fatigue is a dynamic phenomenon that can vary dramatically both individually and among individuals on a daily basis.[30] It is possible that some individuals were unaware of progressing from RRMS to secondary progressive MS, so future studies examining differences in fatigue between MS subtypes should consider confirming diagnosis prior to participation. Nevertheless, this study provides compelling evidence to support the validity and use of the FSIQ in people with PMS.

CONCLUSIONS

Mean fatigue ratings were higher in people with PMS than RRMS; furthermore, persons with PMS endorse both greater mental and physical fatigue. Measuring these subdomains of fatigue with a valid tool is critical for the development of targeted interventions and longitudinal monitoring. In the absence of a gold standard for subjective fatigue in people with MS, it is not possible to establish concurrent validity; however, the FSIQ is a valid and freely available tool with excellent convergent validity to capture the physical, mental, and emotional fatigue of people with PMS. ■

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TABLE S1. Participant Demographics

	Total (N = 806)	RRMS (n = 637)	Progressive MS (n = 169) SPMS: n = 109 PPMS: n = 60
Age, mean years (SD)	50.47 (12.93)	48.20 (12.48)	58.99 (10.93)
Sex (M:F:NB)	132:669:5	92:540:5	40:129:0
Race			
Asian or Pacific Islander	0.9%	0.9%	0.6%
Black or African American	6.0%	6.4%	4.1%
Hispanic or Latino	5.1%	5.2%	4.7%
Native American	0.5%	0.5%	0.6%
White	85.2%	84.8%	87.0%
Biracial or multiracial	1.9%	1.9%	1.8%
Not listed	0.5%	0.3%	1.2%
Symptom duration, mean years (SD)	3.63 (4.67)	3.33 (4.52)	4.81 (5.06)
PDDS, median (range)	2 (0-8)	1 (0-8)	5 (0-8)
DMT, %	82.4	85.6	70.4
AD use inside, %	13.2	7.2	39.2
AD use outside, %	28.4	18.7	70.8
Medication for fatigue, %	30.3	30.1	30.8

AD, assistive device; DMT, disease-modifying therapy; F, female; M, male; MS, multiple sclerosis; NB, nonbinary; PDDS, Patient-Determined Disease Steps; PPMS, primary progressive multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

TABLE S2. Fatigue Scores in Relapsing-Remitting MS and Progressive MS Subtypes

Instrument, (score range)	RRMS n = 806	Progressive MS n = 637	*P*
FSIQ (0-100)			
Physical	36.27 (23.87)	58.47 (23.16)	**<.001**
Cognitive emotional	35.01 (20.50)	37.90 (19.34)	.085
Coping impacts	44.75 (23.83)	53.70 (22.69)	**<.001**
Daily	36.05 (16.35)	40.06 (14.19)	.016
FSS (9-63)	41.34 (13.78)	47.20 (12.71)	**<.001**
MFIS			
Physical (0-36)	19.84 (8.66)	25.74 (7.41)	**<.001**
Cognitive (0-40)	18.82 (9.33)	18.65 (9.65)	.741
Psychosocial (0-8)	3.97 (2.24)	5.10 (2.22)	**<.001**
Total	42.80 (18.10)	49.52 (16.49)	**<.001**
PROMIS Fatigue MS (8-40)	24.29 (7.60)	27.19 (7.04)	**<.001**
Neuro-QOL Fatigue (8-40)	25.64 (7.83)	28.19 (7.46)	**<.001**

Note: All values listed mean (SD). Bold values denote significance between groups at $P < .05$. Higher scores indicate greater fatigue for all measures.
FSIQ, Fatigue Symptoms and Impacts Questionnaire; FSS, Fatigue Severity Scale; MFIS, Modified Fatigue Impact Scale; MS, multiple sclerosis; Neuro-QOL, Quality of Life in Neurological Disorders; PROMIS, Patient-Reported Outcomes Measurement Information System; RRMS, relapsing-remitting multiple sclerosis.