Dimensions of Fatigue in Systemic Lupus Erythematosus: Relationship to Disease Status and Behavioral and Psychosocial Factors

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ABSTRACT. ***Objective.*** To characterize the experience of fatigue in patients with systemic lupus erythematosus (SLE) using a multidimensional assessment and to delineate contributors to physical and mental dimensions of fatigue.

Methods. Fatigue in 130 women with SLE was assessed using the Multidimensional Fatigue Inventory (MFI-20). Participants completed standardized questionnaires assessing sleep quality, depressed mood, social support, and leisure-time physical activity. A clinical examination determined disease activity, cumulative damage, and whether patients fulfilled American College of Rheumatology criteria for fibromyalgia (FM). A series of hierarchical multiple regressions were computed to identify contributors to physical and mental fatigue.

Results. Patients scored high on all 5 MFI-20 fatigue dimensions, with general fatigue and physical fatigue having the highest scores. A hierarchical multiple regression showed that greater disease damage and disease activity, the presence of FM, depressed mood, sleep disturbance, and less participation in leisure-time physical activity contributed to higher physical fatigue scores. The results of the second model found depressed mood to be the strongest determinant of mental fatigue. Disease-related variables were not associated with mental fatigue.

Conclusion. Fatigue in SLE is multidimensional and multidetermined, with physical and mental aspects likely having different etiologies. A multidimensional assessment of fatigue in SLE is needed to tailor and optimize interventions aimed at alleviating fatigue. (First Release June 1 2006; J Rheumatol 2006;33:1282–8)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS
MULTIDIMENSIONAL FATIGUE
BIOPSYCHOSOCIAL DETERMINANTS

Patients with systemic lupus erythematosus (SLE) consistently report fatigue as a significant and debilitating symptom. The etiology of fatigue in SLE is poorly understood, but likely involves multiple factors related to disease, behavior, and psychosocial status.

Disease activity has been one of the most widely studied contributors of fatigue in SLE. To date, findings have been conflicting, some studies showing a significant association between disease activity and fatigue[1-3] and others demonstrating at best only a weak association[4-8]. The presence of secondary fibromyalgia (FM) syndrome has also been proposed to explain persistent fatigue in SLE[8]. Studies, however, have shown the presence of FM, using the American College of Rheumatology (ACR; formerly American Rheumatism Association) diagnostic criteria[9], to account for only a small portion of the variance in fatigue among patients with SLE[10]. Behavioral factors such as lack of exercise participation and poor sleep quality have also been associated with fatigue severity in SLE[11-14]. Among the psychosocial contributors, depression has been consistently associated with fatigue in patients with SLE[1,7,8,12,14,15].

In the general population[16,17] and in other diseases (e.g., multiple sclerosis, chronic fatigue, cancer) fatigue has become recognized as a multidimensional phenomenon[18,19], which can manifest itself with physical and/or mental symptoms. Inherent in this conceptualization is that multidimensional assessment is required to capture the different manifestations of fatigue and their respective determinants. Unidimensional measures are limited in that patients with similar fatigue scores may differ in their experience of fatigue[20]. That is, one patient may feel physically exhausted but mentally alert, while another may feel mentally exhausted but physically fit. Newer measures including the Multidimensional Fatigue Inventory (MFI)[20] address this multidimensionality.

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Empirical support for the multidimensional character of fatigue is emerging. For example, Watt, *et al*[16] found sociodemographic (i.e., age, sex) and clinical variables related differently to the various dimensions of fatigue. Recently, Lim, *et al*[17] found depression to be more strongly related to mental fatigue, while obesity was shown to be a strong predictor of physical fatigue. To date, only a few studies have used multidimensional assessments of fatigue with SLE patients — 2 assessed physical and mental components of fatigue using visual analog scales (VAS)[7,12] and one study used the Piper fatigue scale, which includes a sensory and affective subscale[14]. However, none of these studies evaluated differential correlates or contributors to physical and mental fatigue. While fatigue in SLE seems to be multidetermined, the relative importance of disease-related, psychosocial, and behavioral factors to the various dimensions of fatigue remains virtually unknown.

The goals of our study were (1) to describe the experience of fatigue in patients with SLE using a multidimensional assessment; and (2) to delineate contributors to the different dimensions of fatigue (e.g., physical and mental). We hypothesized that disease-related, psychosocial, and behavioral factors would differentially contribute to physical and mental fatigue.

MATERIALS AND METHODS

Subjects and methods. The sample consisted of patients who fulfilled at least 4 of the ACR criteria for SLE[21,22], were at least 18 years of age, functionally fluent in English or French, and had no major cognitive deficits that would preclude questionnaire completion.

Physicians invited consecutive patients with SLE during their scheduled appointment at the Lupus Clinic of the McGill University Health Centre to participate in the study. The research assistant obtained informed consent and reviewed the questionnaire protocol with the patient during the clinic visit. Patients were provided with a preaddressed stamped envelope to return the self-report questionnaires by mail. Patients underwent a standard medical examination at the time of study entry. The study was approved by the McGill University Faculty of Medicine Institutional Review Board prior to commencement.

Measures. The MFI-20[20] was used to assess various components of fatigue. This 20-item self-report instrument generates 5 subscales of 4 items each. The subscales are General Fatigue (e.g., "I feel tired"), Physical Fatigue ("Physically I feel only able to do a little"), Reduced Activity ("I think I do very little in a day"), Reduced Motivation ("I dread having things to do"), and Mental Fatigue ("My thoughts easily wander"). The response scale presents a choice of 5 boxes and runs from agreement with the statement to disagreement. Higher scores reflect a higher degree of fatigue. The alpha coefficients range from satisfactory to good ($\alpha = 0.76$–0.88)[20,23]. This measure has been validated with healthy and clinical (e.g., cancer, chronic fatigue syndrome) populations[20,23]. Moderate correlations with the Beck Depression Inventory indicate that although the concepts measured may be related, they can be measured in distinct ways[24]. The Physical and Mental Fatigue subscales were used as the outcome measures when examining contributors to fatigue.

The Pittsburgh Sleep Quality Index (PSQI)[25] was used to assess sleep quality. This self-report measure assesses sleep quality and disturbances over a one-month time interval. It comprises 19 items, generating 7 component scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. A global score is obtained by summing the 7 component scores (range 0–21, higher scores reflecting poorer sleep quality). The scale demonstrates good psychometric properties, with a global score > 5 yielding a diagnostic sensitivity of 89.6% and specificity of 86.5% in differentiating good and poor sleepers.

The Center for Epidemiological Studies-Depression Scale (CES-D) was used to assess depressive symptoms[26,27]. This is a 20-item measure designed to assess depressive symptoms in nonpsychiatric populations. Respondents were asked to indicate the frequency with which they had experienced each symptom during the previous week on a 4-point scale from 0 (rarely or none of the time) to 3 (most or all of the time), and a score between 0 and 60 was obtained. The CES-D has been found to have strong psychometric properties[27,28] and has been widely used with patients with chronic medical diseases[29]. Previous work using the CES-D in an arthritis population has shown that 4 items (items 7, 8, 11, and 20) may be more closely associated with arthritis than with depression in persons with rheumatoid arthritis[30]. To avoid overestimating the relationship between depression and fatigue, these 4 items were not included in the total score. The remaining 16 items were summed and multiplied by a constant of 1.25 to retain the original 0–60 range (CESD-AR)[30].

The shortened version of the Social Support Questionnaire (SSQ) was used to assess perceived satisfaction with social support[31]. The SSQ is psychometrically sound and includes 6 items measuring satisfaction with social support[31]. Scores on the satisfaction subscale range from 0 to 6, higher scores indicating greater satisfaction.

The Aerobics Center Longitudinal Study Physical Activity Questionnaire (ACLS-PAQ) is a brief, validated instrument assessing leisure and household activities[32]. Participants provide information about activities performed regularly in the last 3 months, frequency per week, intensity level, and duration per session. A total physical activity score and a total physical activity score excluding household activities, stair climbing, and lawn work can be expressed to distinguish between physical activity and exercise. These scores are estimates of weekly energy expenditure, expressed as MET-hours per week. One MET is equal to the resting metabolic rate of an individual, which is 3.5 ml of oxygen per kilogram body mass per minute[33]. The intensity of each activity reported is converted to a MET value by using various compendia of physical activity[33-35]. The ACLS-PAQ has been well validated in male and female samples and correlates well with objective measures of physical fitness[35-37].

Disease activity was evaluated using the Systemic Lupus Activity Measure-Revised (SLAM-R)[38]. This is a reliable and validated instrument used to measure disease activity over the past month in a number of organ systems — constitutional, integument, ocular, reticuloendothelial, pulmonary, cardiovascular, gastrointestinal, neuromotor, musculoskeletal, hematologic, and renal. Although validation studies refer to the original SLAM rather than the revised version, the differences between the 2 versions are minor. The SLAM-R is based on physician examination and laboratory assessment, which includes a complete blood cell count, erythrocyte sedimentation rate, creatinine clearance, and urinalysis. Scores may range from 0 (no disease activity) to 84 (maximum disease activity). Based on our experience, a score over 8 indicates moderate to severe clinical activity[39]. To avoid overestimating the relationship between disease activity and fatigue, the item measuring fatigue was removed from the total score (SLAM-R less fatigue).

SLE disease damage was measured at baseline using the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC/ACR DI)[40,41]. The SLICC/ACR DI is a physician-rated index that assesses cumulative organ damage due to the disease, to complications of therapy, or to intercurrent illness such as cancer. It covers 12 categories including: ocular, neuropsychiatric, renal, pulmonary, cardiovascular, peripheral vascular, gastrointestinal, musculoskeletal, skin, premature gonadal failure, diabetes, and cancer. Total scores on this index range from 0 (no damage) to 47 (maximum damage).

Sociodemographic and additional clinical information were collected by self-report. Data included disease duration, age, education, and marital and employment status. Participants also reported on prescribed medications. A physician evaluation determined the presence of FM using ACR criteria[9].

Statistical analyses. Descriptive statistics including means, medians, and standard deviations were calculated for all the variables. The variable pertaining to weekly MET-h on the measure assessing leisure physical activity was found to be positively skewed. Following the recommendations of Tabachnick and Fidell[42] for handling positively skewed variables, we applied a log-linear transformation of this variable for all subsequent analyses.

A Pearson correlation matrix was computed with all the variables to examine the bivariate correlations between the outcome variables (physical and mental fatigue) and each potential predictor variable. The pattern of intercorrelations among the possible predictor variables was also examined.

Two hierarchical multiple regression analyses were computed to test the importance of disease-related, psychosocial, and behavioral factors to physical and mental fatigue. Hierarchical multiple regression is the regression strategy of choice when the research goals are to determine the importance of a predictor variable(s) once other predictor variables have already been entered into the equation[43]. Each hierarchical regression analysis determined whether the variance explained by the specific set (i.e., disease-related, psychosocial, or behavioral) contributed significantly to the total variance in physical or mental fatigue, after controlling for the previous set of variables. To this end, as suggested by Cohen and Cohen[43], the increment in R^2 was tested for statistical significance. Variable selection was based on theoretical relevance, pattern of correlation with the outcome variable and other potential predictor variables, and the assumptions underlying multiple regression analysis.

RESULTS

Of the 139 women with SLE who agreed to participate in this study, 130 (93.5%) returned their completed self-report questionnaires. Of the 9 who failed to return questionnaires, 7 were no longer interested in participating and 2 felt too ill to return the questionnaires.

The characteristics of the 130 patients are shown in Table 1. The mean age of the sample was 45.4 years (± 14.0). The average time since diagnosis was 13.8 years (± 10.1). The mean SLAM-R score was 7.7 (± 7.9), indicating moderate disease activity. These clinical characteristics are similar to those reported in other tertiary care centers. The mean score on the CESD-AR was 12.8 (± 10.9), with 31% (n = 40) of the sample scoring at or above the standard cutoff score (≥ 16) for clinically significant depressive symptoms. Studies with primary care patients with a greater number of comorbid medical illnesses have suggested that a cutoff of 21 on the CES-D has the best positive predictive value for major depression[44]. Using this cutoff, 23% (n = 30) of the sample had clinically significant depressive symptoms. Forty–two percent (n = 59) of the sample reported exercising regularly (exerting ≥ 6 MET-h weekly).

In our sample of women with SLE, the highest mean scores on the MFI were found for General Fatigue and Physical Fatigue (mean 13.1 and mean 12.0, respectively), while Reduced Motivation had the lowest score (mean 8.94) (Table 2). As shown in Figure 1, more women scored in the 15–20 range for physical fatigue (35%, n = 46) compared to mental fatigue (11.5%, n = 15).

Pearson correlations between physical and mental fatigue with demographic variables, disease-related variables, depressed mood, sleep quality, social support, and physical activity are shown in Table 3. Significant positive correlations were obtained between physical fatigue, disease activity, disease damage, presence of FM, depression, and impaired sleep quality; and significant negative associations were shown with social support satisfaction and exercise. Mental Fatigue was positively correlated with depressed mood and impaired sleep quality and negatively correlated with social support satisfaction and exercise participation.

Of all the potential correlates examined, depressed mood scores were most strongly correlated with physical (r = 0.47) and mental (r = 0.52) fatigue. Univariate analyses of variance (ANOVA) were computed to determine whether physical and mental fatigue scores differed depending on the severity of depression. As shown in Figure 2, patients who were not depressed scored significantly lower on physical fatigue compared to patients who were mildly ($p < 0.001$) and more severely ($p = 0.001$) depressed. Nondepressed patients also retained significantly lower mean mental fatigue scores compared to patients who were moderately ($p = 0.043$) and severely depressed ($p < 0.001$).

Two hierarchical multiple regressions were computed to determine predictors of physical and mental fatigue (Table 4). Disease-related variables including disease duration, disease

Table 1. Patient characteristics.

	Mean (SD)
Age, yrs	45.4 (14.0)
Education, yrs	13.1 (3.0)
Income*	4.3 (1.8)
Disease duration, yrs	13.8 (10.1)
SLAM-R	7.7 (7.9)
SLICC/ACRDI	1.6 (1.8)
FM, %	16
Psychosocial/behavioral	
CESD-AR	12.8 (10.9)
SSQ-6	5.4 (0.69)
Global PSQI	7.1 (4)
Exercise participation (≥ 6 MET-h-week), %†	42

* Income scale 1–13, e.g., 4 = $30–$40,000; 5 = $40–$50,000. † Weekly energy expenditure expressed as metabolic equivalent hours per week. SLAM-R: Systemic Lupus Activity Measure-Revised; SLICC/ACR DI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; FM: fibromyalgia using ACR criteria; CESD-AR: Center for Epidemiological Studies-Depression Scale-Arthritis Scoring; SSQ-6: Social Support Questionnaire; Global PSQI: global score, Pittsburgh Sleep Quality Index.

Table 2. Mean scores on the 5 MFI-20 fatigue scales.

MFI-20 Subscales	Mean ± SD (range)
General Fatigue (GF)	13.1 ± 4.5 (4–20)
Physical Fatigue (PF)	12.0 ± 4.4 (4–20)
Reduced Activity (RA)	10.1 ± 4.7 (4–20)
Reduced Motivation (RM)	8.9 ± 3.6 (4–20)
Mental Fatigue (MF)	9.0 ± 4.4 (4–20)

Smets, *et al*[45] means ± SD reported in a sample of the general population (n = 139): GF = 9.9 ± 5.2; PF = 8.8 ± 4.9; RA = 8.7 ± 4.6; RM = 8.2 ± 4.0; MF = 8.3 ± 4.8.

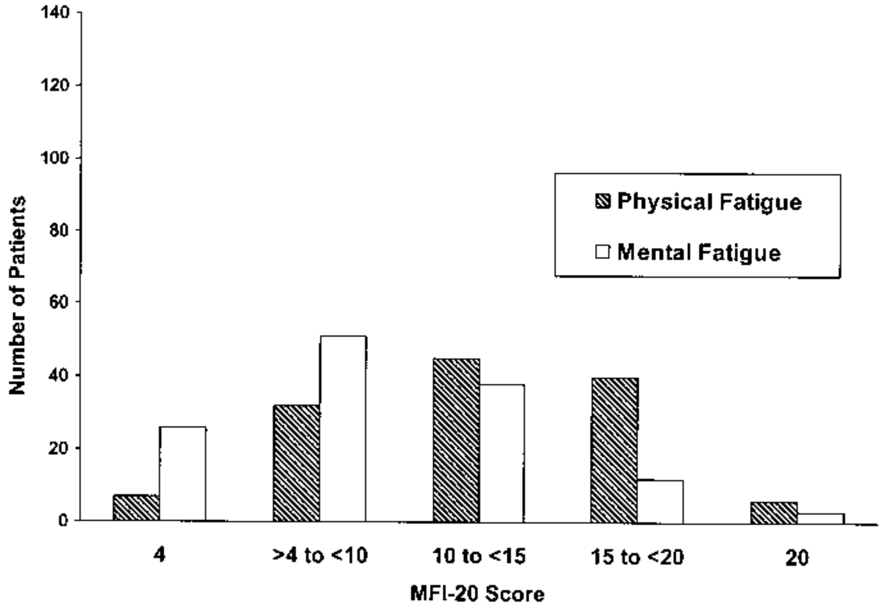

Figure 1. Distribution of scores on the physical and mental fatigue dimensions of the MFI-20 among patients with SLE.

Table 3. Pearson correlations between physical and mental fatigue and potential determinants.

	Physical Fatigue		Mental Fatigue	
	r	p	r	p
Age	0.05	NS	0.03	NS
Disease duration, yrs	0.01	NS	0.04	NS
SLAM-R	0.26	0.004	0.02	NS
SLICC/ACR DI	0.18	0.04	0.11	NS
FM	0.26	0.003	0.16	0.073
CESD-AR	0.47	< 0.001	0.52	< 0.001
SSQ-6	–0.21	0.034	–0.36	0.001
Global PSQI	0.45	< 0.001	0.41	< 0.001
Exercise	–0.40	< 0.001	–0.19	0.018

For definitions see Table 1.

damage (SLICC), disease activity less fatigue (SLAM), and FM diagnosis were entered into the first step of the regression. To determine if psychosocial and behavioral factors explained additional variance in each fatigue dimension beyond that offered by disease-related variables, depression, sleep quality, social support, and exercise were entered into the second step.

In the first step of the model predicting physical fatigue, disease damage ($p = 0.015$), disease activity ($p = 0.002$), and FM diagnosis ($p = 0.002$) were significant independent predictors, explaining 17% of the variance. In the second step, depressed mood ($p = 0.031$), sleep quality ($p = 0.029$), and level of exercise participation ($p = 0.018$) contributed to the equation, resulting in a significant increment in R^2. Together, the variables in the model explained 39% of the variance in physical fatigue ($R^2 = 0.39$, adjusted $R^2 = 0.34$).

Disease-related variables did not contribute to mental fatigue in the first step of the multivariate model. In the second step, depression ($p < 0.001$), sleep quality ($p = 0.07$), and social support ($p = 0.085$) contributed significantly to the equation, and together the variables explained 33% of the variance ($R^2 = 0.33$, adjusted $R^2 = 0.29$).

DISCUSSION

A unique feature of our study was the use of a multidimensional operationalization of fatigue to describe and investigate the experience of fatigue in patients with SLE. The MFI-20 provided a comprehensive portrayal of fatigue in women with SLE. Our findings confirm that fatigue is a major problem in SLE, as evidenced by the elevated scores obtained on general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue. When examining determinants of physical and mental fatigue, we found a different pattern of factors to be associated with each dimension, lending strong empirical support for a multidimensional conceptualization of fatigue in SLE.

Among the disease-related variables we considered, disease activity, disease damage, and the presence of FM were significantly correlated with physical fatigue. These variables remained significant independent contributors in the multivariate analysis. The association between disease activity and physical fatigue is in accord with several previous studies[2,6,7], but other studies have failed to show any association[1,5,8]. Disease activity in these latter studies was not measured using the SLAM, which may in part explain the contradictory findings. It should be noted that the item assessing fatigue in the SLAM-R was removed from the total score in our analyses, thereby eliminating the possibility that the significant relationship observed between disease activity and physical

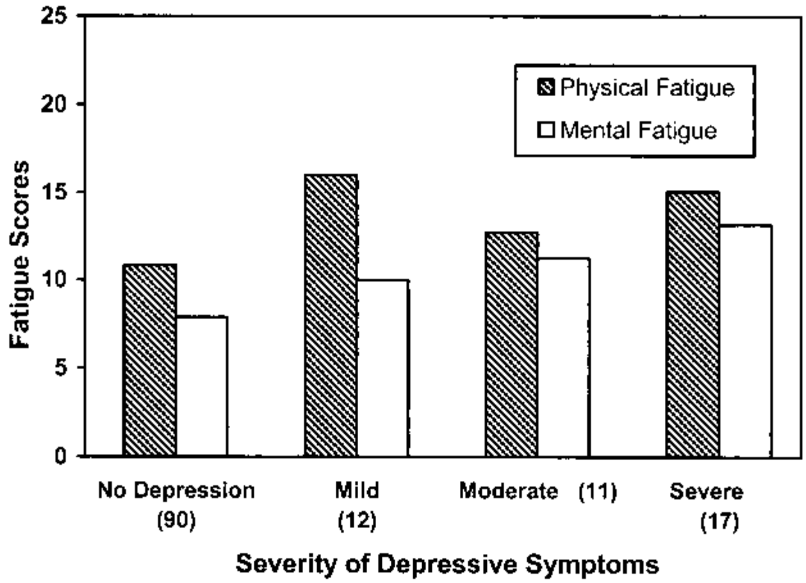

Figure 2. Physical and mental fatigue by severity of depressive symptoms. Severity of depressive symptoms was determined with the CESD-AR[30] (no depression = < 16; mild = 16–20; moderate = 21–25; severe = 26–60)[46].

Table 4. Hierarchical regression predicting physical and mental fatigue.

Independent Variables	Physical Fatigue ß	R^2 Change	F Change	Mental Fatigue ß	R^2 Change	F Change
Step 1						
Disease duration	–0.10			–0.04		
SLICC/ACR DI	0.22*			0.12		
SLAM-R (less fatigue)	0.26**			0.03		
FM	0.27**	0.172	F(4,125) = 6.5***	–0.15†	0.035	F(4,125) = 1.1
Step 2						
CESD-AR	0.20*			0.42***		
SSQ-6	–0.10			–0.14†		
Global PSQI	0.20*			0.17†		
Exercise	–0.19*	0.21	F(4,121) = 10.5***	0.04	0.299	F(4,121) = 13.6***

† $p < 0.10$, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. ß: standardized regression coefficient. For other definitions see Table 1.

fatigue resulted from measurement overlap. The association observed between the presence of FM and greater fatigue in our sample of SLE patients has been previously reported[4,8,10]. However, only 16% of our sample fulfilled ACR criteria for FM, and the association between FM and physical fatigue was modest. These findings suggest that for most patients with SLE, physical fatigue is likely due to a range of other factors.

Disease-related variables were not found to be significant predictors of mental fatigue. In contrast, unlike physical fatigue, physiological mechanisms related to the disease process are less likely to account for mental fatigue in SLE.

Depressed mood was associated with worse physical fatigue and mental fatigue in patients with SLE. This association has previously been reported in SLE[1,7,8,12,14,15]; however, previous studies measured fatigue unidimensionally and failed to examine determinants of physical and mental dimensions separately. Our results extend previous studies by revealing the association between depressed mood and both physical and mental fatigue, lending support for the meaningfulness of a multidimensional operationalization of fatigue in SLE. Interestingly, the results of the multivariate analyses reveal that while depressed mood uniquely contributed to both fatigue dimensions, it is a stronger determinant of mental fatigue. Depressed mood was the most important determinant of mental fatigue. Mental fatigue scores were considerably higher for patients who were more depressed. While fatigue and depression frequently co-occur, studies have shown that fatigue is neither sensitive nor specific to the diagnosis of depression[47-49]. Studies have also shown that fatigue can be measured independently from depression[24,50]. Prospective studies are needed to clarify the relationship between depression and mental fatigue in SLE.

Several studies have documented poor sleep quality in lupus patients[14,51-53]. Our findings suggest that impaired sleep quality is related to worse physical fatigue. McKinley, *et al*[14] also found a strong association between sleep quality and fatigue in patients with SLE. These results lend support to the notion that disrupted sleep is likely playing a role in the pathophysiology of fatigue in SLE. Studies using objective measures of sleep disturbance are needed to identify the mechanisms of sleep disorders in SLE and to assess the effect of treatment of sleep conditions in alleviating fatigue in this patient population.

Exercise participation in the multivariate analyses contributed to physical fatigue. Poor aerobic capacity has been associated with increased fatigue[11,54]. Aerobic exercise has been shown to improve fatigue in SLE patients[11,13], as well as in other patient populations[55,56].

Some limitations are evident in our study. It is cross-sectional and did not allow determination of the temporal sequence of the relationships found to be significant. Prospective studies using a multidimensional conceptualization of fatigue are needed to advance our understanding of fatigue in patients with SLE. Our sample consisted primarily of Caucasian, well educated, middle class women followed at a tertiary lupus clinic, limiting generalizability. We explained 33–39% of the variance in our fatigue outcomes, indicating that studies examining other factors (e.g., work demands, helplessness) not assessed in this study are needed to better understand fatigue in SLE. A multidimensional conceptualization of fatigue, objective physician-completed measures of disease activity and disease damage, and validated measures of the behavioral and psychosocial factors are notable strengths of this study.

Our results suggest that the experience of physical and mental fatigue is common in SLE. Fatigue in SLE is multidetermined, with physical and mental dimensions likely having different etiologies. A multidimensional assessment of fatigue in SLE is needed to tailor and optimize interventions aimed at alleviating fatigue. For example, treating a lupus flare and optimizing pain control may be helpful in reducing physical fatigue, but may not be effective in alleviating mental fatigue. Conversely, treatment aimed at alleviating depressed mood may have a much stronger influence in reducing mental fatigue. Studies to evaluate the efficacy of different therapeutic strategies are needed.

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