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Sociodemographic, Disease, and Symptom Correlates of Fatigue in Systemic Sclerosis

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ABSTRACT

Objective: To assess fatigue levels and demographic, socioeconomic, disease, and psychosocial correlates of fatigue in systemic sclerosis (SSc) patients.

Methods: Cross-sectional, multi-center study of 659 Canadian Scleroderma Research Group Registry patients. Fatigue was assessed during annual Registry visits with the SF-36 Vitality subscale. Patients also completed measures of depressive symptoms and pain and underwent clinical histories and medical examinations. Kendall's tau was used to assess bivariate association of sociodemographic, medical, and psychosocial variables with fatigue. Multivariable associations of demographic (step 1), socioeconomic (step 2), global disease (step 3), specific disease and lifestyle factors (step 4), and psychosocial factors (step 5) with fatigue were assessed using hierarchical multiple linear regression.

Results: Mean score on the SF-36 Vitality subscale was 45.7±10.8, substantially lower (more fatigue) than the norm for the Canadian general population (65.8±18.0). In multivariate analysis, higher fatigue was significantly associated with number of medical comorbidities (standardized β=-0.11, P=.004), breathing problems (standardized β=-0.23, P<.001), number of gastrointestinal symptoms (standardized β=-0.27, p<.001), and current smoking (standardized β=-0.08, p=.018). As a group, specific symptom and lifestyle variables predicted the most incremental variance in fatigue (ΔR^2 = 21.6%, P< 0.001) despite being added to the model after demographic, socioeconomic, and global disease duration/severity indicators. Symptoms of depression (β=-0.42) and pain (β=-0.21) were also independently associated with fatigue (P<0.001).

Conclusion: High levels of fatigue are common in patients with SSc and are independently associated with clinical variables, including number of comorbidities, breathing problems, gastrointestinal symptoms, and smoking.

Persistent fatigue from chronic illness involves ongoing exhaustion that is disproportionate to exertion and not alleviated by rest (1). Although patients with chronic disease rate fatigue as one of the most important factors impacting quality of life (QOL) (1), it is often overlooked by clinicians and researchers (1). In one study, almost 90% of rheumatologists reported that they never assess fatigue (2). Across disease groups, fatigue decreases QOL by diminishing a person's ability to engage in meaningful personal and social activities and has important implications for employment, compliance with prescribed medical treatments, and use of healthcare services (1, 3).

Systemic Sclerosis (SSc), or scleroderma, is a chronic, multi-system disorder of connective tissue characterized by thickening and fibrosis of the skin, involvement of internal organs, substantially reduced QOL, and significant morbidity and mortality (4). Common SSc symptoms associated with reduced QOL include pain, gastrointestinal symptoms, joint deformity, limited mobility, dyspnea, and sleep difficulties (5, 6). Few studies have addressed the impact of fatigue in SSc. One study (N = 49) found the most frequent symptoms of SSc to be stiff joints (79%), pain (75%), and fatigue (75%) (7), and another reported that pain and fatigue were mentioned more than any other symptoms by focus group participants (8). A third study (N = 123) reported that patients rated fatigue as more bothersome than any other symptom (9). These studies, however, all used single-item or counting methods with unknown measurement characteristics. A recent study compared fatigue measured by the Multidimensional Fatigue Inventory in 106 SSc patients to fatigue in other chronic disease samples identified through systematic review, and the level of fatigue in SSc was significantly higher than general population levels and comparable to levels reported by patients with other rheumatic diseases and by cancer patients in active treatment (10).

The pathophysiology of fatigue related to chronic illness is not well understood, although numerous possible factors have been identified, including anemia and malnutrition; interactions of cytokines and serotonin; nausea and other gastrointestinal problems; dyspnea; sleep disturbance; inactivity and deconditioning; and lifestyle factors, such as smoking, excessive alcohol consumption, and exercise; and psychological factors, such as depression, anxiety, and specific cognitions (e.g., catastrophizing) (11). Wagner and Cella (11) classified causes of fatigue in cancer as direct effects of the cancer, treatment side effects (e.g., chemotherapy), comorbid medical conditions (e.g., malnutrition), exacerbating comorbid symptoms (e.g., chronic pain, deconditioning), and psychosocial factors (e.g., depression). There is no research on etiological factors of fatigue in SSc, but possible causes may similarly include *direct effects of the SSc*, including skin tightening limiting movement and chest expansion, interstitial lung disease and pulmonary hypertension leading to dyspnea, gastrointestinal symptoms such as chronic diarrhea, arthralgias/itis impairing mobility, inflammatory muscle disease causing weakness; *comorbid medical conditions*, including anemia, malnutrition, and other comorbidities (e.g., unrelated heart, lung, and thyroid disease); *exacerbating comorbid symptoms*, such as chronic pain, sleep disturbances, and deconditioning; *treatment side effects* of immunosuppresive drugs used to treat skin and lung disease (e.g. methotrexate or cyclophosphamide associated with nausea, diarrhea, malaise) and other symptomatic treatments (e.g., anti-hypertensives causing hypotension); *lifestyle factors*, such as exercise, smoking, and excessive alcohol consumption; and *psychosocial factors*, including overextended coping resources and stress, depression, anxiety, and specific fatigue-related cognitions (e.g., catastrophizing) (8). Figure 1 depicts possible etiological factors for fatigue in SSc.

The objective of this study was to assess fatigue levels in a large sample of patients with

SSc and to identify important demographic, socioeconomic, disease, lifestyle and patient outcome correlates (depressive symptoms, pain).

PATIENTS AND METHODS

Patient Sample. The sample consisted of patients enrolled in the Canadian Scleroderma Research Group Registry from September 2004 through June 2008 who had complete data on study measures. Patients in this Registry were recruited from 15 centers across Canada. To be eligible for the Registry, patients must have a diagnosis of SSc made by a Registry rheumatologist, be $\geq$ 18 years of age, and be fluent in English or French. There are no additional inclusion or exclusion criteria. Registry patients undergo extensive clinical history, physical evaluation, and laboratory investigations and complete a series of self-report questionnaires that includes sociodemographic variables, lifestyle variables (e.g., smoking history), other health problems, environmental exposures, family history of auto-immune diseases, SSc symptoms, disability, quality of life, pain, symptoms of depression, and medical resource utilization. Patients from all sites provided informed consent, and the research ethics board of each study site approved the data collection protocol.

Measures. Fatigue was measured using the Vitality subscale of the SF-36 (12). Analyses of possible predictors of fatigue included self-reported sociodemographic data (age, sex, education, marital status) and variables measuring *direct effects of SSc* (duration, global severity, number of tender joints, number of gastrointestinal symptoms, skin involvement, dyspnea, inflammatory muscle disease), *medical comorbidities*, and *exacerbating comorbid symptoms* (pain, deconditioning/capacity for exercise), *lifestyle factors* (smoking, alcohol consumption) and *psychosocial variables* (symptoms of depression).

Fatigue. The SF-36 Vitality subscale (12) includes 4 Likert items with 5 response options each (*all of the time* to *none of the time*) that assess patients' level of fatigue during the previous 4 weeks. The SF-36 Vitality subscale has been used to measure fatigue in general population samples and in patients with medical illness and injury. A recent systematic review concluded that the SF-36 Vitality subscale has good evidence for validity, reliability, sensitivity to change, and feasibility in rheumatoid arthritis (13). Cronbach's alpha was 0.84 in the current sample of patients with SSc.

Disease-related variables. SSc disease duration was established as the time from onset of the first non-Raynaud's disease symptoms based on a clinical history obtained by study physicians. SSc global disease severity was rated on a 0-10 numerical rating scale by study physicians, a scale that has been shown to be a valid measure of severity in SSc (14). Limited skin disease was defined as skin involvement distal to the elbows and knees with or without face involvement. Skin involvement was also assessed using the modified Rodnan skin score ranging from 0 to 51(15). Tender joint count was recorded by study physicians using a 28-joint count (16). Shortness of breath was rated by the patient on a 0-10 numerical rating scale (17). The number of gastrointestinal symptoms was determined by patient report from a checklist that included weight loss, anorexia, dysphagia, reflux, pyrexia, choking at night, early satiety, bloating, nausea/vomiting, constipation, diarrhea, malabsorption, fecal incontinence, antibiotics for bacterial overgrowth, and hyperalimentation. Patients were considered to have inflammatory muscle disease if physicians indicated the presence of inflammatory myositis, polymyositis, or dermatomyositis.

The number of medical comorbidities was based on a patient self-report version of the medical record-based Charlson Comorbidity Index (18). The comorbidity index includes

myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, hemiplegia, chronic obstructive pulmonary disease, ulcer disease, diabetes, kidney problems, eye problems, renal problems, rheumatoid arthritis (RA), Alzheimer's or dementia, cirrhosis or liver damage, leukemia, lymphoma, skin cancer, other cancer, metastic tumor, and AIDS. The patient-reported comorbidities questionnaire has been found to have good agreement with the medical record-based Charlson Comorbidity Index (18).

New York Heart Association (NYHA) classification was used as a proxy variable for exercise capacity or deconditioning. The NYHA is a subjective, physician-rated measure of physical activity limitation commonly used in heart failure patients to assess disease severity related to exercise tolerance. Patients are rated in four categories: I - no symptoms or limitation, II – mild symptoms and slight limitation during ordinary activity, comfortable at rest, III – marked limitation in activity, comfortable only at rest, IV – severe limitations with symptoms even at rest.

Data on medications collected included calcium channel blockers, promotility agents, corticosteroids, D-penicillamine, methotrexate, ACE inhibitors, anti-platelet agents, warfarin, NSAIDS, narcotics, hormonal replacement therapy, thyroid supplements, and gastroprotective agents. Anti-centromere antibodies were assayed by screening indirect immunofluorescence on HEp-2 cells and confirmed by a line assay (InnoLIA, Innogenetics) and anti-topoisomerase antibodies were assayed by an addressable laser bead immunoassay (QuantaPlex 8, INOVA, San Diego, USA) in a central laboratory (Dr M. Fritzler, Advanced Diagnostics Laboratory, Calgary, Alberta).

Current smoking was assessed by patient report. Alcohol consumption was assessed with a single patient-reported item, “How many alcoholic drinks do you have per week?” Weight loss in kilograms in the last year was assessed by patient report.

Symptoms of Depression. The Center for Epidemiological Studies Depression Scale (CES-D) (19) is a 20-item measure designed to assess the presence and severity of depressive symptomatology. The frequency of occurrence of each symptom during the past week is rated on a 0-3 Likert-type scale (*rarely or none of the time* to *most or all of the time*), and total scores range from 0 to 60. Standard cutoffs are ≥ 16 for “possible depression” and ≥ 23 for “probable depression” (19).

Pain. The Scleroderma-Health Assessment Questionnaire (S-HAQ) consists of the HAQ-Disability Index and visual analogue scales to measure the severity of symptoms specific for SSc, including pain in the past week (20). Unlike the visual analogue scales originally used for the S-HAQ, the pain assessments in this study were made using 11-point numerical rating scales (NRS; 0-10). The NRS has been found to have excellent psychometric properties and perform similarly to visual analog scales for pain (21).

Data Analyses. Kendall’s tau correlations were used to assess the bivariate association between sociodemographic, medical, and psychosocial variables with fatigue (SF-36 Vitality subscale scores). Multivariable associations between demographic (step 1), socioeconomic (step 2), global disease (step 3), and specific disease and lifestyle factors (step 4) with the SF-36 Vitality Scale were assessed using a hierarchical multiple linear regression. Step 1 of the regression consisted of age and gender. Marital status (married or living as married) and education (> high school) were added in step 2. Disease duration and physician-rated global severity were entered in step 3. Diffuse/limited status (or skin score), number of tender joints,

number of gastrointestinal symptoms, breathing problems, inflammatory muscle disease, medical comorbitities, exercise capacity and current smoking status were entered in step 4. Depression and pain were entered in step 5. However, there are bidirectional pathways between symptoms of fatigue, depression, and pain, and it is not clear to what degree fatigue would precede or be influenced by depression and pain (22, 23). To avoid over interpreting a possibly misspecified model, step 5 was considered exploratory (24). All analyses were conducted using SPSS version 15.0 (Chicago, IL), and all statistical tests were 2-sided with a $p < .05$ significance level.

RESULTS

Sample Characteristics. A total of 659 patients were included in the study. Table 1 shows patient demographics, medical, and symptom outcome variables. The mean age of the sample was 55.2 years, 87% of the sample as female, and 91% of the sample was White. The mean time since onset of the first non-Raynaud's Symptoms was 10.8 years, and the mean time since diagnosis of SSc was 8.2 years. Patient comorbidities are shown in Table 2. Sample characteristics were similar to those reported from other large North American and European cohorts (4). The mean score on the Vitality subscale of the SF-36 was 45.6 ± 10.8, which is consistent with other studies of patients with SSc (range 39-50) (25-29) and substantially lower (more fatigue) than the norm for the Canadian general population (65.8 ± 18.0) (30).

The mean score on the CES-D was 14.2 ± 10.5; 241 patients (36.6%) scored ≥ 16, and 135 patients scored ≥ 23, which exceeds rates typically reported for patients with other chronic conditions using the CES-D with the same scoring cut-offs (6). The mean pain rating was 3.61 ± 2.76, which is equivalent to 1.20 ± 0.92 on a 0-3 scale. This is similar to pain ratings reported in a previous study on a 0-3 scale for patients with SSc (N = 43; 1.37 ± 0.90), slightly higher than ratings from patients with RA (N = 42; 1.01 ± 0.73), and substantially higher than ratings from

healthy controls (N = 60; 0.27 ± 0.57) (27).

Predictors of Fatigue. Significant bivariate predictors of fatigue included global disease severity, number of comorbidities, tender joint count, inflammatory muscle disease, dyspnea, number of gastrointestinal symptoms, NHYA classification of III or IV, current smoking, pain, and depressive symptom (Table 1). Results from the hierarchical multiple linear regression for sociodemographic and medical predictors are shown in Table 3. Age, sex, marital status, and level of education were not significant predictors of fatigue, nor were the combination of the variables in step 1 (P= 0.347) and step 2 (P=0.340). Demographic variables accounted for 0.3% of the variance, and socioeconomic variables accounted for another 0.4% of the variance. In step 3, only physician-rated disease severity (P < 0.001) was a significant predictor of fatigue. Global disease duration and severity factors accounted for an additional 4.1% of the variance. Specific disease and lifestyle factors added in step 4 accounted for the largest proportion of the variance (an additional 21.6%). Of the specific disease factors, breathing problems (P < 0.001), number of gastrointestinal symptoms (P < 0.001) and comorbid health problems (P= 0.004) significantly predicted fatigue. When specific disease factors were included in the equation, global physician-rated disease severity was no longer significant (P= 0.183). Both symptoms of depression (standardized regression coefficient (β) = -0.42) and pain (β = -0.21) were significantly related to fatigue (P < 0.001) when added in step 5 (R^2 = 45.2%; not shown). However, the magnitude of the regression coefficients for symptoms of depression and pain, which were approximately 3 times and 2 times, respectively, the next largest predictor (number of gastrointestinal symptoms) suggests that these were not appropriately specified as precursors to fatigue, but rather likely reflected bidirectional relationships or shared method influences. The relationship of breathing

problems, gastrointestinal symptoms, and comorbid health problems with fatigue did not change substantively in step 5. Medications, antibodies, weight loss in the past year, and alcohol consumption were not independently associated with fatigue.

DISCUSSION

This study showed that fatigue levels are high in SSc compared to general population levels, which is consistent with the results of a recent systematic review that found that fatigue related to SSc was significantly higher than in general population samples and similar to patients with other rheumatic diseases or cancer patients in active treatment (10). In multivariate analysis, statistically significant correlates of fatigue included number of medical comorbidities, patient-reported breathing problems, patient-reported number of gastrointestinal symptoms, and smoking. Tender joint count also approached statistical significance. Physician-rated global disease severity was a robust predictor of fatigue on a bivariate basis and after controlling for sociodemographic factors, but was no longer statistically significant when medical comorbidities and specific disease factors were included in the model. Depressive symptoms and pain were robust predictors of fatigue, but sociodemographic variables (age, sex, marital status, education) were not associated with fatigue.

There are no studies of fatigue management in SSc. Research in cancer and other rheumatic diseases shows that fatigue is amenable to intervention. Guidelines for cancer-related fatigue (31) suggest a two-stage approach of first identifying and treating contributing factors (e.g., pain, emotional distress, sleep disturbance, deconditioning), followed by management of residual fatigue. Among nonpharmacologic management strategies (e.g., exercise, sleep hygiene, psychosocial interventions), empirical support is strongest for exercise and psychosocial interventions, including education and stress management groups and cognitive-behavioural

therapy (32). Pharmacological interventions have been used successfully to reduce fatigue in cancer (33), Parkinson's disease (34), and HIV/AIDS (35). In the rheumatic diseases, standard pharmacological treatments, including anti-tumor necrosis factor and adjunctive therapies, reduce fatigue (36-40). A similar approach targeting depression, pain, and smoking among patients with SSc is supported by the findings from this study. Addressing other lifestyle factors, such as sleep and exercise are also promising, although those variables are not collected in the Canadian Scleroderma Group Registry and were not used in this study.

Two important factors that make addressing fatigue in SSc difficult are (1) the lack of an agreed-upon standard for identifying clinically significant fatigue, and (2) a need for greater understanding of fatigue etiology, including the relationship between depressive symptoms, pain, and fatigue. A number of measurement tools have been validated to assess symptoms of fatigue, but these tools are not designed for accurate case detection, are not benchmarked to a case-definition standard, and do not necessarily identify clinically significant fatigue levels that warrant investigation and treatment. Establishing a unified case-definition approach to assessing fatigue would enhance comparability of research results, as well as the ability to detect important differences across groups that could help explain etiology. In addition, a standard case-definition approach would facilitate the benchmarking of cut-off scores on fatigue questionnaires and the development of brief, easy to use screening tools to improve clinical management. Research in cancer has laid the groundwork for this by developing case-definition criteria for Cancer-Related Fatigue (41) that appear in the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* (ICD-10). Four studies that have used the Cancer-Related Fatigue case definition and structured diagnostic interview reported consistent prevalence estimates (17% to 26%) (3, 42-44). Work is currently underway by investigators of the Canadian

Scleroderma Research Group to determine the degree to which this case-definition protocol may be viable as a unifying framework for fatigue assessment across patient groups, including SSc.

From an etiological perspective, high levels of both fatigue (1) and depression (45) are common among patients with chronic medical diseases, including SSc (6, 46, 47). There is substantial overlap between fatigue and depression, and measures of each were highly correlated in this study. Behavioural and cognitive factors link fatigue and depressive symptoms. In addition, basic neuroscience research has demonstrated that proinflammatory cytokines can signal the central nervous system to induce symptoms of fatigue and other *sickness behaviours* (e.g., malaise, listlessness, loss of appetite, depressed mood) (48). Several proinflammatory mediators, including the *acute response* cytokines IL-1β and TNF-α, as well as IL-6 and INFγ, have been linked to altered central nervous system activity, and symptoms of depression and fatigue (49). The presence of chronic inflammation enhances cytokine production, and is one of the three major pathways that cause most of the organ damage in SSc (49). The proinflammatory cytokines IL-1β, IL-6, INFγ, and TNF-α are key components in this process and may also play a role in the pathogenesis of fatigue and depression in SSc (49). Research is needed to clarify the relationship of depression to fatigue in SSc.

Limitations should be considered in interpreting the results of this study. This study did not evaluate factors related to proinflammatory cytokines and the inflammation process. In addition, potentially important variables related to malnutrition, anemia, sleep, exercise, and cognitive factors were not available. Other limitations of this study include its cross-sectional design and the concurrent assessment of both predictor and outcome variables, which did not allow for the evaluation of pathways of influence. Indeed, it was not possible to determine the

nature of the relationship between depression, pain, and fatigue. Similar to fatigue, each of these variables reflects the lived experiences of patients with SSc. Thus, although there are causal pathways and linkages among these variables, they are all potential outcomes related to the demographic, socioeconomic, and disease factors that were the focus of this study. In addition, method overlap related to self-reporting of these variables can inflate associations between these variables. It is important to note that self-report method overlap may also explain the relative predictive importance of specific indicators of disease factors since breathing difficulties, number of gastrointestinal symptoms, and tender joint count were all based on patient report. Even though tender joint count was recorded by a physician, it was based on patient-report of tenderness/pain in each joint.

In summary, findings from this study are consistent with prior evidence showing that fatigue is an important, albeit largely ignored, problem for patients with SSc. Patients with more difficulty breathing, higher numbers of gastrointestinal symptoms, more medical comorbidities, and patients who are current smokers are the most vulnerable. More research is needed on fatigue in SSc, including work on assessment and case identification and the development and testing of interventions to reduce fatigue.

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Table 1. Sociodemographic Variables, Medical Variables, and Correlations with Fatigue as Measured by the SF-36 Vitality Subscale: N = 659

	Number	Percent	Mean	SD	Kendall's Tau Coefficient	P
Demographic Variables:						
Age (years)			55.2	12.3	0.027	0.324
Female Gender	571	86.6			-0.045	0.177
Race/Ethnicity White*	635	90.6			0.001	0.988
Socioeconomic Variables:						
Education Level > Than High School	310	47.0			0.033	0.312
Married or Living as Married	465	70.6			0.037	0.259
Medical Variables:						
Time Since Onset of First Non-Raynaud's Symptoms (years)			10.5	8.7	0.025	0.346
Time Since Diagnosis of Systemic Sclerosis (years)			8.2	7.7	0.016	0.557
Physican-Rated Global Disease Severity (1-10)			2.8	2.5	-0.148	<0.001
Diffuse Systemic Sclerosis	267	40.5			-0.055	0.093
Modified Rodnan Total Skin Score (0-51)			10.8	9.8	-0.049	0.083
Comorbidity Score			0.8	1.1	-0.156	<0.001
Tender Joint Count (0-28)			1.7	4.2	-0.110	<0.001
Inflammatory Muscle Disease	78	11.8			-0.074	0.025
Breathing Problems (0-10)			2.0	2.6	-0.305	<0.001
Number of Gastrointestinal Symptoms (0-14)			4.0	2.9	-0.319	<0.001
New York Heart Association Functional Classification III or IV	61	9.2			-0.198	<0.001
Current Smoker	105	15.9			-0.105	0.001

Alcohol: Number of drinks per week:**					0.047	0.114
< 1	305	47.1				
1-7	280	43.3				
8-14	47	7.3				
>14	15	2.3				
Pain Numerical Rating Scale (0-10)			3.6	2.8	-0.361	<0.001
Depressive Symptoms (CES-D) (0-60)			14.2	10.5	-0.454	<0.001
Fatigue (SF-36 Vitality subscale) (0-100, lower numbers indicate worse fatigue)			45.6	10.8	-----	-----

* N= 635; ** = N = 647.

Table 2. Patient-reported Medical Comorbidities (N=659)

Comorbidity	Number	Percent
Myocardial Infarction	29	3.8
Congestive Heart Failure	39	5.9
Peripheral Vascular Disease	17	2.6
Cerebrovascular Disease	26	3.9
Hemiplegia	4	0.6
Chronic Obstructive Pulmonary Disease	95	14.4
Ulcer Disease	75	11.4
Diabetes	40	6.1
Kidney problems	3	0.5
Eye Problems	3	0.5
Renal Problems	30	4.6
Rheumatoid Arthritis	109	16.5
Alzheimer's/ Dementia	2	0.3
Cirrhosis/ Liver Damage	11	1.7
Leukemia	1	0.2
Lymphoma	1	0.2
Skin Cancer	14	2.1
Cancer, Other	12	1.8
Metastic Tumor	2	0.3
AIDS	0	0.0

Table 3. Hierarchical Linear Regression of the Relationship between Demographic Variables, Socioeconomic Variables, Global Disease Duration/Severity, Specific Disease Factors, and Fatigue as Measured by the SF-36 Vitality Subscale

Step	Variables	B	SE B	β	P	df	R^2	Adjusted R^2	Δ R^2	P
1	**Demographic Variables:**					2, 656	0.003	0.000	0.003	0.347
	Age	0.016	0.034	0.018	0.650					
	Female Gender	-1.672	1.234	-0.053	0.179					
2	**Socioeconomic Variables:**					4, 654	0.007	0.001	0.004	0.300
	Age	0.021	0.035	0.024	0.550					
	Female Gender	-1.691	1.244	-0.053	0.174					
	Education > High School	0.710	0.865	0.033	0.412					
	Married or Living as Married	1.225	0.925	0.052	0.186					
3	**Global Disease Duration/Severity:**					6, 652	0.048	0.039	0.041	<0.001
	Age	0.029	0.035	0.033	0.414					
	Female Gender	-0.968	1.231	-0.030	0.432					
	Education > High School	0.437	0.850	0.020	0.607					
	Married or Living as Married	0.585	0.916	0.025	0.523					
	Time Since Onset of First Non-Raynaud's Symptoms	-0.041	0.049	-0.033	0.406					
	Physician-rated Disease Severity	-1.000	0.189	-0.208	<0.001					

Step	Variables	B	SE B	β	P	df	R^2	Adjusted R^2	Δ R^2	P
4	**Specific Disease and Lifestyle Factors:**					14, 644	0.264	0.248	0.216	<0.001
	Age	0.017	0.033	0.020	0.606					
	Female Gender	-0.520	1.109	-0.016	0.639					
	Education > High School	-0.806	0.765	-0.037	0.293					
	Married or Living as Married	0.162	0.818	0.007	0.843					
	Time Since Onset of First Non-Raynaud's Symptoms	0.004	0.004	0.037	0.296					
	Physician-rated Disease Severity (0-10)	-0.257	0.192	-0.053	0.183					
	Comorbidities/Other Health Problems	-1.042	0.357	-0.106	0.004					
	Diffuse Scleroderma	-1.017	0.696	-0.052	0.144					
	Tender Joint Count	-0.153	0.090	-0.059	0.090					
	Inflammatory Muscle Disease	-0.730	1.171	-0.022	0.533					
	Breathing Problems (0-10)	-0.966	0.186	-0.229	<0.001					
	Number of Gastrointestinal Symptoms	-0.991	0.139	-0.271	<0.001					
	New York Heart Association Functional Classification III or IV	-0.360	0.700	-0.023	0.607					
	Current Smoker	-2.485	1.045	-0.084	0.018					

For each step, individual variable parameters are shown, including raw regression coefficients (B) and their standard errors, as well as standardized regression coefficients (β), and p values. In addition, overall model fit statistics and a P value for the change in variance accounted for (Δ R) are shown for each step.

Figure 1. Hypothesized etiological factors for fatigue in scleroderma.