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Symptom Interference Severity and Health-Related Quality of Life in Pulmonary Arterial Hypertension

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Abstract

Context—While assessing symptom severity is an important component of evaluating symptoms, understanding those symptoms that interfere with patients' lives is also key. Pulmonary arterial hypertension (PAH) is a chronic disease resulting in right heart failure and increased mortality. Patients with PAH experience multiple symptoms but we do not know which symptoms and to what extent their symptoms interfere with daily life.

Objectives—To: 1) describe the prevalence of those symptoms that interfere with life; 2) describe the severity of symptom interference; and 3) determine those sociodemographic and clinical characteristics, and interfering symptoms associated with health-related quality of life (HRQOL) in patients with PAH.

Methods—A convenience sample of 191 patients with PAH completed a sociodemographic form; the Pulmonary Arterial Hypertension Symptom Interference Scale (PAHSIS) and the Medical Outcomes Survey Short Form-36 (SF-36) to measure HRQOL. Hierarchical multiple linear regression was used to analyze demographic and medical characteristics along with symptom interference from the PAHSIS as predictors of HRQOL from the composite mental and physical health summary scores of the SF-36.

Results—The most interfering symptoms reported were fatigue, shortness of breath with exertion and difficulty sleeping. Age, gender, functional class, oxygen use, fatigue, dizziness and Raynaud's phenomenon were associated with the HRQOL physical health summary scores. The symptoms fatigue and SOB while lying down were associated with the HRQOL mental health summary scores.

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Disclosures

The authors declare no conflicts of interest.

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Conclusion—Patients with PAH are experiencing multiple symptoms that are interfering with their HRQOL and ability to function.

Keywords

symptoms; interference; quality of life; pulmonary arterial hypertension

Introduction

The importance of the symptom experience as well as the severity of symptoms can impact a person's activities of daily living and this is important in overall quality of life. Pulmonary arterial hypertension (PAH) is a life-limiting disease that affects primarily young to middle-aged women (1). The etiology for PAH is varied, with over half of these patients diagnosed with idiopathic PAH. There are additional associated disorders that include connective tissue disease (e.g., systemic sclerosis); portopulmonary hypertension, congenital heart disease, schistosomiasis, and side effects of certain drugs (e.g., fenfluramine/phentermine) (1). PAH is characterized by elevated mean pulmonary artery pressures of 25 mmHg or greater and a mean capillary wedge pressure less than 15mmHg; these increased pressures result in remodeling of the right heart and ultimately right heart failure and eventual death (1). Initial symptoms include fatigue and shortness of breath (SOB) on exertion. These symptoms may be attributed to other cardiopulmonary disorders resulting in a delay in diagnosis. Diagnosis is often one of exclusion and may require multiple health care encounters to rule out other disorders (2).

Patients are commonly treated with diuretic therapy, anticoagulation and PAH-approved drugs that promote vasodilation. Common classes of PAH-approved medications include: calcium channel blockers, endothelin receptor antagonists, phosphodiesterase Type-5 inhibitors, and prostanoid analogues. Pharmacological treatments can be complex especially the prostanoid analogues, which are commonly administered intravenously, subcutaneously or inhaled six to nine times per day (3). Although pharmacological therapies have reduced mortality, the mortality rate still remains high, with a median survival of seven years (4). Recent Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management (REVEAL) data show five-year survival for previously diagnosed patients with PAH at 65.4% compared with 61.2% for newly diagnosed patients (5).

Patients with PAH have multiple symptoms that can be severe and impair their health-related quality of life (HRQOL) (6, 7). Some of the most commonly reported symptoms that can be severe are fatigue, SOB on exertion and difficulty sleeping. While patients have limits in their physical functioning, they also report depressive symptoms (8) and anxiety (9). Patients with PAH describe how they must readjust their lives and tailor their activities because of such symptoms as SOB and fatigue (10).

While assessing the severity of symptoms, it is important to gauge how much symptoms interfere with the patient's life in order to understand how patients manage and cope with their symptoms while living with a chronic illness. Even though a symptom may not be reported as severe, it may dramatically interfere with a patient's ability to perform activities of daily living and care for themselves and/or their families. Patients with PAH have

impairment in the ability to function that adversely affects their HRQOL (11, 12). Others have found decreased HRQOL in PAH with increased symptom burden and a lack of awareness of the availability of palliative care (13). Symptoms and physical functioning are important to assess in PAH (14, 15) along with how symptoms interfere with patients' lives.

The University of San Francisco (UCSF) Symptom Management Model was the theoretical framework used for this study (16). There are three dimensions, which include the symptom experience, symptom management strategies and symptom outcomes. Understanding which PAH symptoms interfere the most and the extent of their interference is important to understand in order to develop and implement symptom management strategies. Much of the research investigating symptom interference has been conducted in oncology patients (17, 18–24). Commonly reported symptoms that are severe and interfere with patients' lives include fatigue (24), pain and sleep disturbance (25). We aimed to extend the knowledge of the symptom experience in patients with PAH. By understanding this phenomenon, we can determine those symptoms that most interfere with patients' lives so that targeted interventions can be developed and tested. The objectives of this study were to: 1) describe the prevalence of those symptoms that interfere with life; 2) describe the severity of symptom interference; and 3) determine those sociodemographic and clinical characteristics, and interfering symptoms associated with HRQOL in PAH.

Methods

Sample and Setting

This cross-sectional study included self-identified patients with World Health Organization Group I PAH, which includes the PAH etiologies: idiopathic, familial, connective tissue disease, congenital heart disease, HIV, portopulmonary hypertension, and drugs associated with causing PAH such as anorexigens. The inclusion criteria for this convenience sample included adults 18 years and older who were able to read and write English. Two hundred sixty-two people with PAH were recruited. A total of 191 patients completed the study. The response rate was 69%.

Before recruitment began, the study was approved by both the university and hospital institutional review boards. A PAH clinic, local support groups and international conferences, along with the Pulmonary Hypertension Association website, served as recruitment sites. At the PAH clinic, the nurse practitioner approached the patients to gauge their interest. If they were interested, the principal investigator (PI) then approached the patient to answer questions regarding the study. At the PAH support groups and the conferences, the facilitator introduced the PI who would briefly discuss the study, and interested patients approached the PI after the meeting. The administrator for the Pulmonary Hypertension Association website posted an advertisement describing the study. Those people with PAH contacted the PI. Questionnaires were either completed and returned to the PI on site or participants mailed back the questionnaires to the PI using a self-addressed stamped envelope provided in each packet. The study packet included a demographic and medical form; the Pulmonary Arterial Hypertension Symptom Interference Scale (PAHSIS); and the Medical Outcomes Study Short Form-36 (SF-36®).

Measures

Demographic and Medical Form—The demographic and medical form was developed by the investigator. The participants completed the form, which included the following variables: gender, age, race/ethnicity, type of PAH, date of PAH diagnosis, marital status, educational level, employment status (full time, part time, retired, disabled), occupation, oxygen use and current medications. The PI classified all patients into New York Heart Association (NYHA) functional class (26) based on self-reported symptoms at the time of enrollment in the study. NYHA functional class I includes those who have PAH but do not have any symptoms such as fatigue or dyspnea. NYHA functional class II are those with PAH who are not symptomatic with usual activities, and NYHA functional class III are those who are comfortable at rest but less than usual activities evoke symptoms. NYHA functional class IV are patients who are symptomatic at rest.

PAHSIS—The PAHSIS is an investigator-developed tool to measure the degree to which PAH symptoms interfere with patients' lives (27). The PAHSIS contains 17 PAH symptoms that are assessed on a 0–10 scale. Patient rate how much each of the symptoms interferes with their lives. Zero represents no interference and 10 represents that the symptom is “extremely interfering.” Participants rate how much the symptoms have interfered over the past month. Symptoms included on the PAHSIS measure include: SOB with exertion, SOB lying down, SOB at rest, awakening at night SOB, fatigue, difficulty sleeping, chest pain, abdominal swelling, swelling of ankles and feet, syncope, palpitations, dizziness, cough, nausea, loss of appetite, hoarseness, and Raynaud's phenomenon (cold, numbness of extremities). Initial psychometric properties demonstrate good validity and reliability (27). Cronbach's alpha for the current study was 0.91.

SF-36—The SF-36 is a commonly used and accepted measure of generic HRQOL, and the survey measures both physical and mental health components (28). The SF-36 contains eight subscales: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. The subscales are combined to form composite mental and physical summary scores. The mental health composite summary score is formed by combining the subscores of vitality, social functioning, and role limitations because of emotional problems and general mental health. The physical composite summary score is calculated by combining the subscores for general health problems, physical functioning, and role limitations because of physical health problems and pain. Scores range from 0–100. Higher scores indicate better HRQOL. The psychometrics are widely established (29, 30) and the current study's Cronbach alpha was 0.84.

Statistical Analyses

Continuous variables are expressed as means and standard deviations (SD) and dichotomous and nominal variables are shown as frequencies and proportions. Distributional properties showed that normalizing transformations were not necessary. Visual inspection assessed for outliers. Analyses were performed using SPSS v. 22 (31). Statistical significance was set at the 0.05 level. Hierarchical multiple linear regression was used to analyze demographic and medical variables along with symptom interference from the PAHSIS as predictors of HRQOL from the composite mental and physical health summary scores of the SF-36.

Univariate analyses of demographic and medical characteristics and the symptom interference on the PAHSIS were used to determine correlations with HRQOL. Variables that correlated with the composite mental and physical health summary scores of the SF-36 at the 0.10 level of significance were included in the analysis.

Results

The sample included 191 patients with PAH (Table 1). The mean age was 53 years, the majority were female (85%), and over half of the sample had idiopathic PAH. Most were married with a college education. Forty-three percent were disabled and the majority were NYHA functional class III–IV (69%). Participants had been diagnosed on average six years prior to the current study.

The most prevalent symptoms reported by patients that interfered with their lives were SOB on exertion (92%), followed by fatigue (90%) and then sleep difficulty (57%) (Table 2). Mean symptom interference scores were highest for SOB on exertion, followed by fatigue and difficulty sleeping (Table 2). Overall, general health, physical function, role physical, vitality, and the composite physical summary scores were diminished (Table 3).

The final regression model for composite physical HRQOL included fatigue, oxygen use, dizziness, age, gender and the presence of Raynaud's phenomenon symptoms (Table 4). These variables accounted for 69% of the variance in physical HRQOL scores, $F_{7,143}=43.34$, $P=0.026$. The Durbin-Watson statistic confirmed independence of error (1.89) and the Variance Inflation Factor for predictors ranged from 1.31–1.90, indicating that collinearity was not an issue in the model.

The regression model of the composite mental HRQOL included fatigue and SOB while lying down symptoms (Table 5). These variables accounted for 45% of the variance in the mental HRQOL scores, $F_{2,148}=60.00$, $P<0.0001$. Similar to physical HRQOL, the Durbin-Watson statistic was 2.02 and the Variation Inflation Factor was 1.13 for mental HRQOL.

Discussion

This is the first study to investigate symptom interference and HRQOL in patients with PAH. The symptoms that most interfere with patients' lives and the most severe were fatigue, SOB on exertion and difficulty sleeping. Not surprisingly, general health, physical function, role physical and vitality were decreased compared to the U.S. normative population (32) and in other studies including patients with PAH (12, 13, 15). Age, gender, functional class, oxygen use, fatigue, dizziness and Raynaud's phenomenon symptoms were associated with the composite physical HRQOL summary score. The symptoms fatigue and SOB while lying down were associated with the composite mental HRQOL summary score.

Much of the research investigating the symptoms that interfere in patient's lives has been done in oncology patients. The M. D. Anderson Symptom Inventory (MDASI) is a widely used, psychometrically established, patient-reported outcome to measure commonly encountered symptoms in patients with cancer and how symptoms interfere with daily functioning (19). Symptoms on the MDASI include: pain, fatigue, nausea, disturbed sleep,

distressed, SOB, remembering things, lack of appetite, drowsy, dry mouth, sad, vomiting and numbness or tingling. Many of the symptoms on the MDASI overlap with the symptoms on the PAHSIS (e.g., SOB, fatigue) indicating some common underlying symptoms in patients with acute and chronic illness.

Fatigue is a prominent symptom in acute and chronic illness. A study involving patients with breast, prostate, colorectal and lung cancer, found that fatigue was reported as moderate to severe and was associated with poor physical performance (33). People with HIV can have high fatigue levels that also interfere with their daily physical function (34). A study including patients with advanced lung cancer showed that dyspnea, fatigue and pain impacted daily activities (35). Those activities assessed included normal work, walking, sleep, mood, relations with other people, enjoyment of life, and general activities.

Some patients with cancer experienced different patterns of pain and fatigue (36). Those patients with high pain and high fatigue scores also experienced more psychological symptoms such as depressed mood and increased limitations in activities. Dyspnea and fatigue interfered with at least one activity of daily living in over half of the patients and pain in 40%. Not surprisingly, dyspnea and fatigue interfered mostly with walking and work. An important point to note is that even symptoms that were not reported as severe still interfered with the patient's life. In PAH, syncope is not necessarily a commonly reported symptom or a severe symptom (37). However, syncope is a poor prognostic sign in patients with PAH and needs to be assessed. This shows the importance of assessing symptoms and how they interfere with patients' lives. In the current study, fatigue was a commonly reported symptom that interfered with patients' lives. Fatigue also was associated with both the physical and mental health components of HRQOL. Similarly, a study found dyspnea to interfere not only with physical activities but also psychological domains such as mood and enjoyment (38).

Sleep disturbance, symptom severity, and symptom interference were examined in patients with cancer (39). Sleep was strongly associated with the patient's enjoyment of life, mood and relations with others. A study examining the association between symptom severity, symptom interference and sociodemographic characteristics in women with breast cancer found fatigue, sleep disturbance and drowsiness were the most frequent and severe symptoms reported (22). The MDASI symptom severity total scores were associated with the total symptom interference scores for activities of daily living.

A study investigating the relationship of symptom clusters and symptom interference with the daily life of patients with lung cancer found the most severe symptoms in rank order to be fatigue, sleep disturbance, lack of appetite and SOB (24). These symptoms interfered mostly with work, general activities and walking. Similarly, the most interfering symptoms in the current study were SOB on exertion, fatigue and sleep difficulty. A study including women with early-stage breast cancer found fatigue, sleep disturbance and drowsiness were the most severe symptoms that most commonly interfered with work (22).

A study conducted in China investigated the presence of symptoms and symptom clusters and their association with symptom interference in patients with hepatocellular carcinoma

before and after transcatheter arterial chemoembolization (21). The most severe symptoms were fatigue, distress, sadness, lack of appetite and sleep disturbance which were similar to our findings. These symptoms most often interfered with work and enjoyment of life. Distress, sadness, fatigue, sleep disturbance and lack of appetite were significantly associated with the total symptom interference. Although this was a sample of oncology patients, our results also showed that the symptoms of fatigue and sleep disturbance interfered most with PAH patients' lives.

Schoulte et al. investigated the effect of coping style on symptom interference in hematopoietic stem cell transplantation patients and found that neither age nor gender predicted symptom interference, except for chronic graft-versus-host disease where older patients did experience more interference and breathing problems six months post treatment (23). Breathing problems also were found to interfere in those patients with hematopoietic stem cell transplantation. Some of these results contradict our findings; our current study found age and gender were associated with the composite physical HRQOL score. However, other researchers also found that women reported more interference from the symptoms they experienced. Our study had a small proportion of males (15%), making it difficult to definitely state if males or females had more symptom interference. Those who underwent hematopoietic stem cell transplantation also reported more interference in their daily lives because of breathing problems (23). We also found SOB while lying down to be associated with the composite mental HRQOL score. Other studies have found dyspnea to be associated with mental health states such as anxiety and depression (40).

In a study that included patients with stage IV non-small cell lung cancer, investigators found that symptom interference was prognostic for overall survival for those with poor functional performance status (19). The current study shows how those with worsening functional status also report greater symptom interference and worse HRQOL. This demonstrates the need to perform longitudinal studies to determine those factors such as symptoms that impact HRQOL in patients with PAH. Symptoms may actually be prognostic in patients with PAH but more research is needed.

In a study investigating symptom interference during the menopausal transition stages and early postmenopause in a cohort of women, researchers found that interference with work was associated with perceived health, stress, hot flashes, anxiety, depressed mood, insomnia symptoms (difficulty getting to sleep and awakening during the night), pain (backache, joint pain), and difficulty concentrating and forgetfulness (41). The final model did include mental health-related variables such as depressed mood and anxiety showing the effect that symptoms can interfere with a person's mental health. Our study demonstrated how symptoms interfered with both the physical and mental components of HRQOL in patients with PAH.

Composite physical HRQOL was associated with fatigue, oxygen use, dizziness, age, gender and Raynaud's phenomenon. Fatigue is a multidimensional symptom that can have both physical and mental components (42). In PAH there are physical limitations because of the presence of right heart failure resulting in physical fatigue that can impact HRQOL. Additionally, as a result of vasoconstriction and plexiform lesions in the pulmonary

vasculature, hypoxemia can result (3). Those patients with PAH with more physical limitations tend to be more likely to have advanced disease and be classified as disabled (37). Dizziness can limit the ability of patients to stand and move safely, putting them at risk for falls. Dizziness in patients with PAH may be a result of the vasodilator therapy they are on and/or the less than optimal functioning of the right ventricle. Age and declining physical functioning has been previously described (43). The presence of Raynaud symptoms is associated with pain, decreased functioning and disability in patients with scleroderma (44).

Composite mental HRQOL was associated with fatigue and SOB while lying down in the current study. Fatigue has been associated with psychological states such as anxiety and depression in cancer patients receiving chemotherapy (45). Forty-seven percent of the variance in HRQOL was explained by psychological components. Fatigue in patients with systemic lupus erythematosus was associated with both the physical and mental health composite summary scores on the SF-36 (46). Dyspnea in patients with chronic obstructive pulmonary disease (47) was associated with the mental health composite summary score on the SF-36 and in patients with idiopathic pulmonary fibrosis (48).

Not only have symptoms been shown to affect domains of HRQOL, symptoms have been shown to be associated with employment status (7, 37). Residual symptoms in oncology patients impacted their ability to work after cancer treatment (49). In our current study, although the mean age was 53 years, over 40% of the sample reported being disabled. This is a significant finding demonstrating how symptoms play an important role in the ability of people with chronic illness to function and live.

Limitations and Future Directions

Several limitations need to be addressed. First, this was a cross-sectional design. Future studies will need to address how symptom trajectories change over time and those factors that are modifiable or amenable to interventions. Second, all participants in this study self-identified their PAH diagnosis. There was no confirmation through health provider report or clinical records. Third, follow-up studies need to include a more diverse sample with more racial/ethnic groups represented. Fourth, we did not specifically delineate which activities each symptom interfered with; this should be included in future research. Additionally, the SF-36 is a widely used measure of generic HRQOL that can be compared to a many other populations including health individuals. The SF-36 uses a Likert scale whereas other measures, such as the United States Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) (15), use a dichotomous “yes” or “no” and “true” or “false” format, not allowing for nuances in the measure.

Next steps include developing and testing interventions to improve symptoms that are severe and interfere with patients’ lives along with improving HRQOL. A more extensive profiling of what activities of daily living are affected and how best to improve patients’ physical and mental functioning is needed. Some possible future interventions that have shown some success or have some preliminary results include mindfulness-based stress reduction and cognitive behavioral therapy (50). Mindfulness-based stress reduction has shown to significantly improve fatigue and sleep disturbance symptoms and symptom interference in

women breast cancer survivors (51). Cognitive behavioral therapy was found to be effective in treating pain, fatigue and sleep disturbance in patients with advanced cancer (50).

Conclusions

This is the first study to describe how symptoms in patients with PAH interfere with daily life and affect HRQOL. Some of the most interfering symptoms reported were fatigue, SOB with exertion and difficulty sleeping. The physical components of HRQOL are worse in PAH while the mental health components are actually better than the U.S. normative data from the SF-36. Age, gender, functional class, oxygen use, fatigue, dizziness and Raynaud's phenomenon symptoms were associated with the HRQOL physical health summary scores. The symptoms fatigue and SOB while lying down were associated with the HRQOL mental health summary scores.

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Table 1

Sociodemographic and Clinical Variables

Variable (N=191)	Total N=191
Mean \pm SD age (yrs)	53.2 \pm 15.1
Gender: female	162 (85%)
Ethnicity ^a	
Caucasian	168 (88%)
Marital Status ^a	
Married	97 (51%)
Living Arrangements	
With family/friends	141 (74%)
Education:	
College graduate	113 (59%)
Employment Status ^a	
Full-time	36 (19%)
Part-time	21 (11%)
Retired	43 (23%)
Disabled	77 (43%)
PAH Etiology	
Idiopathic	104 (55%)
Connective Tissue Disease	34 (18%)
Congenital Heart Disease	8 (4%)
Drugs (fenfluramine/phentermine)	8 (4%)
NYHA Functional Class	
I	22 (12%)
II	36 (19%)
III	54 (28%)
IV	79 (41%)
Oxygen Use	115 (60%)
Years since diagnosis	6.3 \pm 6.6
Medications	
Calcium Channel Blockers	46 (24%)
Endothelin Receptor Antagonists	95 (50%)
Phosphodiesterase Type-5 inhibitors (PDE-5)	110 (58%)
Prostanoid analogues	75 (39%)
Diuretics	117 (61%)

Variable (N=191)	Total N=191
Digoxin	29 (15%)

PAH = pulmonary arterial hypertension; NYHA = New York Heart Association.

^a $P < 0.05$.

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Table 2

Symptom Interference Prevalence and Severity in Pulmonary Arterial Hypertension

Symptom Interference	<i>n</i> (%) ^a	Mean ± SD
SOB on exertion	176 (92%)	5.4 ± 3.0
Fatigue	171 (90%)	4.9 ± 3.0
Sleep difficulty	108 (57%)	2.9 ± 3.4
Swelling of ankles and feet	99 (52%)	2.2 ± 2.8
Raynaud's phenomenon	79 (41%)	1.9 ± 3.0
Dizziness	101 (53%)	1.9 ± 2.5
Palpitations	101 (53%)	1.8 ± 2.4
Chest pain	87 (46%)	1.6 ± 2.4
Cough	82 (43%)	1.6 ± 2.4
Abdominal swelling	66 (35%)	1.5 ± 2.7
Loss of appetite	71 (37%)	1.3 ± 2.3
SOB at rest	75 (39%)	1.2 ± 2.0
SOB while lying down	62 (32%)	1.2 ± 2.1
Nausea	68 (36%)	1.1 ± 2.1
Hoarseness	47 (24%)	0.9 ± 2.0
Awaken at night SOB	48 (25%)	0.8 ± 1.8
Syncope	19 (10%)	0.4 ± 1.3

SOB=shortness of breath.

^aIncludes subjects reporting 1 on the symptom interference scale.

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Table 3

Health-Related Quality of Life

Subscale PAH	Total N=191 Mean \pm SD
General Health	37.1 \pm 25.9
Physical function	41.5 \pm 25.9
Role physical	36.4 \pm 40.3
Pain	66.4 \pm 27.6
Vitality	41.3 \pm 22.7
Social function	65.5 \pm 26.4
Mental health	71.9 \pm 19.3
Role emotional	67.0 \pm 41.5
Composite Summary Mental health	61.5 \pm 21.0
Composite Summary Physical health	45.4 \pm 22.7

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Table 4

Predictors of Physical Health Summary Scores for SF-36

Predictor	B	SE of B	β	t	P
Constant	91.98	7.55		12.06	<0.0001
Fatigue	-2.66	0.49	-0.36	-5.48	<0.0001
Functional Class	-4.98	1.45	-0.22	-3.44	0.001
Oxygen use	-7.58	2.61	-0.16	-2.90	0.004
Dizziness	-1.67	0.54	-0.19	-3.09	0.002
Age	-0.20	0.08	-0.13	-2.63	0.010
Gender	8.71	3.49	0.13	2.50	0.014
Raynaud's phenomenon	-0.95	0.42	-0.12	-2.26	0.026

Table 5

Predictors of Mental Health Summary Scores for SF-36

Predictor	<i>B</i>	SE of <i>B</i>	β	<i>t</i>	<i>P</i>
Constant	82.15	2.45		33.60	<0.0001
Fatigue	-3.64	0.45	-0.53	-8.13	<0.0001
Shortness of breath while lying down	-2.52	0.63	-0.26	-4.03	<0.0001