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Understanding the Association of Fatigue With Other Symptoms of Fibromyalgia: Development of a Cluster Model

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Objective. **To develop a symptoms cluster model that can describe factors of fibromyalgia syndrome (FMS) associated with fatigue severity as reported by the sample and to explore FMS clinical symptom subclusters based on varying symptom intensities.**

Methods. **FMS individuals (n = 120, 82% ages 31–60 years, 90% women, 59% white) diagnosed with the 1990 or 2010 American College of Rheumatology diagnostic criteria were enrolled. Participants completed multiple validated self-report questionnaires to measure fatigue, pain, depression, anxiety, pain catastrophizing, daytime sleepiness, cognitive function, and FMS-related polysymptomatic distress. Cluster analysis using SPSS 19.0 and structural equation modeling using AMOS 17.0 were used.**

Results. **Final structural equation modeling the symptoms cluster model showed good fit and revealed that FMS fatigue was associated with widespread pain, symptoms severity, pain intensity, pain interference, cognitive dysfunction, catastrophizing, anxiety, and depression ($\chi^2 = 121.72$ (98df), $P > 0.05$, $\chi^2/df = 1.242$, comparative fit index = 0.982, root mean square error of approximation = 0.045). Two distinct clinical symptom subclusters emerged: subcluster 1 (78% of total subjects), defined by widespread pain, unrefreshed waking, and somatic symptoms, and subcluster 2 (22% of total subjects), defined by fatigue and cognitive dysfunction with pain being a less severe and less widespread occurrence.**

Conclusion. **Overall, subcluster 1 had more intense symptoms than subcluster 2. FMS symptoms may be categorized into 2 clinical subclusters. These findings have implications for an illness whose diagnosis and management are symptom dependent. A longitudinal study capturing the variability in the symptom experience of FMS subjects is warranted.**

INTRODUCTION

Fibromyalgia syndrome (FMS) is characterized by a widespread chronic bodily pain, profound fatigue, and sleep disturbance and appears to represent the end of the spectrum of polysymptomatic distress (1). Based on the 2010 diagnostic criteria, FMS affects 6% of the US population (2). In some patients with FMS, fatigue interferes with the performance of daily activities, as much as or more than bodily pain. Because most studies have primarily investigated the mechanisms and treatment of FMS-related pain, less is known about other FMS symptoms, including fatigue (3–6). Patients with FMS are often unemployed and have high medical utilization rates related to their fatigue symptoms (7).

Fatigue is defined as a subjective sense of persistent tiredness that interferes with the performance of daily life activities and is not relieved by rest (6). The etiology of fatigue is unknown, but studies agree on its multidimensionality (3,5). Fatigue is categorized into peripheral and central components (8). In FMS and chronic fatigue syndrome, peripheral fatigue (physical fatigue) has been associated with the reduction of muscle contraction from impaired energy resources (9), while central fatigue (mental fatigue) has been associated with cognitive impairment (8,9). In FMS, fatigue manifests within a cluster of symptoms that include pain, sleep disorders, depression, difficulty with concentration, and worsening memory (10). Previous FMS studies reported

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Significance & Innovations

- This study investigated the symptoms cluster experienced by patients with fibromyalgia syndrome (FMS), using the score from the American College of Rheumatology 2010 FMS diagnostic tool with sophisticated statistical analysis.
- The result of this study is a first step to help clinicians classify and provide personalized interventions for FMS patients.
- Our study suggested 2 FMS subclusters and demonstrated the differences between the 2 subclusters.

that pain and depression are strongly associated with fatigue, while sleep quality has moderate and inverse association with fatigue (6). Psychobehavioral symptoms reported by FMS patients include depression, anxiety, and catastrophizing (11). The mutual relationship between behavioral symptoms, specifically depression and pain, has been demonstrated, indicating that both share common biologic pathways and neurotransmitters (12). The association between depression and fatigue has also been reported in patients who have cancer (13), arthritis (14), or FMS (15). One study found that among 839 FMS patients, fatigue was significantly associated with depression while pain was associated with anxiety (16). Pain catastrophizing was also found to be correlated with pain intensity (17). Our recent review demonstrated that catastrophizing has a large impact on fatigue severity (18); however, only 1 study has explored the associations among catastrophizing, pain, and fatigue, altogether in FMS patients (19).

The multidimensional model of fatigue was investigated in 1 study of patients with rheumatoid arthritis using structural equation modeling (SEM), and results from that study suggested that fatigue is significantly linked to disease activity, psychological factors, and sleep (20). FMS is a polysymptomatic condition that is characterized by manifest (e.g., fatigue intensity) and latent variables (e.g., cognitive vulnerabilities). The SEM approach is advantageous to use in this complex, polysymptomatic condition because it tests interrelationships among observable and latent variables. Compared to other cluster analytical strategies, the SEM approach is the only technique that can do complete and simultaneous analyses of the relationships between these variables (21).

No studies have investigated the association of fatigue with other symptoms experienced by individuals with FMS using the SEM approach. This study developed a symptoms model describing the symptoms experience of fibromyalgia patients, based on existing literature of the relationship among polysymptomatic distress experienced by fibromyalgia patients, attributed to specific symptoms such as pain, depression, anxiety, catastrophizing, cognitive dysfunction, daytime sleepiness, and fatigue. We then used the statistical approach of a previous rheumatoid arthritis study (20) to address its purposes, which was to develop a symptoms cluster model that can describe the associations of fatigue with other FMS symptoms and to explore FMS symptom subclusters based on varying symptom intensities reported by the sample.

MATERIALS AND METHODS

Participants. This study is part of a prospective, longitudinal, observational study from an institutional review board protocol. Participants diagnosed with FMS using the 1990 (self-report history of widespread pain with at least 11 of 18 tender sites on examination) or the 2010 American College of Rheumatology (ACR) criteria (widespread pain index [WPI] $\geq$7 of 19 and symptom severity scale [SSS] $\geq$5 of 12, or WPI = 3–6 of 19 and SSS $\geq$9 of 12) were included in the analyses (22). Based on the hypothesized model for SEM, 2 latent variables (that contain subscales) and 10 observed variables (that can be directly measured) were tested. To achieve statistical power at the level of 0.80 with a 0.05 significance level, the sample size was calculated using an a priori sample size calculator for SEM software (23). The minimum number of participants needed for model structure was 100.

Design. Participants' demographic information and the symptoms scores were obtained on 1 initial outpatient visit. No intervention was provided in this cross-sectional study. Patients were receiving a wide array of different therapeutic interventions obtained from community physicians and practitioners at the time of the study visit.

Measures. Demographic data (sex, age, marital status, educational level, and employment status) were obtained from the participants' medical charts. Participants' symptom experiences were assessed using methods described below.

Polysymptomatic distress was measured by the sum of the WPI and SSS scores. The WPI measures the number of bodily areas (total = 19) that a patient has had pain in over the past week. The SSS is a 4-item, 0–3 rating scale (total = 12) to measure severity of unrefreshed waking, cognitive problems, fatigue, and other somatic symptoms (e.g., irritable bowel syndrome, numbness/tingling, dizziness, depression, constipation, nausea, nervousness, chest pain, blurred vision, fever, dry mouth, itching, wheezing, Raynaud's phenomenon, hives/welts, ringing in the ears, heartburn, oral ulcers, loss of/change in taste, seizures, dry eyes, shortness of breath, loss of appetite, sun sensitivity, hearing difficulties, easy bruising, hair loss, and frequent urination). Higher scores for both instruments indicate widespread painful bodily locations and more severe symptoms, respectively (24). These questionnaires have been validated in previous studies and are currently used as part of the 2010 FMS diagnostic criteria (22,24).

The number of tender points reported (conducted by applying $<$4 kg pressure on 18 bodily areas) and the participant's pain threshold (the average kilogram pressure tolerated on the 18 bodily areas) were measured using dolorimetry, a reliable tool to measure tenderness in FMS (25).

The Brief Pain Inventory–Short Form (BPI-SF) measures pain intensity (4 items) and pain interference (7 items)

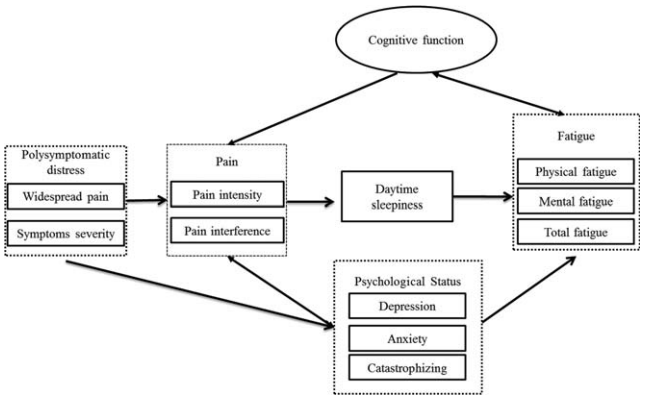

Figure 1. Hypothesized fibromyalgia syndrome symptoms cluster model. Hypothesized structural model on the relationship between polysymptomatic distress, pain, psychological status, cognitive function, daytime sleepiness, and fatigue.

using a numeric rating scale of 0–10 (where 0 = no pain/interference and 10 = pain as bad as you can imagine/complete interference) (26). The internal consistency of BPI-SF as measured by Cronbach's α for pain intensity = 0.88 and pain interference = 0.87 (27).

Fatigue was measured by the Multidimensional Fatigue Inventory, a 20-item self-report questionnaire composed of 5 subscales: general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue (28). Each of the 5 subscales is measured with 4 items using a rating scale of 1 (completely true) to 5 (not true), which have been found to have internal consistency reliability of Cronbach's $\alpha < 0.80$ (28).

Anxiety and depression were measured by the 14-item, 2-subscale, self-report Hospital Anxiety and Depression Scale (29). Each item is rated on a 4-point Likert scale and each subscale (anxiety and depression) has a score that ranges from 0 to 21. High scores indicate greater anxiety and depressive symptoms. Both subscales have internal consistency with Cronbach's $\alpha = 0.89$ (29,30).

Catastrophizing was measured using the Pain Catastrophizing Scale (PCS), a 13-item, self-report questionnaire consisting of 3 subscales: rumination, magnification, and helplessness. Participants were asked to rate their thoughts and feelings on a scale of 0 (not at all) to 4 (all the time). The internal consistency of the PCS showed Cronbach's $\alpha = 0.87$ (31,32).

Self-perceived cognitive difficulties were measured by the Multiple Ability Self-Report Questionnaire (MASQ). This instrument evaluated 5 domains of cognitive difficulties, based on a neuropsychological evaluation that includes language, visual-perceptual ability, verbal memory, visual-spatial memory, and attention/concentration (33). MASQ contains 38 items on a 1–5 Likert rating scale. The total score for each domain ranges from 8 to 40, except for visual-perceptual ability, which ranges from 6 to 30 (34). Higher MASQ scores indicate greater perception of cognitive difficulties. The internal consistency reliability of MASQ showed Cronbach's $\alpha = 0.72$–0.74 (35).

Daytime sleepiness was measured by the 8-item Epworth Sleepiness Scale (ESS). Each item was rated on a 4-point Likert scale (range 0–3), with total scores ranging from 0 to 24, with higher sum scores meaning higher daytime sleepiness (36). The internal consistency of the ESS showed Cronbach's $\alpha = 0.70$ (37).

Statistical analysis. Subjects were grouped based on their symptom scores. The agglomerative hierarchical cluster analysis with Ward's methods and squared Euclidean distances were performed using SPSS software, version 19.0. SEM analysis was used to test and estimate the relations among polysymptomatic distress to pain severity and interference, depression, anxiety, catastrophizing, cognitive dysfunction, daytime sleepiness, and fatigue. The hypothesized symptoms cluster model (Figure 1) was tested using the AMOS software, version 17.0 (38). Prior to testing the

Table 1. Demographic and clinical characteristics of sample

Characteristics	No. (%)	Mean ± SD
Sex		
Men	12 (10)	
Women	108 (90)	
Age, years (range 21–82)		46.30 ± 11.00
21–30	12 (10)	
31–40	26 (21.7)	
41–50	35 (29.2)	
51–60	38 (31.7)	
≥61	9 (7.5)	
Race		
White	71 (59.2)	
African American	35 (29.2)	
Hispanic/Asian	4 (3.3)	
Others	4 (3.3)	
Missing data	6 (5.0)	
Education		
Less than 12th grade	6 (5.0)	
12th grade	20 (16.7)	
Trade school	4 (3.3)	
College	49 (40.8)	
Graduate school	35 (29.2)	
Missing data	6 (5.0)	
Marital status		
Never married	32 (26.7)	
First marriage	44 (36.7)	
Divorced	22 (18.3)	
Widowed	3 (2.5)	
Remarried	12 (10.0)	
Missing data	7 (5.8)	
Employment		
Full time	35 (29.2)	
Part time	13 (10.8)	
Unemployed	21 (17.5)	
Disability	30 (25.0)	
Students	8 (6.7)	
Retired	6 (5.0)	
Missing data	7 (5.8)	
Pain threshold*		
No. tender points (range 0–18.0)	120	14.28 ± 4.54
Pain threshold, kg (range 0–8.13)	120	2.89 ± 1.56

* Percentage not applicable.

Table 2. Demographic and clinical characteristics of sample*

	Cluster 1 (n = 94)	Cluster 2 (n = 26)	$F_{univariate}$	*P*
Sex, %				
Women	85 ± 90.4	23 ± 88.5		
Men	9 ± 9.6	3 ± 11.5		
Age, years	46.30 ± 11.3	46.30 ± 10.2	1.11	0.34
Race, %				
White	49 ± 52.1	22 ± 84.6		
African American	33 ± 35.1	2 ± 7.7		
Other	12 ± 11.8	2 ± 7.7		
BMI	31.14 ± 8.1	31.39 ± 8.8	0.05	0.82
Polysymptomatic distress				
WPI	14.15 ± 2.5	5.77 ± 2.4	238.4	0.00†
SSS-fatigue	2.45 ± 0.7	1.96 ± 0.8	8.87	0.00†
SSS-unrefreshed waking	2.46 ± 0.8	2.04 ± 1.0	5.09	0.03‡
SSS-cognitive symptoms	1.83 ± 0.9	1.35 ± 1.0	5.71	0.02‡
SSS-somatic symptoms	2.17 ± 0.6	1.65 ± 0.6	16.47	0.00†
Tender point				
No. of tender points	14.77 ± 4.2	12.50 ± 5.4	5.266	0.02‡
Average pain threshold	2.69 ± 1.4	3.60 ± 1.8	7.44	0.01‡
Pain				
Intensity	6.02 ± 1.7	3.62 ± 2.1	35.37	0.00†
Interference	6.48 ± 2.0	4.05 ± 2.9	23.98	0.00†
Fatigue				
Physical	16.03 ± 3.36	13.77 ± 3.09	9.54	0.00†
Mental	15.25 ± 3.9	13.19 ± 4.1	5.57	0.02‡
Total	76.98 ± 13.4	64.84 ± 12.3	17.37	0.00†
Daytime sleepiness	9.28 ± 4.5	8.55 ± 3.67	0.59	0.45
Depression	8.39 ± 3.9	5.96 ± 3.8	7.88	0.01‡
Anxiety	9.69 ± 4.5	7.12 ± 4.2	6.85	0.01‡
Catastrophizing				
Rumination	8.12 ± 4.7	4.82 ± 3.8	10.74	0.00†
Magnification	4.72 ± 3.2	2.55 ± 2.3	10.67	0.00†
Helplessness	10.86 ± 6.3	5.65 ± 5.4	14.85	0.00†
Cognitive dysfunction				
Language	20.50 ± 4.6	17.65 ± 4.3	8.00	0.01‡
Visual-perceptual ability	15.27 ± 5.1	13.73 ± 4.1	1.97	0.16
Verbal memory	22.82 ± 4.9	21.66 ± 4.7	1.07	0.30
Visual-spatial memory	18.94 ± 4.8	17.31 ± 94.0	2.49	0.12
Attention/concentration	22.77 ± 5.5	21.10 ± 4.7	2.00	0.16

* Values are mean ± SD unless otherwise indicated. BMI = body mass index; WPI = widespread pain index; SSS = symptoms severity scale.
† $P < 0.01$.
‡ $P < 0.05$.

hypothesized symptoms cluster model, data were screened for normal distribution. Missing data were managed using the expectation maximization method, by finding the maximum log-likelihood parameters for the missing data (39). The hypothesized symptoms cluster model was assessed for multiple goodness-of-fit criteria to include a model chi-squared goodness-of-fit statistic, the χ^2/df ratio, the comparative fit index (CFI), and the root mean square error of approximation (RMSEA). The criterion of nonsignificant chi-squared statistic ($P > 0.05$) was suggested as a good fit between data and the tested symptoms cluster model (40). Other indications for the goodness-of-fit included χ^2/df <2 and a CFI ≥ 0.95 (41). RMSEA <0.06 was considered acceptable to minimize type I and II errors (42). Symptoms cluster model modifications were performed to interpret the model fit. Using a previous approach (43), relationship paths that were theoretically justifiable and empirically explainable based on existing literature were added and the nonsignificant paths were dropped.

To identify the number of distinct subclusters from the data, the maximum percentage change in the agglomeration coefficient recorded between successive subcluster profiles was used. Following the formation of subclusters, discrimination function analysis using SPSS, version 19.0 was conducted to investigate the relative weight of each predictive variable in discriminating between the subclusters. Multiple analyses of variance were performed to investigate differences in symptom experience between subclusters and to explore whether the goodness-of-fit of the symptoms cluster model remained unchanged between the identified FMS subclusters. Multiple sample SEM analyses were used to examine the differences between FMS symptoms sub-

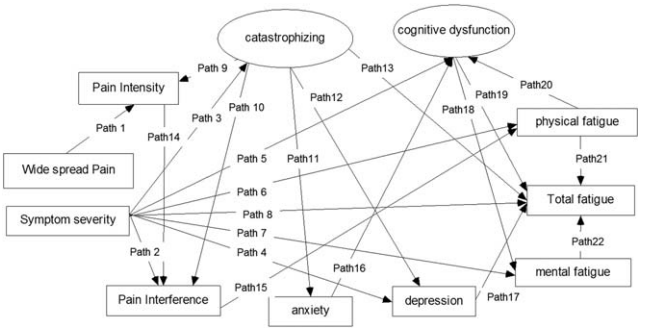

Figure 2. Final fibromyalgia syndrome symptoms cluster model using structural equation modelling. Standardized path coefficient, standard error, and unstandardized path coefficients are shown in Table 4.

clusters 1 and 2. The chi-square difference statistic was used to test differences between the constrained model, where regression weights of all relationship parameters were constrained to be equal between the 2 subclusters, and the unconstrained model, where regression weights of all relationship parameters were allowed to vary. If the chi-square results revealed a significant difference between the constrained and unconstrained models, then the SEM models for subclusters 1 and 2 were considered unique for each FMS subcluster. Then each relationship path was tested to determine whether relationships between variables in that path had equal regression weights in the model for both subclusters by allowing 1 relationship path to be unequal between the 2 subclusters. Significant chi-square differences between the unconstrained and constrained models indicated that the specific relationship path significantly differed between the 2 FMS subclusters.

RESULTS

Participant characteristics. The sample included a total of 120 participants with 12 men (10%) and 108 women (90%) ages 21–82 years (mean ± SD age 46.30 ± 11.00 years). The majority of these participants were white (59%), married (37%), and college educated (41%). About 40% were employed, and 25% were on disability (Tables 1 and 2).

SEM results. *Hypothesized model.* Based on the goodness-of-fit criteria, the hypothesized model shown in Figure 1 showed a poor fit to the data ($\chi^2 = 259.6$ (113df), $P < 0.01$, $\chi^2/df = 2.6$, CFI = 0.89, RMSEA = 0.10). The hypothesized model was modified based on the theoretical and statistical plausibility of the data using the modification indices suggested by the AMOS software. The daytime sleepiness variable was dropped from the FMS symptoms cluster model because it was not associated with fatigue or any of the other variables. Only statistically significant paths ($P < 0.05$) as shown in Figure 2 and Table 3 were included in the model. The modified model had a better fit to the data ($\chi^2 = 121.7$ (98df), $P < 0.05$, $\chi^2/df = 1.24$, CFI = 0.98 and RMSEA = 0.04) than did the hypothesized model. The most striking observation from the FMS symptoms cluster model was the negligible impact of pain symptoms on the severity of fatigue, cognitive dysfunction, anxiety, and depression of FMS.

Cluster analysis and discriminant function analysis. Two FMS subclusters were identified as being a good fit to the data based on the largest agglomeration coefficient difference of 1431.6. The 2 FMS subclusters had approximately equal percentages of males (9.6% in subcluster 1 and 11.5% in subcluster 2) and were similar ($P < 0.05$) in age, body mass index, daytime sleepiness, and self-perceived cognitive dysfunction on visual-perceptual ability, verbal memory, visual-spatial memory, and attention/concentration. Subcluster 1 included 94 FMS subjects (78%) and subcluster 2 had 26 subjects (22%). Comparing symptom severities, subcluster 1 subjects reported more intense symptoms compared to subcluster 2, and these symptoms include higher WPI (mean ± SD subcluster 1 = 14.18 ± 2.5, subcluster 2 = 5.77 ± 2.4; $P < 0.05$), higher tender point count (subcluster 1 = 14.77 ± 4.2, subcluster 2 = 12.50 ± 5.4), and lower pain threshold as measured by dolorimetry (subcluster 1 = 2.69 ± 1.4, subcluster 2 = 3.60 ± 1.8; Table 2).

The discriminant function analysis results shown in Table 4 indicated that the 2 FMS subclusters were significantly distinct from each other ($\chi^2 = 130.990$ [5df], $P < 0.001$), suggesting that each subcluster has its own distinct symptoms characteristics. Widespread pain and somatic symptoms were important in separating the 2 FMS subclusters. Based on function loading (Table 4), FMS subcluster 1 was distinguished from FMS subcluster 2 by widespread pain, unrefreshed waking, and somatic symptoms, while FMS subcluster 2 had fatigue and cognitive symptoms coupled with less intense and widespread pain that was distinct from FMS subcluster 1. About 94% of subcluster 1 subjects (widespread pain cluster) and 42% of subcluster 2 subjects (fatigue cluster) met the 2010 FMS diagnostic criteria of WPI ≥7 and SSS ≥5, while no subcluster 1 subject and about 23% of subcluster 2 subjects met the 2010 FMS diagnostic criteria of WPI = 3–6 and SSS ≥9. A small proportion of patients (6% in subcluster 1, 35% in subcluster 2) met only the 1990 criteria, indicating that clinically substantial tenderness can occur in the absence of self-reported widespread pain when measured in a clinical setting.

Multiple-sample SEM analysis. To examine the conformity of the FMS symptoms cluster model for the 2 identified FMS subclusters, a multiple-sample SEM analysis was conducted to compare the fully constrained FMS symptoms cluster model (all parameter estimates in the model between the 2 samples were the same) and the unconstrained FMS symptoms cluster model (all parameter estimates in the model between 2 samples varied). The results showed a significant difference between the fully constrained and unconstrained models ($\Delta\chi^2 = 44.3$, $\Delta df = 28$, $P = 0.03$), indicating that each FMS subcluster has a distinct symptom subcluster model.

The significant paths that differed between the 2 subclusters using multiple-sample SEM analyses are presented in Figure 3. The paths between pain intensity and pain interference (subcluster 1 $\beta = 0.54$, $P < 0.05$; subcluster 2 $\beta = 1.06$, $P < 0.05$) and between symptoms severity and mental

Table 3. Standardized path coefficient, SE, and unstandardized path coefficient of significant paths in final FMS symptoms cluster model (n = 120)*

Path	Predictors, dependent variables	β	SE	Unstandardized path coefficient
	Widespread pain index			
1	Pain intensity	0.201	0.036	5.550†
	Symptom severity			
2	Pain interference	0.258	0.058	4.449†
3	Catastrophizing	0.502	0.169	2.978‡
4	Depression	0.470	0.115	4.079†
5	Cognitive dysfunction	0.311	0.145	2.150§
6	Physical fatigue	0.433	0.128	3.381†
7	Mental fatigue	0.546	0.127	4.291†
8	Total fatigue	1.038	0.270	3.848†
	Catastrophizing			
9	Pain intensity	0.164	0.039	4.174†
10	Pain interference	0.146	0.036	4.039†
11	Anxiety	0.690	0.088	7.861†
12	Depression	0.422	0.082	5.146†
13	Total fatigue	0.311	0.150	2.076§
	Pain intensity			
14	Pain interference	0.665	0.068	9.723†
	Pain interference			
15	Physical fatigue	0.485	0.125	3.887†
	Anxiety			
16	Cognitive dysfunction	0.268	0.068	3.921†
	Depression			
17	Total fatigue	0.337	0.153	0.199§
	Cognitive dysfunction			
18	Mental fatigue	0.589	0.098	5.994†
19	Total fatigue	−0.653	0.222	−2.943‡
	Physical fatigue			
20	Cognitive dysfunction	0.303	0.099	3.056‡
21	Total fatigue	2.077	0.171	12.174†
	Mental fatigue			
22	Total fatigue	1.619	0.181	8.965†

* FMS = fibromyalgia syndrome; β = standardized path coefficient.
† $P < 0.001$.
‡ $P < 0.01$.
§ $P < 0.05$.

fatigue (subcluster 1 $\beta = 0.40$, $P < 0.05$; subcluster 2 $\beta = 0.95$, $P < 0.05$) were significantly different in FMS subcluster 2, compared to the FMS subcluster 1 model. These FMS symptoms subcluster models suggest that pain appears to only influence physical fatigue, and only in FMS patients whose symptom experience is primarily defined by pain.

Table 4. Discriminant function analysis for FMS subcluster characteristics*

		Classification function coefficients	
	Saturation loading	Subcluster 1	Subcluster 2
Widespread pain	0.979	2.217	0.815
Symptom severity			
Fatigue	0.189	1.167	1.293
Unrefreshed waking	0.143	2.078	1.674
Cognitive symptoms	0.152	−1.092	−0.547
Somatic symptoms	0.257	5.185	3.960
Constant		−24.990	−8.926

* FMS = fibromyalgia syndrome. $\chi^2 = 130.990$ (5df), $P < 0.001$; Eigenvalue of function 1 = 2.108; 100% variance.

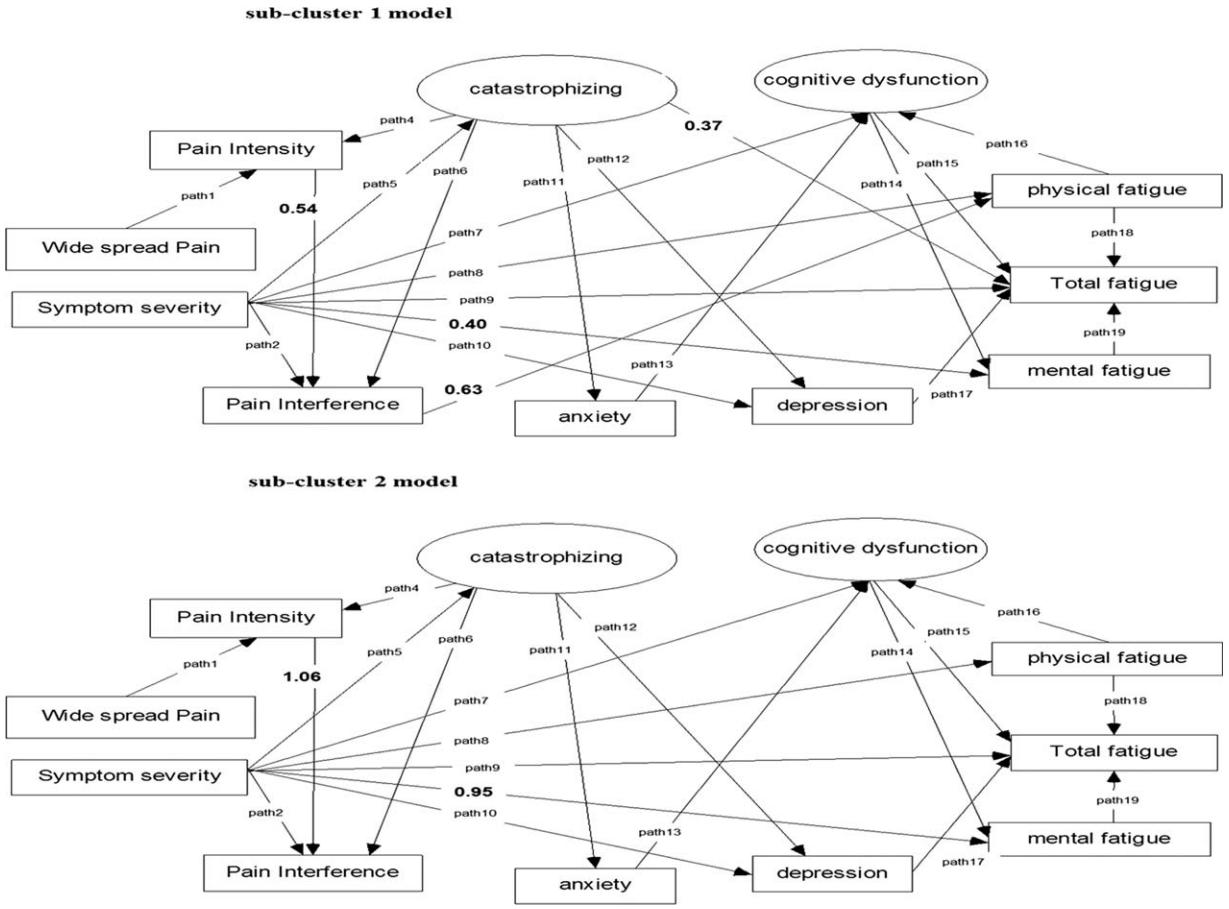

Figure 3. Fibromyalgia syndrome symptoms subcluster models, with error terms not shown. In symptom subcluster model 2, the path from pain interference to physical fatigue and the path from catastrophizing to total fatigue were not significant.

The paths between catastrophizing and total fatigue and between pain interference and physical fatigue became nonsignificant ($P > 0.05$) in FMS subcluster 2.

DISCUSSION

The FMS symptoms cluster model developed in this study using SEM showed that fatigued FMS subjects have high pain severity, cognitive dysfunction, depression, anxiety, and catastrophizing, a consistent finding from previous studies (43,44). Further investigation of this FMS symptoms cluster model revealed clinical subclusters of FMS patients. Previous studies identified heterogeneous clinical subgroups of patients with FMS based on their symptoms, using the Multidimensional Pain Inventory (45), the Short Form 36 health survey (46), and the visual analog subscale of the Fibromyalgia Impact Questionnaire (47). One study categorized FMS subjects into 3 subtypes based on mood, cognition, and hyperalgesia (48). Our study reported 2 FMS clinical subclusters: 1 (defined by pain) and 2 (defined by fatigue). These clusters provide further evidence that FMS is best considered an illness of polysymptomatic distress rather than a primary pain disorder.

One distinguishing feature between the FMS subcluster models points to how increasing pain intensity had a stronger impact on pain interference in FMS subcluster 2 subjects (fatigue subcluster) compared to FMS subcluster 1 subjects (pain subcluster), suggesting that FMS subcluster 1 subjects may have adapted to their daily, persistent, and more intense widespread pain compared to FMS subcluster 2 subjects. Further, FMS subcluster 2 subjects also reported worse mental fatigue with increasing symptom severity, compared to FMS subcluster 1 subjects, confirming that fatigue is a more bothersome symptom for FMS subcluster 2 subjects with increasing symptom severity, compared to FMS subcluster 1 subjects.

The observation that 35% of the subjects in subcluster 2 did not meet the 2010 FMS diagnostic criteria indicates that the 2010 FMS diagnostic criteria is most sensitive in capturing moderate to severe widespread pain symptoms. These results also demonstrate that a minority of persons can demonstrate the substantial widespread tenderness, as indicated by meeting the 1990 ACR criteria (49), despite not having substantial widespread pain within the last week. While there is a close relationship between clinical pain reporting and tenderness, it is not absolute.

Our FMS symptom subcluster models revealed that high pain intensity was not significantly associated with fatigue severity, but high depression was, which is consistent with previous findings in FMS (45) and other chronic conditions (e.g., rheumatoid arthritis, cancer) (13,50). This important

observation suggests that pain is not the main driver of the other symptoms experienced by FMS subjects. In fact, we also found in this study that depression is significantly associated with total fatigue, pain interference with physical fatigue, and cognitive dysfunction with mental fatigue. Previous studies in FMS and chronic fatigue syndrome reported a similar significant association between cognitive dysfunction and fatigue (51). The influence of cognition and the perception of fatigue support the proposed central mechanism of fatigue, suggesting that the sensation of fatigue is controlled by the combination of the afferent feedback from the periphery, current knowledge of the external environment, and prior experiences (51).

The study findings cannot be generalized because of limitations. First, this is a cross-sectional study that attempted to identify relationships among self-reported symptoms. It is commonly known that the intensities of FMS symptoms change frequently. Therefore, FMS patients might shift from 1 subcluster to another based on the varying intensities of symptoms, day after day. Although this structural equation analysis precludes an interpretation of causality or directionality among symptoms, our FMS symptoms model was examined based on hypothesized relationships of symptoms from existing literature. Other plausible linkages among these variables may need to be investigated, because their indirect and reciprocal relationships were not tested. Therefore, a longitudinal study is warranted to explore causal relationships between the variables being investigated in this study. Additional investigations to include physiologic measurements, such as physical performance assessments, cognitive function tests, autonomic dysfunction measures, and biologic profiling, such as genetic and proinflammatory markers from a larger number of subjects, will be useful.

In conclusion, our study suggested 2 heterogeneous categories of patients with FMS based on their symptom experiences. These symptoms subcluster models provide relevant information that can be useful for clinical diagnosis and management of FMS. A longitudinal study capturing the variability in symptom experience of FMS subjects and comparing the symptom subcluster models reported in our cross-sectional study will be informative.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Lukkahatai had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Lukkahatai, Walitt, Saligan.
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