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Biobehavioral Examination of Fatigue Across Populations: Report from a P30 Center of Excellence

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Abstract

Objectives—This paper reports the cross-studies analysis of projects from the P30 Center of Excellence for Biobehavioral Approaches to Symptom Management. Although the projects investigated diverse populations, a consistent theoretical and empirical approach guided each project.

Methods—Common data elements included measures of psychobehavioral variables: the PROMIS Shortform fatigue scale, the Center of Epidemiologic Studies Depression Scale (CES-D), and the Perceived Stress Scale (PSS). Plasma cytokines were measured as the shared biological data element.

Results—Data were analyzed from 295 participants with fibromyalgia (N=72), second trimester pregnancy (N=73), sickle cell anemia (N=60), and cardiometabolic risk (N=91). The mean age of participants was 35.4 years and most participants were female. Levels of symptoms were generally elevated across samples: the level of fatigue ranged from 18.9 to 24.7, depressive symptoms from 12.5–23.4 and perceived stress from 16.5–21.8. Inter-correlations among symptom measures and perceived stress were strong across the samples. However, correlations among psychobehavioral variables and cytokines were variable, indicating a separate relationship for the measures with cytokines.

Conclusion—Future work in symptom science could benefit from common data elements, including biomarkers, across populations to better develop the taxonomy of symptom profiles across conditions.

Keywords

Fatigue; PROMIS; Depressive Symptoms; P30; Big data

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Fatigue is a highly prevalent, complex, multidimensional symptom that adversely impacts quality of life (QOL) and health outcomes across the lifespan. In terms of economic burden, fatigue is associated with significant health-related lost productive time in U.S. workers, resulting in over \$136 billion dollars annually in lost productivity (Ricci, Chee, Lorandeau & Berger, 2007). Fatigue is associated with decreased quality of life across the life-span (Eddy & Cruz, 2007; Rimes, Goodman, Hotopf, Wessely, Meltzer & Chalder, 2007). Given such health-related costs, it is not surprising that publishing rates for studies of fatigue increased by about 90% over 2002–2011 (Friedberg, Caikauskaite, Adamowicz, Bivona, & Njoku, 2013). However, most studies of fatigue have focused on single populations and relatively few investigators have concurrently measured biomarkers and associated symptoms. Further, the use of multiple instruments to measure fatigue and the use of diverse sources of biological measures and measurement platforms for fatigue biomarkers have also contributed to the difficulty in comparing results across populations and from study to study. The Center of Excellence in Biobehavioral Symptom Management (P30 NR011403, Grant PI; 2009–2014) at Virginia Commonwealth University School of Nursing was designed in to examine fatigue, associated symptoms (depressive symptoms and perceived stress), and biomarkers in different clinical populations using a consistent theoretical and empirical approach. In this paper, we report the shared conceptualization, the selection of measures, and the results from the cross-studies analyses of studies that comprised the projects of the Center. While each study was designed to answer a population-specific research question with relevant population-specific measures, common data elements (CDEs) were selected a priori to guide the measurement of symptoms and biological variables across studies as part of the Center's goals.

Background

Symptom science has been identified as a priority in nursing research (Grady, 2010). Although there have been advancements towards the goal of describing symptoms in health and illness, the symptom science field has been stymied by the lack of uniformity of measures and conceptualizations of concepts and measures. The symptom of fatigue may be a particularly vexing concept for research because it is pervasive and highly subjective; hence, there are multiple definitions of fatigue and many different measures. Some studies have used population specific measures and others have used general measures: typically one measure, either general or population specific, has been selected without considering the benefits of using a standardized measure of fatigue. Not surprisingly, given the backdrop of conceptual and operational heterogeneity in the measurement of fatigue, there have been conflicting results from studies focused on uncovering possible biological mechanisms or biomarker correlates of fatigue. Although data from animal models have generally supported a relationship of pro-inflammatory activation with fatigue (Kurrock, 2001), studies in humans have been more variable across studies and disease conditions (Gibney & Drexhage, 2013). Even so, a number of studies have pointed to the importance of inflammation in the pathophysiology of fatigue (reviewed in Dantzer, 2014).

In accord with the **big data** era in science (Henly, 2013) the Center was designed with elements of theoretical and operational “harmonization” so that we could examine variables of interest in the collective, in addition to each individual project. Given the importance of

fatigue in terms of clinical outcomes and the lack of clarity in the conceptualization and measurement of fatigue, it was important to ground the definition and operationalization of fatigue within a theoretical framework that accounted for both the psychobehavioral and the biological factors relevant to fatigue in diverse populations. It also was important to select a theoretical framework that was appropriate for all target populations of the Center. The biobehavioral framework that we selected was a psychoneuroimmunology (PNI) framework that considers the relationships among commonly co-occurring symptoms and putative biological correlates (Figure 1). Given that psychoneuroimmunology is useful for understanding the interrelationships among mind-body interactions in health and illness (Zeller, McCain, & Swanson, 1996), PNI provides a theoretical framework that is appropriate for both populations living with chronic diseases and for individuals who are contemplating or initiating health promotion activities. We selected the PROMIS definition and measure of fatigue. Related variables that provided conceptual and operational associations with fatigue included perceived stress and depressive symptoms. The biological variable, levels of peripheral cytokines, provided an immune/inflammatory marker that is theoretically associated with fatigue and related psychobehavioral variables (perceived stress and depressive symptoms). Therefore, the specific aim of this study was to examine the levels of fatigue, perceived stress, depressive symptoms, and cytokine measures across samples of individuals with fibromyalgia (FMS), women in the second trimester of pregnancy (PREG), individuals with sickle-cell disease (SCD), and individuals with elevated cardiometabolic risk (CMR).

Methods

Data for these analyses were obtained from the Center of Excellence for Biobehavioral Approaches to Symptom Management (P30 NR011403, Grap, PI). The Center grant was comprised of five projects and was designed at the outset for cross-studies analysis (Table 1). Four projects are complete to date and comprise the data for this analysis. Institutional Review Board (IRB) approval was obtained for each study prior to study enrollment and the Center, as a whole, obtained IRB approval. Data collection was conducted from January 2010 to August, 2013. The present study employed secondary analysis of de-identified data.

Measures

In congruence with the overall Center aims, all Projects included the following common data elements (CDEs): fatigue (PROMIS Fatigue Short-Form), perceived stress (PSS), depressive symptoms (CES-D) and cytokine measures. Further, the standardized demographic form for Center Projects included a Cofactor Module addressing sleep and exercise patterns and use of tobacco, alcohol, caffeine, and medications.

The PROMIS® Fatigue Short-Form assesses the impact (4 items) and experience (3 items) of fatigue during the past week. ("Patient Reported Outcomes Measurement Information System"). In the PROMIS® initiative, fatigue is divided into the *experience of fatigue* (frequency, duration, and intensity) and the *impact of fatigue* (upon physical, mental, and social activities). Item responses are rated on a 5-point scale ranging from 'never' to 'always' and are summed for a Total score and transformed to a T-score metric, which has a

mean of 50 and a SD of 10. Higher scores indicate more fatigue. The PROMIS Fatigue Short-Form has demonstrated robust reliability and validity across multiple samples (K. Cook et al., 2012; K. F. Cook, Molton, & Jensen, 2011; Lai et al., 2011). Complete reliability and validity information on the PROMIS Fatigue can be found on the Assessment Center website (www.assessmentcenter.net).

The Perceived Stress Scale (PSS) (Cohen & Williamson, 1988) measures the degree to which situations in an individual's life are appraised as stressful. The 10 items are general in nature, with respondents indicating how often each statement applied to them during the past month on a five-point scale, with response options ranging from 0 (Never) to 4 (Very Often). Higher scores indicate greater perceived stress. The PSS is a widely used general measurement of perceived stress and it has accrued considerable reliability and validity data since inception with internal consistency alphas ranging from 0.83 – 0.87 (Bay & Xie, 2009; Ezzati et al., 2013; Mahon, Yarcheski, Yarcheski, & Hanks, 2007).

The Center for Epidemiological Studies-Depression (CES-D) is a widely used, psychometrically sound instrument designed to detect depressive symptoms in the general population, including adolescents. For internal consistency reliability, Cronbach's alphas have ranged from 0.79 – 0.90. (Radloff, 1977, 1991) Because it focuses on the affective component of depression rather than physical manifestations, it also is appropriate for use with physically ill individuals. The CES-D is comprised of 20 items reflecting the domains of depressive affect, somatic symptoms, positive affect, and interpersonal relations. Participants are asked to report the frequency with which they experienced each symptom in the previous week on a four-point scale, with response options ranging from 0 (less than 1 day per week) to 3 (most of the time). Higher scores indicate greater depressive mood.

Blood samples were collected into EDTA vacutainer tubes for measuring cytokine levels. Plasma samples were cryopreserved and batch processed in duplicate to reduce inter-assay variability. Plates from the same lot were used for the cross-studies cytokine measures. Plasma levels of cytokines [(IL)-1 β (IL-1 β), IL-2, IL-4, IL-5, IL-6, IL-7, IL-10, IL-12p70, IL-13, IL-17, G-CSF, GM-CSF, IFN- γ , and TNF- α] as well as chemokines [CXCL8 (IL-8), CCL2 (MCP1), and CCL4 (MIP1 β)] were analyzed using the 17-plex Bio-Rad® (Bio-Rad; Hercules, CA) cytokine, chemokine, and growth factor assay kit per the manufacturer's protocol.

Data Analysis

Data were analyzed using JMP® Statistical Discovery Software version 8.0. For each study variable, distributional properties to assess normality were examined. As expected, the cytokine data were non-normal (skewed positively), thus we used a log transformation to normalize their distribution (Osborne, 2002). We examined the internal consistency reliability of the scales and subscales using Cronbach's alpha and calculated correlations using Pearson's correlation coefficient. The level of significance was set at $p < .05$.

Results

Sample

The sample for this pooled analysis consisted of 296 individuals, 272 females and 24 males (Table 2). Full description of screening and enrollment using CONSORT guidelines (Calvert, 2013) may be found in the original reports from each study (Menzies et al., 2012; Jallo et al., 2014) in review; Ameringer, 2013 in press; Robins et al., 2013, in review). The mean age was 35.4 years and the racial distribution of the sample was 59 % African Americans and 37% Caucasians with the remaining consisting of Asians and “other” races. 97.6% of the sample belonged to a non-Hispanic or Latino ethnic background. A sharp contrast in the distribution of marital status was observed among the four studies. The majority of the SCD and PREG participants were never married while the FMS and CMR participants were primarily married individuals or living with a partner. There was also variability in levels of employment: 37% of the entire sample was employed full time, with higher levels of fulltime employment (76.4%) in the CMR and FMS group (34.3%). Higher levels of unemployment were noted in the PREG and SCD samples. Differences in income levels were noted. Approximately one-third of the study participants had an income less than \$15,000 (34.4%). The majority of the participants with FMS, PREG, or SCD earned less than \$15,000 while the majority of the CMR participants earned greater than or equal to \$105,000. The participants were primarily overweight with a mean BMI of 29.4; however, participants in the SCD group had a normal mean BMI of 24.2. Thirty-nine percent (39.1%) of the participants exercised for less than 15 minutes per day. The mean duration for sleep and exercise was 6.9 hours and 2.2 days respectively. Eighty-one percent (81.7%) of the participants were non-smokers; however, the mean number of smoking years in the participants who smoked was 11.4 years, and the cohort of people diagnosed with fibromyalgia had the highest number of smoking years (18.0 years). Fifty-nine percent (59.3 %) of the participants consumed alcohol, with a mean of 2.3 drinks per week.

Fatigue

The impact and experience of fatigue were measured by the PROMIS-Fatigue Short-Form (Table 3). The mean score was 21.1. The cohort diagnosed with FMS had the highest mean (24.7) followed by PREG (21.4). The means of individuals diagnosed with SCD (19.8) and those with CMR (18.9) were lower than the total sample mean (21.1). The mean T-score was 57.9 with similar patterns noted across the groups. The FMS participants had the highest T-score (63.3) followed by PREG (58.3). The T-scores of individuals diagnosed with SCD (55.9) and those with CMR (54.7) were lower than the total sample T-score (57.9).

Depressive Symptoms

Depressive symptoms as measured by the CES-D instrument had a mean level of 17.6. A score of 16 or higher on the CES-D suggests risk for clinical depression (Radloff, 1977). The highest score was reported in the participants with FMS (23.4) followed by PREG (19.4). Participants with SCD also had a mean score higher than the cutoff (16.1).

Perceived Stress

The degree to which situations in an individual's life are appraised as stressful was measured by the PSS. The mean level on the PSS was 18.8 with the highest levels in the cohort diagnosed with FMS (21.8), followed by PREG (19.5). The individuals diagnosed with SCD had the lowest scores (16.5).

Cytokines

Several cytokines had significant correlations with depressive symptoms: IL-4 ($p=0.0026$), IL-5 ($p=0.0070$), IL-10 ($p=0.0068$), IL-12 ($p=0.0268$), IL-17 ($p=0.0138$), G-CSF ($p=0.0232$) and TNF- α ($p=0.0406$) (Table 3). A significant correlation was noted between perceived stress and IL-4 ($p=0.0282$). There were no statistically significant relationships between any cytokine and fatigue.

Discussion

The research projects associated with the Center for Excellence were designed on two levels: first, to answer the research questions related to fatigue in a specific population; and second, to collect data that would contribute to across studies analysis of biobehavioral phenomena related to fatigue. Including the common data elements permitted a broader examination of variables across multiple populations. Interestingly, levels of fatigue were higher in all samples than in the general population (Junghaenel, Christodoulou, Lai, & Stone, 2011). Levels of depressive symptoms were also quite high across samples. Although one might expect individuals with fibromyalgia or sickle-cell anemia, who are living with chronic disease, to have an increased propensity for depressive symptoms, the finding that both second trimester pregnant women and individuals with no known chronic disease (i.e. those with elevated risk of cardiometabolic disease) also showed elevated depressive symptoms is surprising. Perhaps this is an artifact resulting from a difference in individuals who choose to participate in a research study of a complementary and alternative modality (i.e., use of Tai Chi in the elevated risk of cardiometabolic disease project) compared to those who do not. Multiple studies have linked complementary and alternative medicine (CAM) usage with poorer psychological health while some have found no significant association (Bishop, 2008). This perspective remains controversial yet important for better understanding possible selection bias in research samples of CAM modalities.

Results from this analysis revealed the expected strong positive inter-correlations among measures of fatigue, depressive symptoms and perceived stress. Fatigue and depression have been indicated as components of a symptom cluster and, in some studies, have shared a common biological mechanism (Raison, Capuron, & Miller, 2006). However, the results of this analysis demonstrated a difference in cytokine patterns across the psychobehavioral variables that does not fully support the premise that fatigue, perceived stress, and depressive symptoms share a common biological mechanism as measured by peripheral cytokine levels. The positive correlation between several cytokines and level of depressive symptoms warrants further investigation. The relationship of TNF- α and depressive symptoms has been found in multiple other studies (Himmerich, 2008). Although not typically measured in many clinical studies, IL4 is an important anti-inflammatory cytokine:

recent work has shown a link between an IL4 SNP (rs2243248) and a symptom cluster with findings suggesting that carrying the minor allele may result in alterations in the regulation of several pro-inflammatory cytokines and thereby conferring higher risk for multiple symptoms (Illi, 2012). In this study, the relationship between IL4 and depression and perceived stress indicates that higher levels of IL4 are correlated with higher levels of depressive symptoms and perceived stress. Anti-inflammatory cytokines IL5 and IL10 were also correlated with depressive symptoms as were pro-inflammatory cytokines IL12 and IL17, supporting the importance of both pro- and anti-inflammatory perturbations in relationship to depressive symptoms.

The hypothesis that inflammation as measured by cytokine patterns may be a common pathway for fatigue was not supported in this sample. Although there were notable relationships among several cytokines and symptoms of depression and perceived stress, findings from the combined sample do not contribute to the evidence that fatigue is associated with cytokine perturbations. The lack of support for the relationship between levels of fatigue and cytokines may have resulted from measurement issues in either the fatigue questionnaires and/or cytokine measures. In addition, the cross-sectional comparison could not account for the relationships of the psychobehavioral variables and cytokine measures over time. It could be that cytokine levels and their association with fatigue could have a different pattern over time than the relationship of cytokines with depressive symptoms and perceived stress. In addition, the cytokine levels as measured by multiplex technology, while giving a systems view of cytokine networks, are dependent on laboratory best practices and may not be concordant with traditional ELISA methods, thus leading to difficulty in making comparisons with extant research (Leng et al., 2008). However, in this analysis, the difference in cytokine patterns gives some validity to the notion that the measures of fatigue, depressive symptoms, and perceived stress, while sharing similar conceptual components, have some distinct differences in their association with a theoretically-related biological measure. These differences warrant further study, as confirming the biological measures with standardized instruments may lead to further strides towards distinguishing similar, yet distinct symptoms such as fatigue and depression. Further elucidating the biobehavioral mechanisms underlying fatigue and associated psychobehavioral symptoms could ultimately lead to a decrease in the symptom burden through translation of rigorous science to a full range of prevention and treatment strategies.

Limitations

Limitations common across the four studies include convenience sampling, relatively small sample sizes, missing data, and self-report measures. Although the samples were composed of individuals with clinically relevant health conditions and included a high percentage of females and ethnic minority individuals, there was no healthy comparison group and no attempt to balance the samples with equal numbers of males and females or to age-match participants. In addition, the cross-studies analysis could not take into account a number of possible covariates including genetic predisposition and environmental influences such as nutritional intake and circadian patterns.

Conclusion

The cross-studies analysis reported here is an initial effort at designing a Center of Excellence to fit with the scientific movement towards “big data.” Given that this work represents an initial attempt to coordinate measures across studies in disparate populations affected by fatigue, there are noted limitations. However, the future direction of symptom science will benefit from establishing scientific networks, such as within and among Centers of Excellence, to derive the most benefit from studies of important, yet difficult to measure human phenomena such as fatigue and associated psychobehavioral phenomena. It is unlikely that continuing the practice of small studies with lack of standardized measures will adequately represent the next phase of symptom science.

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Figure 1.

Psychoneuroimmunology (PNI) Framework of the P30 Center of Excellence for Biobehavioral Approaches to Symptom Management

The psychoneuroimmunology (PNI) framework focuses on the interactions among biological, social and behavioral factors and their effects on health outcomes. A critical health experience is a change in health or perception of change that places an individual at risk of experiencing distressing symptoms. Common biological, social and behavioral variables as well as immunological mediators and psychobehavioral symptoms were used to examine the relationships between study variables across projects.

Table 1

Description of Center Projects

Pilot Study/Project PI (PPI)	Purpose	Sample		Major Findings
		Description (N)	Inclusion & Exclusion Criteria	
Effects of Guided Imagery on Biobehavioral Factors in Women with Fibromyalgia Syndrome (FMS)/PI: Menzies	Randomized controlled trial to test the effects of a 10-week guided imagery (GI) intervention on self-efficacy, perceived stress, & selected biobehavioral factors	Women > 18 years of age diagnosed with FMS (N=72)	Inclusion: (1) Able to read, write, and understand English Exclusion: (1) Other rheumatologic conditions; (2) history of epilepsy; (3) no known major psychiatric or neurological conditions that would interfere with study participation; any psychiatric disorder involving a history of psychosis; (4) immunocompromised (e.g., HIV/AIDS); (5) current use of corticosteroids; or (6) pregnancy	Psychobehavioral: As measured by the Brief Fatigue Inventory (BFI), Center for Epidemiological Studies-Depression (CES-D) scale and the Perceived Stress Scale (PSS) respectively, there were statistically significant decreases in fatigue ($p<0.01$), depression ($p<0.01$) and perceived stress ($p=0.05$) from baseline to week 10 in the GI vs. control group. Biological: No statistically significant differences between groups in levels of pro- and anti-inflammatory cytokines or C-reactive protein at baseline, 6- or 10-weeks.
Effects of Guided Imagery on Pregnancy Symptoms and Outcomes/PI: Jallo	RCT to test the effects of a GI intervention on maternal stress and the related symptoms of fatigue, anxiety, depression, and unhappiness as well as biological mediators	African American women > 18 years of age & pregnant at 14-17 weeks gestation (N=72)	Inclusion: (1) Able to read, write, and understand English; (2) verbalize a source of social support Exclusion: (1) Multiple pregnancy; (2) cervical cerclage; (3) current use of oral corticosteroids; (4) uterine or cervical abnormality; (5) dissociative disorders, borderline personalities, or psychotic pathology; (6) medical and/or pregnancy complications known to impact neuroendocrine hormones; or (7) current use of GI.	Psychobehavioral: Significantly lower PSS scores at week 8 but not week 12 were found in the GI group compared to UC group. GI group reported significantly less fatigue and anxiety compared to UC group. No significant differences in happiness or depressive symptom scores were found between groups. Biological: No significant differences between groups in corticotropin-releasing hormone or cytokine levels.
Exploring the Effects of Tai Chi on Cardiometabolic Risk (CMR) in Women/PI: Robins	RCT to assess feasibility, acceptability and effectiveness of a novel tai chi intervention on CMR	Women aged 35-50 years with increased waist circumference and a family history of CVD (N=63)	Inclusion: (1) Able to read, write, & understand English; (2) premenopausal; (3) abdominal adiposity; (4) family history of CVD. Exclusion: (1) Prior cardiovascular disease, diabetes mellitus, and/or uncontrolled or severe HTN (BP 180/120); (2) morbid obesity (BMI 40); (3) unstable major depressive disorder; or (4) baseline fasting blood sugar > 120mg/dl or LDL > 160mg/dl.	Psychobehavioral: Significant decreases in fatigue and depressive symptoms, and significant increases in mindfulness, self-compassion, and spirituality in the intervention group compared to the control group. Biological: Significant decreases in multiple cytokines associated with inflammation, immune function and insulin resistance in the intervention group compared to the control group.
Fatigue in Adolescents and Young Adults (AYA) with Sickle Cell Disease (SCD)/PI: Ameringer	Descriptive study to describe fatigue and examine relationships between fatigue and biobehavioral factors	AYA aged 15-30 years diagnosed with SCD (N = 60)	Inclusion: Ability to read, write, and understand English (participant, minor participant, parent) Exclusion: Pregnancy	Psychobehavioral: Mild to moderate levels of fatigue in the sample. Lower levels of fatigue (on all measures) were significantly associated with higher levels of depressive symptoms, perceived stress, anxiety, sleep, and pain. Lower levels of fatigue (on all measures) were significantly associated with higher levels of quality of life. Biological: None of the fatigue scale scores were significantly associated with cytokines (inflammation), age, or disease severity. PROMIS Fatigue-Short Form scores were inversely correlated with hemoglobin levels, with higher fatigue significantly associated with lower hemoglobin. PROMIS Fatigue-Short Form scores differed

Pilot Study/Project PI (PPI)	Purpose	Sample		Major Findings
		Description (N)	Inclusion & Exclusion Criteria	
				significantly by sex, with females having higher fatigue levels significantly by sex, with females having higher fatigue levels

Table 2

Demographic and Health Habit Summary

Variable	FMS (n=72)	Preg (n=72)	SCD (n=60)	CMR (n=91)	Total (n=296)
Age	46.9 ± 1.58	24.4 ± 0.64	22.5 ± 0.53	43.6 ± 0.46	35.4 ± 0.77
Gender					
Female	72 (100.0%)	73 (100.0%)	36 (60.0%)	91 (100.0%)	272 (91.9%)
Male	0 (0.0%)	0 (0.0%)	24 (40.0%)	0 (0.0%)	24 (8.1%)
BMI	29.6 ± 0.81	29.4 ± 0.77	24.2 ± 0.83	32.8 ± 0.44	29.4 ± 0.39
Race					
Black/African American	21 (29.2%)	69 (94.5%)	58 (96.7%)	26 (28.6%)	174 (58.8%)
White	47 (65.3%)	0 (0.0%)	0 (0.0%)	63 (69.2%)	110 (37.2%)
Native American	0 (0.0%)	1 (1.4%)	1 (1.7%)	0 (0.0%)	2 (0.7%)
Asian	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Multi-Racial	3 (4.2%)	3 (4.1%)	1 (1.7%)	2 (2.2%)	9 (3.0%)
Other	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Ethnicity					
Not-Hispanic or Latino	68 (94.4%)	71 (97.3%)	59 (98.3%)	91 (100.0%)	289 (97.6%)
Hispanic or Latino	4 (5.6%)	2 (2.7%)	1 (1.7%)	0 (0.0%)	7 (2.4%)
Marital Status					
Divorced/Separated	16 (22.2%)	3 (4.1%)	0 (0.0%)	20 (22.0%)	40 (12.1%)
Married/Partner	38 (52.8%)	6 (8.2%)	1 (1.7%)	59 (64.8%)	115 (34.9%)
Single Never Married	16 (22.2%)	63 (86.3%)	56 (93.3%)	12 (13.2%)	169 (51.2%)
Widowed	2 (2.8%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	3 (0.9%)
Other	0 (0.0%)	0 (0.0%)	3 (5.0%)	0 (0.0%)	3 (0.9%)
Income					
< than 15,000	15 (21.1%)	49 (67.1%)	32 (56.1%)	4 (4.4%)	100 (34.4%)
15,000 – 29,999	11 (15.5%)	14 (19.2%)	8 (14.0%)	7 (7.8%)	40 (13.8%)
30,000 – 44,999	10 (14.1%)	6 (8.2%)	8 (14.0%)	8 (8.9%)	32 (11.0%)
45,000 – 59,999	11 (15.5%)	3 (4.1%)	5 (8.8%)	13 (14.4%)	32 (11.0%)

Variable	FMS (n=72)	Preg (n=72)	SCD (n=60)	CMR (n=91)	Total (n=296)
60,000 – 74,999	6 (8.5%)	0 (0.0%)	2 (3.5%)	9 (10.0%)	17 (5.8%)
75,000 – 89,999	4 (5.6%)	1 (1.4%)	1 (1.8%)	13 (14.4%)	19 (6.5%)
90,000 – 104,999	8 (11.3%)	0 (0.0%)	1 (1.8%)	15 (16.7%)	24 (8.3%)
105,000	6 (8.5%)	0 (0.0%)	0 (0.0%)	21 (23.3%)	27 (9.3%)
Education					
8 th grade or less	1 (1.4%)	1 (1.4%)	1 (1.7%)	0 (0.0%)	3 (1.0%)
Started high school	2 (2.8%)	10 (13.7%)	16 (26.7%)	1 (1.1%)	29 (9.8%)
Completed high school	12 (16.9%)	24 (32.9%)	16 (26.7%)	4 (4.4%)	56 (19.0%)
Started technical training	1 (1.4%)	3 (4.1%)	0 (0.0%)	0 (0.0%)	4 (1.4%)
Completed technical training	2 (2.8%)	5 (6.9%)	2 (3.3%)	2 (2.2%)	11 (3.7%)
Started college	25 (35.2%)	20 (27.4%)	18 (30.0%)	11 (12.1%)	74 (25.1%)
Completed college	15 (21.1%)	6 (8.2%)	3 (5.0%)	36 (39.6%)	60 (20.3%)
Started post-college	8 (11.3%)	2 (2.7%)	3 (5.0%)	9 (9.9%)	22 (7.5%)
Completed post-college	5 (7.0%)	2 (2.7%)	1 (1.7%)	28 (30.8%)	36 (12.2%)
Work Status					
Employed Full-Time	24 (34.3%)	9 (12.5%)	7 (11.9%)	68 (76.4%)	108 (37.2%)
Employed Part-time	8 (11.4%)	20 (27.8%)	6 (10.2%)	11 (12.4%)	45 (15.5%)
Retired	4 (5.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (1.4%)
Unemployed	9 (12.9%)	32 (44.4%)	11 (18.6%)	2 (2.3%)	54 (18.6%)
Disabled	14 (20.0%)	2 (2.8%)	12 (20.3%)	0 (0.0%)	28 (9.7%)
Student	5 (7.1%)	7 (9.7%)	20 (33.9%)	1 (1.1%)	33 (11.4%)
Homemaker	5 (7.1%)	2 (2.8%)	0 (0.0%)	5 (5.6%)	12 (4.1%)
Other	1 (1.4%)	0 (0.0%)	3 (5.1%)	2 (2.3%)	6 (2.1%)
Exercise Time					
Less than 15 minutes	22 (31.9%)	41 (56.2%)	23 (42.6%)	25 (28.4%)	111 (39.1%)
Between 15 and 30 minutes	20 (29.0%)	16 (21.9%)	16 (29.6%)	18 (20.5%)	70 (24.7%)
Between 30 and 45 minutes	13 (18.8%)	9 (12.3%)	5 (9.3%)	19 (21.6%)	46 (16.2%)
Between 45 and 60 minutes	12 (17.4%)	4 (5.5%)	7 (13.0%)	18 (20.5%)	41 (14.4%)
More than 60 minutes	2 (2.9%)	3 (4.1%)	3 (5.6%)	8 (9.1%)	5 (5.6%)

Table 3

Summary statistics of psychobehavioral measures across studies

Variable*	FMS (N=72)	PREG (n=72)	SCD (n=60)	CMR (n=91)	Total (n=295)
PROMIS-Fatigue Score	24.7 ± 0.51	21.4 ± 0.55	19.8 ± 0.68	18.9 ± 0.52	21.1 ± 0.31
PROMIS-Fatigue T-score	63.3 ± 0.76	58.3 ± 0.79	55.9 ± 1.03	54.7 ± 0.80	57.9 ± 0.46
CESD Score	234 ± 1.55	194 ± 1.28	16.1 ± 1.20	12.5 ± 1.05	17.6 ± 0.68
PSS Score	21.8 ± 1.02	19.5 ± 0.83	16.5 ± 0.85	17.3 ± 0.70	18.8 ± 0.44

* continuous variables are displayed as mean ± standard error