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Post-Exertional Malaise is Associated with Greater Symptom Burden and Psychological Distress in Patients Diagnosed with Chronic Fatigue Syndrome

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Abstract

Objective—Post-exertional malaise (PEM) is often considered a cardinal symptom of Chronic Fatigue Syndrome (CFS). There is no gold standard diagnostic method for CFS, however, and the Centers for Disease Control (CDC) Fukuda case definition does not require PEM. Research has identified differences in symptom burden between patients according to PEM, but whether it is associated with psychological distress has not been investigated.

Methods—The CDC CFS Inventory, Fatigue Symptom Inventory, Profile of Mood States, Center for Epidemiologic Studies Depression Scale, Perceived Stress Scale, and subscales of the Sickness Impact Profile were administered to 261 patients diagnosed with the Fukuda criteria. PEM status (loPEM/hiPEM) was determined via self-reported post-exertional fatigue severity. Analyses of covariance (ANCOVA), controlling for age and gender, assessed cross-sectional group differences, and cross-sectional linear regressions using the continuous PEM severity predictor paralleled these analyses.

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Competing Interest Statement
The authors have no competing interests to declare.

Results—hiPEM patients reported greater symptom severity, frequency, and interference than loPEM counterparts (p's<.001). hiPEM patients also reported greater social disruption, depressive symptoms, and mood disturbance (p's≤.011). Groups did not differ in recent negative life experiences, perceived stress, or demographic variables. The results of regression analyses mirrored those of ANCOVAs.

Conclusion—This study replicates the association between PEM and symptom burden and additionally associates PEM with psychological distress; psychological distress could, however, be a consequence of symptom burden. Differences between hiPEM and loPEM CFS patients amplify the heterogeneity of diagnoses resulting from the Fukuda criteria. It is also possible that PEM identifies particularly distressed patients for whom psychological intervention would be most beneficial.

Keywords

CDC Fukuda Case Definition for CFS; Fatigue; Myalgic Encephalomyelitis/Chronic Fatigue Syndrome; Post-Exertional Malaise; Psychological Distress; Symptom Burden

Introduction

Chronic Fatigue Syndrome (CFS) is a debilitating condition characterized by persistent fatigue that is unresponsive to rest. The disorder is associated with significant impairment at the individual level and with substantial economic costs at the societal level. For patients, a CFS diagnosis is often associated with severe emotional distress, including comorbid anxiety and depression (Cella, White, Sharpe, & Chalder, 2013). CFS patients are more likely to be unemployed than the general population (Jason et al., 1999; Reynolds, Vernon, Bouchery, & Reeves, 2004), and the functional impairment that characterizes the disorder has financial consequences. In the US, a Centers for Disease Control and Prevention (CDC) extrapolation of population-based studies in Kansas, Chicago, and Georgia estimated that at least one million individuals suffer from CFS (Unger et al., 2016), with prevalence rates in the individual studies ranging from 0.23% (Reyes, Nisenbaum, Hoaglin, & Unger, 2003) to 0.42% (Jason et al., 1999) to 2.54% (Reeves et al., 2007). Utilizing the 0.42% prevalence rate, the annual direct cost of the medical care of CFS in the US has been estimated at $7 billion annually (Jason, Benton, Valentine, Johnson, & Torres-Harding, 2008). The indirect cost of CFS in the US, including work productivity losses and disability reimbursements, has been estimated at nearly $17 billion annually (Jason et al., 2008; Reynolds et al., 2004).

The high costs that CFS poses to patients and to society as a whole imply the need for an understanding of its precipitating and maintaining factors in order to identify the appropriate preventative measures and treatments. However, the etiology of CFS remains unknown, and research in the field is limited by the lack of a gold standard diagnostic method. Providers make use of case definitions and clinical judgment to determine the presence of the disorder (Institute of Medicine (IOM), 2015). Since diagnostic definitions draw from expert consensus and the pathophysiology of ME/CFS is neither apparent nor agreed upon, there is variation between sets of criteria, limiting their comparability and the progress of research (IOM, 2015).

The Fukuda case definition for CFS (Fukuda et al., 1994), supported by the CDC, is the most widely used in research and clinical practice (IOM, 2015; Johnson, 2013). It requires the presence of prolonged fatigue accompanied by four of eight additional symptoms (e.g., sore throat, impaired memory or concentration), for at least six months (Fukuda et al., 1994). Though they are, in effect, the standard for research and practice, the Fukuda criteria have been widely criticized. Because they are polythetic, heterogeneous patients with potentially very little symptom overlap can be diagnosed with the disorder (IOM, 2015), further limiting comparability and reproducibility of studies. Relatedly, post-exertional malaise (PEM) and neurocognitive symptoms are not required for the diagnosis, and these are considered by many to constitute core symptoms of CFS (IOM, 2015).

PEM refers to an exacerbation of fatigue-related symptoms following exertion (Carruthers et al., 2003), and sufficient evidence appears to support PEM as a distinguishing feature of CFS (2015). Indeed, a community-based study of 213 individuals originally evaluated for epidemiological purposes found that PEM best differentiated healthy controls from those who met Fukuda criteria (Jason et al., 2011). Further, a study that used an exercise task to induce and assess PEM, conceptualized as ‘symptom flares,’ in patients diagnosed with the Fukuda criteria, found differences in inflammatory biomarkers (changes in cytokine levels in response to physical activity over time) by PEM status, suggesting distinct pathophysiological mechanisms between groups (White et al., 2010).

After conducting studies of CFS stakeholders and existing literature, the IOM proposed its own diagnostic criteria for the disorder: it requires the presence of fatigue, unrefreshing sleep, and PEM, as well as either cognitive impairment or orthostatic intolerance (IOM, 2015). IOM renamed the disorder ‘Systemic Exercise Intolerance Disease’ (SEID), in part because of the stigmatization and trivialization associated with ‘CFS.’ SEID is conceptualized as a combination of the disorders Myalgic Encephalomyelitis (ME) and CFS, both of which are defined by profound fatigue and autonomic and neurocognitive symptoms, and SEID is sometimes called ME/CFS. It is important to note that some have criticized this approach, arguing that CFS is distinct from and dissimilar to ME (Twisk, 2016), which requires post-exertional muscle weakness, neurological symptoms, and circulatory impairment (e.g., Dowsett, Ramsay, McCartney, & Bell, 1990). Regardless of whether ME and CFS should be considered jointly as in SEID or whether they should be considered separately, PEM appears to be a defining characteristic, either of or between ME/CFS, and this is not reflected in current diagnostic practices.

Maes, Twisk, and Johnson (2012) compared patients who experienced chronic fatigue but did not meet Fukuda criteria, patients with CFS per Fukuda criteria who endorsed “no post-exertional malaise”, and patients with CFS per Fukuda criteria who endorsed experiencing PEM (conceptualized as ME). The latter group included patients who endorsed “mild exacerbations of fatigue/pain/neurocognitive symptoms following exercise (either cognitive or physical),” “moderate exacerbations of symptoms following exercise,” “severe, incapacitating exacerbations lasting 24 h,” “incapacitating exacerbations lasting >24h but less than 2 days,” “incapacitating exacerbations lasting >2 days,” or “a clinical relapse” (Maes et al., 2012, p. 755).

In comparing CFS patients with and without PEM, authors found significantly greater total symptom burden and individual symptoms assessed with the Fibromyalgia and Chronic Fatigue Syndrome Rating Scale (Zachrisson, Regland, Jahreskog, Kron, & Gottfries, 2002) in the patients who experienced PEM (Maes et al., 2012). After correcting for comparisons between three groups, patients with PEM had significantly higher scores on subjective experience of infection and concentration difficulties, as well as higher levels of inflammatory markers; patients who experienced chronic fatigue but did not meet Fukuda criteria also differed from patients with and without PEM. The authors concluded that these three groups are distinct diagnostic categories and speculated that immune activation is a predisposing factor for the development of PEM (Maes et al., 2012).

It appears that some of the heterogeneity of the CFS patient population is related to the presence or absence of PEM, which has demonstrated associations with symptom burden and inflammatory biomarkers. Despite that evidence for PEM as a defining feature of CFS exists, the polythetic Fukuda criteria, which do not take this evidence into account, remain widely utilized. The present cross-sectional study aims to investigate differences in CFS patients according to PEM status in order to add to the literature on the importance of the PEM criterion in CFS diagnoses.

Further, this study extends consideration of PEM-associated differences in CFS-diagnosed patients from symptom burden to include variables of psychological distress. As a general exacerbation of CFS symptoms, PEM is likely to have substantial effects on patients' quality of life and be uniquely distressing in psychological terms. It is also possible that PEM inhibits patients from engaging in physical or cognitive exertion, thereby precluding them from the benefits of such pursuits and sustaining the expression of CFS. Seen in this light, PEM could play a role in the maintenance of CFS phenomenology by way of its psychological effects.

In a large sample of patients diagnosed with CFS per the Fukuda criteria, we aim to replicate the finding that PEM is associated with higher symptom burden, using measures different than those of Maes and colleagues (2012). Further, we hypothesize that patients with greater PEM will report greater levels of psychological distress, thereby potentially identifying a patient group that would most benefit from psychological intervention targeting distress management.

Methods

Sampling and Procedures

The study sample was drawn from two distinct randomized controlled trials of stress management interventions for patients diagnosed with CFS. Cross-sectional baseline data were used for the present analyses. Study recruitment for one study, known as Teleconferenced Stress Management, took place from 11/2005 through 07/2010, and recruitment for the other, known as Videoconferenced Stress Management, took place from 07/2010 through 11/2016. Results from the Teleconference trial have been previously published (Antoni et al., 2015; Hall et al., 2017; Hall et al., 2014; Lattie et al., 2012; Milrad et al., 2017).

Inclusion in these studies required the presence of a physician-determined CDC criteria (Fukuda et al., 1994) CFS diagnosis. Subjects were also required to be fluent in English and 2175 years of age. Presence of another condition that could influence CFS-associated biological processes (e.g., AIDS, rheumatoid arthritis) or taking medications that would modulate immune or neuroendocrine functioning (e.g., corticosteroids) excluded participants from participation. Psychiatric exclusion criteria, including substance abuse, suicidality, and past psychiatric hospitalizations, were assessed via a brief screening measure adapted from the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders-IV (First, Gibbon, & Spitzer, 1997). All participants were part of clinical trials involving multiple assessments and group-based interventions. Thus, in order to ensure comprehension of study questionnaires and intervention material, cognitive impairment, operationalized as 4 or more errors on the Short Portable Mental Status Questionnaire (Pfeiffer, 1975), a score <20 on the Telephone Interview for Cognitive Status (Brandt, Spencer, & Folstein, 1988), or a score ≤23 on the Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975), was also an exclusion criterion.

Potential participants were identified through physician referral, community support groups, and advertisements, and a telephone screening interview determined study eligibility. The battery of baseline measures relevant to the present study was completed using paper and pencil in the Teleconferenced trial and online in the Videoconferenced trial. In the Teleconferenced trial, participants independently completed the measures during a home visit. In the Videoconferenced trial, participants completed the measures at their leisure via the SurveyMonkey electronic platform, and this was also likely done at home. In both trials, participants were compensated $50 for completing this baseline assessment.

Sociodemographic Characteristics

All participants self-reported on demographic variables including age, gender, and ethnicity. Ethnicity was trichotomized into non-Hispanic Caucasian (n=187), Hispanic (n=62), and Other (African-American, n=5; Caribbean Islander, n=3; Asian/Asian-American, n=2; Biracial, n=1; Other, n=1) categories. Participants also indicated their level of education (Less than 8th grade; Some high school; High school graduate; GED; Trade school; Some college; College graduate; Graduate degree), income in USD (<$5,000; $5,001–$10,000; $10,001–$20,000; $20,001–$30,000; $30,001–$40,000; $40,001–$50,000; $50,001–$60,000; >$60,000), and occupational status. Occupational status was conceptualized as Employment/Disability status and trichotomized into Employed (Employed full-time; Employed part-time), On disability, and Other (Student; Retired; Unemployed; Volunteer worker; Other) categories. Participants were asked to disclose whether they were currently taking medications prescribed by a medical doctor for pain, sleep, depression, or anxiety.

In the Videoconference trial, participants additionally provided their date of diagnosis, the nature of CFS-related symptom onset (Gradual; Sudden), and height and weight, which were used to calculate body mass index (BMI). These participants were also asked about the number of times in the past 90 days they had utilized services including physician's office visits, group-based psychotherapy sessions, individual therapy sessions, and outpatient psychiatric facilities (0 visits, ≥1 visits).

CDC CFS Symptom Inventory and PEM Status

The CDC CFS Symptom Inventory is a 19-item scale based on the Fukuda criteria (1994) that collects information about CFS-related symptoms experienced during the previous month, with higher scores indicating greater symptom burden (Wagner et al., 2005). For each item, individuals describe the frequency and intensity of a particular symptom (e.g., "Nausea," "Chills"). In the original scale, symptom frequency is rated on a five-point scale and symptom intensity is rated on three equidistant points on a five-point scale. Item frequency and intensity ratings are summed to create a Frequency Score and an Intensity Score. A Total Score is calculated by summing the products of item frequency and intensity ratings (Wagner et al., 2005).

We utilized a modified version of the scale, which we have published on previously (e.g., Lattie et al., 2013). This 20-item version of the scale is similar to the one available from the CDC (https://www.cdc.gov/me-cfs/pdfs/symptom-inventory-questionnaire-508.pdf) in that it utilizes six-point frequency (0=N/A; 1=A little of the time; 2=Some of the time; 3=A good bit of the time; 4=Most of the time; 5=All of the time) and intensity (0=N/A; 1=Very mild; 2=Mild; 3=Moderate; 4=Severe; 5=Very Severe) rating scales. The PEM item was removed from calculation of Frequency (range: 0–76; α=0.84 in the sample), Intensity (range: 0–76; α=0.81), and Total Scores (range: 0–304; α=0.85), and was instead utilized to determine PEM status.

Participants were categorized into PEM groups on the basis of their response to this PEM item, which asks about "unusual fatigue following exertion that lasts for at least 24 hours". Patients who described PEM as *Severe* or *Very severe* were classified as hiPEM, and patients who described the symptom as *Very mild*, *Mild*, or *Moderate*, or who did not endorse the symptom, were classified as loPEM[1]. Although the dichotomization of continuous variables is clinically useful, we appreciate that manipulation of data in this manner can lead to loss of information. We have therefore also retained the continuous PEM variable for use in regression analyses.

Fatigue Symptom Inventory (FSI)

The FSI was used to assess the intensity and duration of fatigue as well as fatigue-related illness burden, also known as fatigue interference (Hann et al., 1998). Four individual items ask participants to rate their level of fatigue ("on the day you felt [most/least] fatigued during the past week," "on the average in the past week," and "right now") on an 11-point scale (0=Not at all fatigued; 10=Extreme fatigue). We also averaged these items to form a mean Intensity item score (α=0.86). Fatigue interference is assessed with 7 items that ask

[1]We chose to differentiate between patients experiencing *Severe* (40.6%) or *Very severe* (12.6%) PEM vs. those not endorsing PEM (10.7%) or experiencing *Very mild* (0.8%), *Mild* (4.2%), or *Moderate* (31.0%) PEM to align with PEM prevalence rates found in previous studies. Dichotomizing the sample in this way yielded 53.3% hiPEM and 46.7% loPEM patients; the sample analyzed by White and colleagues (2013) included 46.7% classified as high symptom flare patients and 53.3% classified as low symptom flare patients, and the sample analyzed by Maes and colleagues (2012) comprised 45.8% patients with PEM and 54.2% without PEM. Maes and colleagues aligned findings with prevalence rates from epidemiological analyses that found 47.0% of patients diagnosed with Fukuda criteria (1994) also met the Canadian Consensus Criteria (Carruthers et al., 2003), which requires PEM (Nacul et al., 2011). Because our research is based on the conceptualization of PEM as a cardinal symptom of CFS (IOM, 2015), however, and in order to more closely replicate the PEM status assessment of Maes and colleagues (2012), we have included analyses that dichotomize groups into with PEM (*Very mild*, *Mild*, *Moderate*, *Severe*, or *Very Severe*) and without PEM (no endorsement of PEM) in supplementary material (see Supplementary Tables S1 and S2).

participants to indicate how much, in the past week, fatigue interfered with various aspects of functioning (e.g., “enjoyment of life”). Items are rated on an 11-point scale (0=No interference; 10=Extreme interference) and summed (range: 0–70; α=0.88 in the present sample), with higher scores indicating greater interference.

Sickness Impact Profile (SIP)

The SIP is a measure of perceived health status that indicates the extent of dysfunction experienced in relation to illness, with higher scores indicating greater sickness impact (Bergner, Bobbit, Carter, & Gilson, 1981). The full measure consists of 136 statements of sickness-related behavioral change to which participants respond dichotomously (0=No; 1=Yes). The Social Interaction (5 items, e.g., “I am going out less to visit people”; range: 0–5, α=0.75 in the present sample) and Recreation and Pastimes (11 items, e.g., “I am going out for entertainment less often”; range: 0–11, α=0.72) categories were administered to participants in the present sample and summed to obtain subscale scores.

Center for Epidemiologic Studies Depression Scale (CES-D)

The CES-D was designed to assess depressive symptomatology in the general population (Radloff, 1977). Participants respond to 20 items (e.g., “I felt fearful”) based on how often, during the past week, they have felt this way (0=Rarely or none of the time (less than 1 day); 1=Some or a little of the time (1–2 days); 2=Occasionally or a moderate amount of time (3–4 days); 3=Most or all of the time (5–7 days)). Responses are summed (range: 0–60; α=0.90 in the sample), with higher scores indicating greater frequency of depressive symptom occurrence.

Profile of Mood States (POMS)

The POMS assesses the degree to which an individual has experienced distinct mood states over the past week (McNair, 1971). Sixty-five items list specific feelings (e.g., “annoyed,” “unhappy,” “listless,” “on edge,”) and participants indicate the extent to which they have been feeling that way over the past week (0=Not at all; 1=A little; 2=Moderately; 3=Quite a bit; 4=Extremely). Responses are summed to arrive at subscale scores(α’s = 0.79–0.90 in the sample). The overall Total Mood Disturbance score is a summation of negatively and positively weighted subscale scores (range: −32 to +200), with greater scores indicating greater mood disturbance. Two participants endorsed negative scores (−12 and −9), and a constant of 12 was therefore added to all Total Mood Disturbance scores.

Recent Negative Life Experiences

To assess external stressors, participants were asked whether each of 16 stressful life experiences, taken from the Life Experiences Survey (Sarason, Johnson, & Siegel, 1978), had occurred within the past 90 days. Participants indicated how these experiences had affected their lives (−3=Extremely Negative to 3=Extremely Positive). A count of items endorsed as having had a negative impact (i.e., −3, −2, −1) served as a proxy measure for recent negative life experiences.

Perceived Stress Scale (PSS)

The PSS measures the degree to which participants appraise situations in their lives as stressful, with higher scores indicating greater perceived stress (Cohen, Kamarck, & Mermelstein, 1983). Fourteen items ask about the frequency with which a participant has experienced aspects of stress in the last month (e.g., "felt difficulties were piling up so high that you could not overcome them"). Items are rated on a five-point scale (0=Never; 1=Almost never; 2=Sometimes; 3=Fairly often; 4=Very often) and ratings are summed to arrive at a scale score (range: 0–56; α=0.88 in the present sample).

Statistical Analyses

Analyses were performed in Statistical Package for Social Sciences (SPSS) Version 24.0 and R statistical software Version 3.4.3. Group differences (hiPEM vs. loPEM) on categorical variables were analyzed with Pearson's χ^2 tests of homogeneity; all expected cell counts were greater than five. Group differences on continuous demographic variables were analyzed with independent samples *t*-tests (α=.05). Education and income were treated as continuous variables. Because *t*-tests are robust to violations of the assumption of normality, non-normal variables were not transformed. If the assumption of equal variances was violated, results of *t*-tests were adjusted using the Welch-Satterwaite method. Univariate outliers were identified using the Tukey method (i.e., values falling outside of 1.5 times the interquartile range below the first quartile or above the third quartile), and analyses were performed with within-group outliers both winsorized and retained. If results of both analyses were equivocal in terms of significance, only the results of the analyses conducted with outliers retained are presented.

Differences between hiPEM and loPEM groups in terms of symptom burden and psychological distress variables were analyzed with individual ANCOVAs (α=.05) that included age and gender entered hierarchically as covariates, as these variables were likely to impact outcomes (e.g., fatigue, social activities). To complement these results, multiple linear regressions predicted outcomes from age, gender, and the continuous PEM variable, entered hierarchically. Variables with non-normal within-group distributions (skew >|3.0| or kurtosis >|8.0|) were transformed such that distributions achieved normality, and univariate outliers were handled as previously described.

For ANCOVAs, linear relationships between the continuous covariate and the dependent variable by PEM status were ascertained with visual inspection of scatterplots. Nonsignificant interactions (*p*'s≥.05) between covariates and PEM status confirmed homogeneity of regression slopes. Levene's test confirmed homogeneity of variances (*p*'s≥.05). Normality of residuals was determined with evaluation of skew and kurtosis and homoscedasticity of residuals was determined visually with plots of standardized residuals against predicted values. Partial η^2 was utilized as a measure of effect size, with values of .0099, .0588, and .1379 reflecting small, medium, and large effects, respectively (Cohen, 1969; Richardson, 2011).

For regression analyses, linearity and homoscedasticity were evaluated with visual inspection of plots of studentized residuals against unstandardized predicted values. Cases

were considered multivariate outliers if the studentized residual value was >±3 standard deviations from the mean; these were removed if the Leverage value was <0.2 or the Cook's Distance value was >1. Tolerance values >1 confirmed absence of multicollinearity, and inspection of a Q-Q plot confirmed that the assumption of normality was met.

Across the 182 symptom burden and psychological distress items, less than 1% of values were missing. Missing values were imputed at the item level (Gottschall, West, & Enders, 2012), with 5 imputations for 50 iterations, using the MICE package for R statistical software (Van Buuren & Groothuis-Oudshoorn, 2011). The FSI Highest Fatigue item was non-normally distributed and therefore reverse square root transformed (maximum − x + 1). Across all ANCOVAs, five variables did not meet the assumption of homogeneity of variances: the CDC CFS Symptom Inventory Total Score, the transformed FSI Highest Fatigue item, the FSI Lowest Fatigue item, the SIP Recreation and Pastimes score, and the PSS score. The SIP Recreations and Pastimes Score was not improved with transformations (p<0.001) and results should be interpreted with caution. The transformed FSI Highest Fatigue item was normalized by taking its inverse (thus, 1 / maximum − x + 1), and the remaining four variables were normalized with square root (x + 1) transformations. In regression analyses, no multivariate outliers met the Leverage or Influence removal criterion; all values were therefore retained. The regression analysis predicting Number of Negative Life Events did not initially meet the assumption of normality, but markedly improved with a reverse log transformation (*log*(maximum − x + 1)).

Results

Three patients were missing data on the PEM variable and were therefore excluded. A total of 139 hiPEM patients and 122 loPEM patients were included in analyses. Results of the comparisons of hiPEM and loPEM groups in terms of demographic variables are presented in Table 1. More hiPEM patients were on disability while more loPEM patients were employed (p<0.001), and hiPEM patients reported lower income than did loPEM patients (p=0.007). Additionally, there was a borderline statistically significant finding for data source (p=0.050), with a greater number of loPEM patients coming from the Videoconferenced versus Teleconferenced dataset (63.1%) as compared to hiPEM patients (51.1%)[2].

The series of ANCOVAs indicated that hiPEM patients reported greater symptom burden and psychological distress on most measures compared to loPEM patients when controlling for age and gender (see Tables 2 and 3). hiPEM patients reported greater overall CFS symptom severity and frequency, and greater fatigue severity and interference than their loPEM counterparts (all p's<.001); all effects were large. hiPEM patients also reported greater social disruption (p's<.001), depressive symptoms (p=.002), and mood disturbance (p=.011) than loPEM patients, with effect sizes ranging from small to large. There were no main effects of PEM status on PSS score or recent negative life experiences[3].

[2]Given this finding, additional ANCOVAs of psychological distress and symptom burden variables that included data source as a covariate were conducted. There were no meaningful differences in terms of significance or magnitude between these results and those of the analyses presented in this manuscript.

The results of regression analyses mirrored the results of ANCOVAs. Controlling for age and gender, main effects of PEM significantly and positively predicted CFS symptom severity and frequency as well as fatigue severity and interference (all *p*'s<.001; see Table 4). In terms of psychological status, there were main effects of PEM on social disruption (*p*'s≤.001), depressive symptoms (*p*=.002), and mood disturbance (*p*=.001; see Table 5). Similar to the results of the ANCOVAs, regression analyses found no main effects for PEM on perceived stress (*p*=.07) or on the transformed number of negative life events variable (*p*=.35).

Discussion

CFS is a disabling condition that constitutes significant costs for individuals and society (e.g., Cella et al., 2013; Jason et al., 2008). Research in the field is limited by the lack of a gold standard method of CFS diagnosis, with present methods varying in terms of criteria and relying on clinical judgment (Johnson, 2013). The commonly used Fukuda case definition (1994) is comprised of polythetic criteria, such that two patients with different symptom presentations can both be diagnosed with CFS. It is possible that the resulting heterogeneity of the CFS patient group impedes the reproducibility of research. PEM, for example is considered by many to be a cardinal symptom of CFS, and it is necessary for most other CFS case definitions (IOM, 2015). Thus, research supporting distinction of CFS patients by PEM status is important to the refinement of diagnostic criteria and the reproducibility of future research.

In a reasonably sized convenience sample, we found that hiPEM patients demonstrated greater impairment than loPEM patients in terms of nearly all symptom burden and psychological distress variables considered, with effect sizes ranging from small-to-medium to large. Replicating some of the findings of Maes and colleagues (2012), groups differed significantly on all symptom burden variables including fatigue intensity and overall symptom intensity and frequency. These analyses yielded the most robust effects.

We also documented, to our knowledge for the first time, PEM-related group differences in psychological variables including social disruption, depressive symptoms, and mood disturbance. Notably, both loPEM and hiPEM subgroups were elevated on SIP Social Interaction and SIP Recreation and Pastimes scores, likely due to limitations in energy. Nevertheless, the estimated marginal means of the hiPEM patients were 8.7% higher on disruption of social interaction and 24.2% higher on disruption of recreation and pastimes in terms of scale range. For depressive symptoms as assessed by the CES-D, estimated marginal means of both groups were well above the widely accepted clinical cut-off of 16, indicating that individuals in both groups are likely to suffer from depression; the estimated marginal mean of hiPEM patients was 7.6% greater than that of loPEM patients in terms of scale range. Neither the hiPEM nor the loPEM group scored extremely high on POMS Total

[3]The series of ANCOVAs was additionally run with participants grouped into 'with PEM' (*Very mild*, *Mild*, *Moderate*, *Severe*, or *Very Severe*) and 'without PEM' (no endorsement of PEM), rather than 'hiPEM' (*Severe* or *Very severe*) and 'loPEM' (*No endorsement of PEM, Very mild*, *Mild*, or *Moderate*), as previously described. Results of these analyses mirrored those of the hiPEM vs. loPEM analyses (see Supplementary Tables S1 and S2), with effect sizes ranging from small to medium.

Mood Disturbance, and the 5.3% difference between the estimated marginal means of groups was also smaller

Groups did not differ on measures of perceived stress or negative life experiences, suggesting that hiPEM patients were not necessarily dealing with more general distress, but rather that their greater reports of depressive symptoms and social disruption may reflect challenges of dealing with PEM symptoms and greater overall symptom burden. Due to the exploratory nature of this study in terms of the psychological distress variables considered, we chose not to apply a Bonferroni correction to significance levels. Were such a correction applied, however, significance would be set at p=0.003. The results of all analyses of symptom burden variables and the results of most analyses of psychological distress variables would survive this correction.

These results indicate differences between patients according to PEM status in terms of the severity of symptom burden and psychological distress, and we have interpreted this as support for the notion that including PEM as a polythetic criterion for CFS is inappropriate. We dichotomized our sample by PEM status rather than primarily considering PEM as a continuous variable, and we believe this to be a strength of our study: in order to add to the discussion of PEM, particularly self-reported PEM, as a defining feature of CFS, group differences must be explored, and the present approach to PEM is useful for that purpose. Recognizing the loss of data that is a natural consequence of dichotomizing continuous data, however, we have additionally corroborated the results of our group analyses with analyses of PEM as a continuous variable.

It is important to note possible alternative explanations for our results. For example, while it is possible that PEM defines a distinct patient group within CFS, it is also possible that PEM is simply a marker for patients who experience greater symptom burden (i.e., that patients who experience more PEM experience more symptomatology in general). Psychological distress could be a consequence of this (e.g., social disruption may be a consequence of PEM-associated limitations, such as those captured by the FSI Interference score), and depression could also follow from low income, social disruption, stigma, or other CFS-associated factors. Indeed, previous work has found that ME/CFS patients differ from patients with multiple sclerosis and healthy controls primarily in terms of physical and social functioning and less so in terms of mental health (Kingdon, Bowman, Curran, Nacul, & Lacerda, 2018). Nevertheless, we believe that the demonstrated differences between hiPEM and loPEM patients, particularly the 7.6% difference in depressive symptoms on the CES-D, are clinically relevant, especially given the lack of group differences on life stress and general distress measures.

Several strengths of this study deserve consideration. First, combined baseline samples of separate clinical trials yielded a relatively large analytic sample of 261 individuals. Trial recruitment spanned over a decade, supporting the generalizability of results. Further, PEM subgroups were statistically equivalent in terms of nearly all sociodemographic characteristics, including BMI and type of symptom onset, as well as on measures of stress, including perceived stress and recent negative life experiences. The hiPEM individuals demonstrated lower levels of employment/higher levels of disability and lower income than

loPEM individuals; particularly as education levels were equivalent, these differences provide further evidence of the heightened levels of impairment experienced by the hiPEM group.

Results will need to be replicated with more valid PEM assessment methodology (e.g., White et al., 2010), as our analysis of pre-existing data was limited by the assessment of PEM status with a single self-report item (see Jason, Evans, So, Scott, & Brown, 2015). We chose to dichotomize PEM on the basis of severity rather than absence/presence in order to approximate the prevalence rates of PEM in patients diagnosed with the Fukuda criteria found in previous studies (e.g., Maes et al., 2012), and when we dichotomized patients on the basis of those who endorsed or did not endorse any PEM, results were similar.

This study relies on cross-sectional secondary data analysis that is limited to self-report, and it is therefore in itself insufficient to answer the question of whether or not PEM identifies a distinct subgroup of CFS patients. We have suggested possible alternative explanations for our results in the preceding paragraphs. Our study is further limited by the lack of a control or quasi-control group; as such, it cannot directly replicate the analyses of Maes and colleagues (2012), and claims cannot be made about PEM in CFS compared to PEM in the general population. Despite the methodological shortcomings of our study design and our assessment of PEM, the present study provides useful evidence for the heterogeneity of CFS patients diagnosed with the Fukuda criteria (1994) and the potential differentiation of CFS patients according to PEM status. A longitudinal study would be necessary, however, to identify whether PEM status influences CFS symptom expression over time to thereby more definitively establish the value of PEM status in CFS diagnosis. Our research does suggest that PEM is, at the very least, a uniquely distressing symptom of CFS. Because this psychological distress is a potential maintaining factor of CFS (i.e., by inhibiting patients from engaging in tasks requiring physical or cognitive exertion and thereby compromising quality of life), PEM may also identify those patients who are in the greatest need of and would potentially benefit the most from psychological intervention. Future research could seek to determine whether hiPEM and loPEM patients respond differently to these treatments.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Patients high in PEM endorse greater symptom burden than those low in PEM
- Patients high in PEM endorse greater psychological adversity than those low in PEM
- Results suggest the Fukuda case definition does not define a heterogeneous group
- PEM may identify patients who would most benefit from psychological intervention

Table 1.

Sociodemographic Characteristics: Group Differences by PEM Status

	N	hiPEM	loPEM	*P*
Age ($\bar{x}$ ± s, range)	139, 122	48.6 ± 11.8, 20–72	49.9 ± 10.6, 25–73	0.361
Gender (% Female)	139, 122	84.9%	86.1%	0.789
Ethnicity (% non-Hispanic Caucasian; % Hispanic)	139, 122	75.5%; 20.9%	67.2%; 27.0%	0.313
Education (% College graduate and above[†])	138, 122	59.0%	61.5%	0.400
Employment/Disability status (% Employed; % On disability)	126, 109	22.2%; 47.6%	47.7%; 22.0%	<0.001[*]
Income (% above $60,000[†])	123, 108	36.0%	50.8%	0.007[*]
CFS onset[‡] (% gradual vs. sudden)	66, 75	62.1%	74.7%	0.109
Months since diagnosis[‡] ($\bar{x}$ ± s, range)	69, 76	75.3 ± 99.1, 0–477	66.3 ± 83.9, 0–377	0.554
BMI[‡] ($\bar{x}$ ± s, range)	70, 75	28.0 ± 7.2, 16.8–56.7	27.6 ± 6.4, 18.8–50.3	0.709
Taking medication prescribed for: pain	137, 121	59.0%	54.1%	0.390
Taking medication prescribed for: sleep	136, 118	61.9%	52.5%	0.146
Taking medication prescribed for: depression	136, 118	48.9%	41.0%	0.224
Taking medication prescribed for: anxiety	136, 118	43.2%	30.3%	0.037[*]
Physician's office visits in past 90 days[‡] ($\bar{x}$ ± s, range)	70, 76	0.7 ± 2.0, 0–9	0.7 ± 2.1, 0–12	0.484
Therapy group session(s) in past 90 days[‡] (% >0)	70, 76	10.0%	10.5%	0.917
Individual therapy session(s) in past 90 days[‡] (% >0)	70, 76	31.4%	43.4%	0.135
Outpatient psychiatric facility visit(s) in past 90 days[‡] (% >0)	70, 76	14.3%	18.4%	0.501
Data source (% Videoconference trial)	139, 122	51.1%	63.1%	0.050

Significance statistics correspond to independent samples *t*-tests (α=.05) conducted for continuous variables, including education and income, and Pearson's χ^2 tests of homogeneity for categorical variables.

[*] p<0.05

[†] Variable dichotomized for descriptive statistics, not for significance testing

[‡] Data only available in Videoconference trial dataset

Table 2.

Symptom Burden: Estimated Marginal Means, Significance Tests, and Effect Size for PEM Status

				hiPEM			loPEM		
Scale (range of scores possible in sample)	***F*(1,257)**	***p***	**partial η^2**	$\bar{x}$	***SE***	**95% CI**	$\bar{x}$	***SE***	**95% CI**
FSI Interference Score (0–10)	30.97	<0.001	.108	7.29	0.18	(6.93–7.65)	5.86	0.19	(5.48–6.24)
FSI Highest Fatigue Intensity Item (0–10)				9.03	0.17	(8.70–9.37)	7.81	0.18	(7.45–8.16)
FSI Highest Fatigue Intensity Item †	37.67	<0.001	.128						
FSI Lowest Fatigue Intensity Item (0–10)				5.37	0.16	(5.05–5.69)	3.62	0.17	(3.28–3.96)
FSI Lowest Fatigue Intensity Item ‡	57.26	<0.001	.182						
FSI Average Fatigue Intensity Item (0–10)	42.23	<0.001	.141	7.04	0.15	(6.74–7.34)	5.66	0.16	(5.34–5.97)
FSI Current Fatigue Intensity Item (0–10)	14.46	<0.001	.053	6.80	0.20	(6.41–7.19)	5.75	0.21	(5.35–6.16)
FSI Mean Intensity Item Score (0–10)	47.42	<0.001	.156	7.06	0.14	(6.78–7.34)	5.71	0.15	(5.42–6.00)
CDC CFS Inventory Total Score (0–304)				157.05	4.83	(147.54–166.57)	100.39	5.09	(90.36–110.42)
CDC CFS Inventory Total Score †	74.69	<0.001	.225						
CDC CFS Inventory Frequency Score (0–76)	45.63	<0.001	.151	2.24	0.06	(2.12–2.35)	1.67	0.06	(1.55–1.80)
CDC CFS Inventory Severity Score (0–76)	63.99	<0.001	.199	2.18	0.06	(2.07–2.29)	1.55	0.06	(1.43–1.67)

Test statistics correspond to ANCOVA analyses comparing hiPEM and loPEM groups, controlling for age and gender. In the case of variables that were transformed to meet assumptions, inferential statistics are presented for analyses conducted with transformed versions of the variables. For clarity in terms of scaling, estimated marginal means are presented for analyses conducted with original, untransformed variables considering female participants of average age (49.22 years). Partial η^2 values are presented only for analyses that indicated significant main effects for PEM status.

‡Inverse of reverse square root transformation

†Square root transformation

Table 3.

Psychological Distress: Estimated Marginal Means, Significance Tests, and Effect Size for PEM Status

				hiPEM			loPEM		
Scale (range of scores possible in sample)	***F*(1,257)**	***p***	**partial η^2**	$\bar{x}$	***SE***	**95% CI**	$\bar{x}$	***SE***	**95% CI**
SIP Social Interaction (0–11)	20.60	<0.001	.074	6.73	0.23	(6.28–7.19)	5.28	0.24	(4.80–5.76)
SIP Recreation and Pastimes[†] (0–5)	39.01	<0.001	.132	3.82	0.12	(3.58–4.05)	2.78	0.13	(2.53–3.02)
CES-D (0–60)	10.17	0.002	.038	25.76	1.05	(23.70–27.82)	21.10	1.10	(18.92–23.27)
POMS Total Mood Disturbance (0–212)	6.62	0.011	.025	75.03	3.16	(68.81–81.24)	63.69	3.33	(57.14–70.24)
PSS (0–56)				31.92	0.82	(30.31–33.54)	29.91	0.86	(28.21–31.61)
PSS[‡]	2.31	0.129							
Negative Life Experiences in past 90 days (0–16)	1.448	0.230		1.51	0.14	(1.23–1.78)	1.27	0.15	(0.99–1.56)

Test statistics correspond to ANCOVA analyses comparing hiPEM and loPEM groups, controlling for age and gender. In the case of variables that were transformed to meet assumptions, inferential statistics are presented for analyses conducted with transformed versions of the variables. For clarity in terms of scaling, estimated marginal means are presented for analyses conducted with original, untransformed variables considering female participants of average age (49.22 years). Partial η^2 values are presented only for analyses that indicated significant main effects for PEM status.

[†]The SIP Recreations and Pastimes score did not meet the assumption of homogeneity of variances as assessed by Levene's test ($p<0.001$)

[‡]Square root transformation

Table 4.

Symptom Burden Predicted from Continuous PEM

				PEM Coefficient			
Scale (range of scores possible in sample)	***F*(3,257)**	***p***	**adj. R^2**	***B***	**95% CI**	***t*(257)**	***p***
FSI Interference Score (0–10)	17.23	<0.001	.158	0.55	(0.40–0.70)	7.18	<0.001
FSI Highest Fatigue Intensity Item [†] (0–10)	10.48	<0.001	.099	−0.11	(−0.15–−0.07)	−5.51	<0.001
FSI Lowest Fatigue Intensity Item (0–10)	16.77	<0.001	.164	0.49	(0.35–0.63)	6.76	<0.001
FSI Average Fatigue Intensity Item (0–10)	12.58	<0.001	.118	0.40	(0.27–0.54)	6.03	<0.001
FSI Current Fatigue Intensity Item (0–10)	9.68	<0.001	.091	0.42	(0.26–0.59)	5.02	<0.001
FSI Mean Intensity Item Score (0–10)	17.56	<0.001	.160	0.43	(0.31–0.55)	7.02	<0.001
CDC CFS Inventory Total Score (0–304)	13.60	<0.001	.127	14.02	(9.68–18.36)	6.37	<0.001
CDC CFS Inventory Frequency Score (0–76)	11.19	<0.001	.105	0.15	(0.10–0.21)	5.78	<0.001
CDC CFS Inventory Severity Score (0–76)	11.17	<0.001	.105	0.15	(0.10–0.20)	5.71	<0.001

Test statistics correspond to multiple regression analyses predicting outcomes from age, gender, and the continuous PEM variable. Only the regression coefficients of the continuous PEM variable are presented.

[†]Reverse square root transformation

Table 5.

Psychological Distress Predicted from Continuous PEM

				PEM Coefficient			
Scale (range of scores possible in sample)	***F*(3,257)**	***p***	**adj. R^2**	***B***	**95% CI**	***t*(257)**	***p***
SIP Social Interaction (0–11)	4.37	0.005	.037	0.36	(0.16–0.56)	3.59	<0.001
SIP Recreation and Pastimes (0–5)	9.20	<0.001	.086	0.26	(0.16–0.37)	5.04	<0.001
CES-D (0–60)	4.08	0.007	.045	1.54	(0.65–2.43)	3.39	.001
POMS Total Mood Disturbance (0–212)	4.02	0.008	.034	4.32	(1.64–7.00)	3.18	.002
PSS (0–56)	3.00	0.031	.023	0.64	(−0.06–1.35)	1.81	.072
Negative Life Experiences in past 90 days (0–16)[†]	1.37	0.254	.004	−0.01	(−0.02–0.01)	−0.85	.394

Test statistics correspond to multiple regression analyses predicting outcomes from age, gender, and the continuous PEM variable. Only the regression coefficients of the continuous PEM variable are presented.

[†]Reverse natural log transformation