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Are Myalgic Encephalomyelitis and chronic fatigue syndrome different illnesses? A preliminary analysis

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Abstract

Considerable discussion has transpired regarding whether chronic fatigue syndrome is a distinct illness from Myalgic Encephalomyelitis. A prior study contrasted the Myalgic Encephalomyelitis International Consensus Criteria (ME-ICC; Carruthers et al., 2011) with the Fukuda et al. (1994) CFS criteria and found that the ME-ICC identified a subset of patients with greater functional impairment and physical, mental, and cognitive problems than the larger group who met Fukuda et al. (1994) criteria (Brown et al., 2013). The current study analyzed two discrete data sets and found that the ME-ICC identified more impaired individuals with more severe symptomatology.

Keywords

chronic fatigue syndrome; diagnosis; methodology; grounded theory; chronic illness

The term Myalgic Encephalomyelitis (ME) was first used in an anonymous editorial in an issue of the Lancet (Anonymous Editorial, 1956). Using this term, Ramsay (1988) published a case definition for ME (Hyde et al., 1992). Subsequently, a case definition was developed utilizing the term Myalgic Encephalomyelitis/chronic fatigue syndrome (ME/CFS; Carruthers et al., 2003), known as the 2003 Canadian Clinical ME/CFS case definition. These criteria required the occurrence of seven specific ME/CFS symptoms. Several of the individuals who were involved in creating the ME/CFS criteria, along with other scientists and clinicians, recently published the International Consensus Criteria for Myalgic Encephalomyelitis (ME-ICC; Carruthers et al., 2011). In addition to requiring the presence of eight symptoms from four domains, these criteria specify that the impact of the illness must result in a 50% or greater reduction in the patient's premorbid activity level.

In contrast, most scientists have used the Fukuda et al. (1994) case definition in researching chronic fatigue syndrome (CFS). This case definition requires an individual to experience six or more months of chronic fatigue of a new or definite onset that is not substantially alleviated by rest, not the result of ongoing exertion, and results in substantial reductions in occupational, social, and personal activities (Fukuda et al., 1994: 956). The Fukuda et al.

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case definition employs a polythetic approach for assessing symptomatology. Thus, in contrast to the ME/CFS (Carruthers et al., 2003) and ME-ICC (Carruthers et al., 2011) case definitions, the Fukuda et al. criteria require any four symptoms out of a possible eight, so individuals who meet Fukuda et al. criteria may not have core CFS symptoms such as post-exertional malaise.

In a study of individuals who had been diagnosed using the Fukuda et al. (1994) CFS criteria, Brown et al. (2013) examined whether these participants also met the ME-ICC (Carruthers et al., 2011). Findings indicated that the ME-ICC identified individuals with more serious symptomatology and functional disability than those who met only the Fukuda et al. criteria. Unfortunately, there were two limitations in this initial effort to compare the CFS and ME-ICC. First, individuals recruited into the sample had to have been diagnosed with CFS, so this requirement may have led to a selection bias. Second, the instrument used to measure ME-ICC symptoms was created prior to the criteria's publication, so a number of the symptoms could only be assessed indirectly. The present study used a new instrument that better assessed ME-ICC symptoms and examined two groups of participants who were recruited using different case ascertainment methods to reduce selection bias. We hypothesized that the ME-ICC would identify a more impaired, symptomatic group than the Fukuda et al. criteria.

Method

Case Definitions

CFS Case Definition (Fukuda et al., 1994)—A case of chronic fatigue syndrome is defined by Fukuda et al. (1994) as the presence of the following criteria: (1) clinically evaluated, unexplained, persistent or relapsing chronic fatigue that is of new or definite onset (has not been lifelong); is not the result of ongoing exertion; is not substantially alleviated by rest and results in substantial reduction in previous levels of occupational, educational, social, or personal activities, and (2) the concurrent occurrence of four or more core symptoms, all of which must have persisted or recurred during six or more consecutive months of illness and must not have predated the fatigue (Fukuda et al., 1994: 956). Because frequency and severity criteria were not specified for the symptoms required in this case definition, participants needed to report frequency and severity scores of at least 1 for a symptom to be counted toward the four required symptoms. Using the Fukuda et al. criteria, 96.3% met criteria in the DePaul sample and 86.5% in the Newcastle sample. Table 1 provides a summary of the Fukuda et al. criteria.

ME-ICC Case Definition—The International Consensus Criteria for ME (Carruthers et al., 2011) state that symptom severity must result in a 50% or greater reduction of a patient's premorbid activity level for a diagnosis. Additionally, symptoms from four major groupings are required. First, to meet criteria, a person must experience Post-Exertional Neuroimmune Exhaustion. Within the Neurological Impairment symptom grouping, a patient must have at least one symptom from three of the following four symptom categories (1) neurocognitive impairments (e.g., difficulty processing information, short-term memory loss), (2) pain, (3) sleep disturbance, and (4) neurosensory, perceptual and motor disturbances (e.g. inability to

focus vision, sensitivity to light, feeling unsteady on feet). The third category is Immune, Gastro-intestinal and Genitourinary Impairments, and individuals must have at least one symptom from three of the following five symptom categories: (1) flu-like symptoms, (2) susceptibility to viral infections with prolonged recovery periods (3) gastro-intestinal tract symptoms (e.g., nausea, abdominal pain), (4) genitourinary symptoms (e.g., urinary urgency), and (5) sensitivities to food, medications, odors, or chemicals. The final category is Energy Production/Transportation Impairments, and at least one symptom from one of the following four symptom categories must be present: (1) cardiovascular (e.g. orthostatic intolerance), (2) respiratory (e.g. labored breathing), (3) loss of thermostatic stability (e.g. subnormal body temperature), and (4) intolerance of extremes of temperature. Participants needed to report frequency and severity scores of at least 2 for a symptom to meet criteria. In the DePaul sample, 57.1% met the ME-ICC, and 58.3% of the Newcastle sample met these criteria. Table 1 provides a summary of the ME-ICC.

Research Participants

The *DePaul sample* was a convenience sample of adults self-identifying as having ME, CFS, or ME/CFS that was collected between May 2010 and April 2012. The *Newcastle sample* was collected between June and September 2012 and consisted of patients referred to the Newcastle-upon-Tyne Royal Victoria Infirmary from primary care who fulfilled the Fukuda et al. CFS (1994) diagnostic criteria. Patients were given a complete medical work up. These two case ascertainment methods represent varied methods of patient recruitment that are currently used in studies of this illness.

DePaul Sample—To be eligible for inclusion in the DePaul sample, an individual needed to be between the ages of 18 and 65, capable of reading and writing English, and have a self-reported current diagnosis of ME, CFS, or ME/CFS. Following approval by DePaul University's Institutional Review Board, participants were recruited from a variety of sources: internet forums, support groups, individuals who had participated in the DePaul ME/CFS Research Team's studies in the past and had indicated interest in future studies, and individuals who had emailed the team's address with interest in future studies. Participants were given three options for completing the surveys: an electronic survey, a hard-copy survey, or a verbal survey over the telephone. Participants could complete these surveys at home or in person at the Center for Community Research at DePaul University. Participants were not given a timeline for survey completion due to the unpredictable nature of this illness that can result in unexpected, rapid declines in functioning. The first 100 individuals who completed the survey received a $5.00 gift card to Amazon.com for participation.

Of the original 217 individuals who completed the study measures, 28 participants were excluded due to endorsing lifelong fatigue or exclusionary medical or psychological conditions that preclude a diagnosis of CFS based on the Fukuda et al. (1994) case definition. The ME-ICC (Carruthers et al., 2011) does not consider lifelong fatigue to be exclusionary, so only 21 participants were excluded when applying this case definition.

Demographically, the sample was 83.5% female and 16.5% male. Regarding self-reported race, 97.9% of the sample identified as Caucasian, 0.5% as Asian, and the remaining 1.6% identified as "Other." In reporting work status, 55.3% of the sample stated that they were currently on disability, while 12.8% of the sample were working part- or full-time. With regard to educational level, 39.9% of the sample held a graduate or professional degree; 35.6% held a college degree; 17.6% had completed at least one year of college; and 6.9% had completed high school or an equivalent degree (e.g., GED). The mean age of the sample was 51.6 (*SD* = 11.2).

Newcastle Sample—Participants were consecutive patients referred to the Newcastle-upon-Tyne Royal Victoria Infirmary from primary care who fulfilled the Fukuda et al. (1994) diagnostic criteria for CFS. These criteria exclude those with a number of significant psychiatric disorders and other confounding medical conditions such as cancer. Primary care physicians referred patients with a suspected CFS diagnosis for complete medical assessment at Newcastle-upon-Tyne Royal Victoria Infirmary clinic. At the infirmary, a comprehensive medical history and examination was performed by an experienced consultant physician. Those who met eligibility criteria completed a written informed consent process before being included in the sample. They completed the study measures by hard copy. The Newcastle sample consisted of 100 participants. One participant was excluded due to morbid obesity, and three additional participants were excluded due to lifelong when applying the Fukuda et al. (1994) criteria.

Demographically, the sample was 81.3% female and 18.7% male. Regarding self-reported race 99.0% of the sample identified as Caucasian and 1.0% as multiracial. In reporting work status, 30.2% of the sample stated that they were currently on disability, while 36.1% of participants were working part- or full-time. With regard to education level, 18.8% held a graduate or professional degree; 28.1% held a college degree; 20.8% had completed at least one year of college; 13.5% had completed high school or an equivalent degree (e.g., GED); and 11.5% had not completed high school. The mean age of the sample was 46.0 (*SD* = 14.2).

Measures

The DePaul Symptom Questionnaire (DSQ)—All participants completed the DePaul Symptom Questionnaire (DSQ; Jason et al., 2010), a self-report measure of CFS, ME/CFS, and ME symptomatology, demographics, and medical, occupational, and social history. The DSQ contains items that tap the dimensions of the ME-ICC (Carruthers et al., 2011) and the Fukuda et al. (1994) CFS criteria. Participants were asked to rate each symptom's frequency over the past six months on a 5-point Likert scale (0=none of the time, 1=a little of the time, 2=about half the time, 3=most of the time, and 4=all of the time). Likewise, participants were asked to rate each symptom's severity over the past six months on a 5-point Likert scale (0=symptom not present, 1=mild, 2=moderate, 3=severe, 4=very severe). The DSQ has evidenced good test-retest reliability among both patient and control groups. (Jason et al., 2014) The development of the DSQ was based upon the CFS Questionnaire (Jason et al., 1997), which evidenced good inter-rater and test-retest reliability and was able to sensitively distinguish among individuals with CFS, Major Depressive Disorder, and healthy controls

(Hawk et al., 2006). Like the DSQ, the CFS Questionnaire assesses for frequency and severity over the past six months, but the severity rating is on a scale from 0–100, whereas the DSQ uses a Likert scale. To facilitate comparison with the CFS Questionnaire, the DSQ frequency and severity scores were multiplied by 25 to create a 100-point scale. Each symptom's 100-point frequency and severity scores were then averaged to obtain a composite score. The final difference between these two questionnaires is that the CFS Questionnaire was not developed to tap the ME-ICC requirements, while the DSQ was developed to assess these criteria. The DSQ is available through REDCap's (Harris et al., 2009) shared library (https://redcap.is.depaul.edu/surveys/?s=tRxytSPVVw).

Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) or RAND Questionnaire—The SF-36 is a 36-item self-report measure of health and its impact on one's functioning (Ware and Sherbourne, 1992). Lower scores indicate worse health or more impaired functioning. Test construction studies of the SF-36 have demonstrated sufficient psychometric properties (McHorney et al., 1994), and the SF-36 has also been shown to be a valid measure of functional status in a CFS population (Buchwald et al., 1996).

Statistics

Because most participants who met the ME-ICC (Carruthers et al., 2011) also met the Fukuda et al. (1994) criteria, two independent groups were created for comparison purposes. Participants who met the ME-ICC (referred to as the ME-ICC group) were compared to participants who met the Fukuda et al. case definition but did *not* meet the ME-ICC case definition (referred to as the CFS group). MANOVAs were used to analyze the DePaul sample. We were not able to use MANOVAs for the Newcastle sample due to the smaller sample size and violations of MANOVA assumptions, so individual ANOVAs (or adjusted F-tests, in cases of unequal variances) were conducted for each symptom. Note that, due to the number of comparisons, results that are significant at the $p < 0.01$ level can be interpreted with more confidence than those that are significant at the $p < 0.05$ level.

Results

Demographics

Table 2 presents demographic, psychiatric, and illness onset data for the CFS and ME-ICC groups. In the DePaul sample, there was a significant difference in age between the CFS group (M = 54.0, *SD* = 11.4) and the ME-ICC group (M = 49.8, *SD* = 10.9), $t(183) = 2.57$, $p = 0.01$. In addition, the two groups differed in their responses about what they believed to be the cause of their fatigue ($p = 0.01$, two-tailed Fisher's exact test). There were no significant differences between the two groups in the Newcastle sample.

Functional Status

Table 3 presents data from the SF-36. In the DePaul sample, a MANOVA indicated that the ME-ICC group was significantly different from the CFS group [Wilks' Lambda = .84, $F(8, 173) = 4.08$, $p < .001$]. Upon examination of the univariate tests, the ME-ICC condition showed significantly worse scores than the CFS group on the following five subscales: Physical Functioning [$F(1, 180) = 6.87$, $p = .01$], Role Physical [$F(1, 180) = 5.67$, $p = .02$],

Bodily Pain [$F(1,180) = 19.71$, $p < .001$], General Health [$F(1, 180) = 7.78$, $p < .01$], and Vitality [$F(1, 180) = 4.30$, $p = .03$]. In the Newcastle sample, a Brown-Forsythe test of the General Health subscale indicated significantly worse scores in the ME-ICC group [$F(1, 32.22) = 11.29$, $p < .01$]. For all remaining subscales, with the exception of Mental Health, scores of the ME-ICC group were directionally worse, but not significant.

When conducting the analysis above, the large amount of variance in Role Physical scores led to a significant Box's M test, which tests the MANOVA assumption of homogeneity of covariance matrices. Therefore, the results of this MANOVA were confirmed through conducting a MANOVA on the remaining seven subscales [Wilks' Lambda = .85, $F(7, 173) = 4.31$, $p < .001$] and an adjusted F-test on the Role Physical subscale [$F(1, 103.18) = 4.24$, $p = .04$].

Symptoms

Table 4 lists the symptoms analyzed in the DSQ. To compare the CFS and ME-ICC groups in the DePaul sample, an ANOVA was conducted on the Fatigue symptom, and MANOVAs were conducted on the following categories of symptoms: Post-Exertional Malaise, Sleep, Pain, Autonomic, Neuroendocrine, and Immune. Significant differences were found for the Post-Exertional Malaise, Pain, Autonomic, Neuroendocrine, and Immune categories. Univariate tests revealed significant differences in 46 symptoms in the DePaul sample. In the Newcastle sample, ANOVAs showed significant differences between the CFS and ME-ICC groups' scores for 33 symptoms. For all significant differences, the ME-ICC group reported worse symptom scores. Across both samples, most differences were significant at the $p < 0.001$ level.

Discussion

The present study compared the ME-ICC (Carruthers et al., 2011) with the Fukuda et al. (1994) CFS criteria through analyzing two distinct samples. While the Fukuda et al. criteria are the most widely used, the Carruthers et al. (2011) criteria have received considerable attention due to the large number of ME and CFS experts who authored them. To our knowledge, only one other study to date has compared these two case definitions (Brown et al., 2013), but the study was limited by its case ascertainment method. The current study found that the ME-ICC case definition identified patients with more functional impairments and worse symptoms than the group of patients who met the Fukuda et al. criteria.

Using the Fukuda et al. (1994) CFS case definition, 96.3% met criteria in the DePaul sample and 86.5% in the Newcastle sample. However, when using the Carruthers et al. (2011) ME-ICC case definition, only 57.1% met criteria in the DePaul sample and 58.3% in the Newcastle sample. These consistent findings suggest that about 60% of patients meet the ME-ICC case definition, whereas the Fukuda et al. criteria identify a larger group of patients.

In Table 3, the ME-ICC group showed significantly worse scores in subscales measuring physical health, but no differences were found in subscales measuring mental health. Additionally, in Table 4, the ME-ICC group reported worse symptoms than the CFS group.

These findings support the notion that the ME-ICC identify a more impaired sample, even across different patient recruitment methods.

The first US case definition by Holmes et al. (1988) required patients to report at least eight of eleven minor symptoms. The requirement of eight or more minor symptoms raised concerns that this case definition could inadvertently select for individuals with psychiatric problems (Katon and Russo, 1992). A few years later, an international working group developed the revised case definition for CFS (Fukuda et al., 1994), which was followed by the creation of the ME/CFS (Carruthers et al., 2003) and ME-ICC (Carruthers et al., 2011) case definitions that included more specific symptom requirements. Maes et al. (2012) demonstrated the importance of requiring specific symptoms through dividing individuals with Fukuda-defined CFS into two groups: CFS with post-exertional malaise and CFS without post-exertional malaise. This study showed that individuals with post-exertional malaise had more severe symptoms and more immune abnormalities than those without it.

While post-exertional malaise may need to be a required symptom in case definitions, the Canadian ME/CFS criteria (Carruthers et al., 2003) required seven symptoms, rather than the four required by Fukuda et al. (1994), and the ME-ICC (Carruthers et al., 2011) required eight symptoms, similar in number to what was required by Holmes et al. (1988). The implications of requiring larger numbers of symptoms might need to be considered, particularly in terms of psychiatric comorbidity (Brown et al., 2013). While the present study did not find differential rates of psychiatric comorbidity between the CFS and ME-ICC groups, these findings were not based on a structured clinical interview.

The authors of the ME-ICC case definition recently published a primer (Carruthers et al., 2012) in which they provided guidelines for determining if symptoms meet thresholds for criteria. As an example, post-exertional malaise is referred to as post-exertional neuroimmune exhaustion (PENE). In the self-report questionnaire included in the primer, PENE is characterized by (a) “Marked, rapid physical or cognitive fatigability in response to exertion;” (b) “Symptoms that worsen with exertion;” (c) “Post-exertional exhaustion;” (d) “Exhaustion is not relieved by rest;” and (e) “Substantial reduction in pre-illness activity level due to low threshold of physical and mental fatigability” (Carruthers et al., 2012: 10). This imprecise level of specification leads to a number of issues in operationalizing the criteria. First, it is unclear whether all five characteristics must be present for PENE to exist. Furthermore, the precise definition of these characteristics is still ambiguous. For example, the description of the onset and duration of PENE is vague, as it does not specify the length of time that individuals must experience this symptom in order to meet criteria.

In addition, the ME-ICC primer (Carruthers et al., 2012) designated severity levels for the assessment of activity reduction; however, these levels deviated from the original case definition. Instead of the three levels of severity indicated in the ME-ICC (Carruthers et al., 2011), the primer includes four levels (mild, moderate, severe, and very severe): the mild level signifies that a person “meets criteria” and is experiencing “significant” reductions in activity; the moderate level signifies that a person has experienced approximately a 50 percent reduction in pre-illness activity level; the severe level signifies individuals who are unable to function outside of the home; and the very severe level signifies individuals who

are confined to their beds and who have difficulty caring for their own basic needs. It is unclear why the ME primer (Carruthers et al., 2012) implemented four severity levels of activity reduction, while only three were specified in the ME-ICC (Carruthers et al., 2011). More importantly, the mild level equated to an approximate 50 percent reduction in activity levels in the Carruthers et al. (2011) criteria, but the moderate level equated to a 50 percent reduction in the Carruthers et al. (2012) criteria. Furthermore, the language used in both the ME-ICC (Carruthers et al., 2011) and the ME primer (Carruthers et al., 2012) lacked specific definitions and assessment tools for consistently and accurately assessing substantial activity reductions and symptom severity in individuals with the illness. For instance, it is unclear how to determine whether someone is experiencing a “significant” reduction in activity versus a 50 percent reduction in activity. Without clearly defined criteria and adequate assessment tools, determining whether an individual meets these criteria is left to clinical discretion, which can differ greatly across clinicians. Thus, scientists and clinicians might encounter reliability problems when utilizing this new case definition.

Sources of variance can be divided into the following five categories: subject variance, occasion variance, information variance, observation variance, and criterion variance (Jason and Choi, 2008). Criterion variance accounts for the largest source of diagnostic unreliability, and is most likely to occur when operationally explicit criteria do not exist for diagnostic categories. In other words, inclusion and exclusion criteria must be consistent across measures to adequately compare fatigue states across patients. When diagnostic categories lack reliability, the validity (i.e., usefulness) of a diagnostic category is inherently limited. In other words, the extent to which a diagnostic category is unreliable places on its potential validity for any type of clinical, research, or administrative use.

Diagnostic criteria should specify which diagnostic instrument to use, which individuals to interview, and how to determine the presence and severity of symptoms. It is also necessary to specify the number and type of symptoms that must be present in order to make a particular diagnosis. Definitions of fatigue should also include specific guidelines pertaining to the importance of symptom severity in the diagnostic procedure. For example, if a patient endorses a symptom such as post-exertional malaise, standardized questions should identify the duration, frequency, and severity of the symptom, including its onset, pattern, intensity, and other associated factors.

Based on the present analyses, the ME-ICC (Carruthers et al., 2011) appear to a select a more functionally impaired and symptomatic group of individuals when compared to those who met only the Fukuda et al. (1994) criteria. Given the high level of interest among clinicians and scientists regarding the ME-ICC, more research should be conducted to investigate how these criteria, as well as the specific instruments developed to assess these criteria, potentially select different patient cohorts than the Fukuda et al. criteria. Additional studies are needed to determine if biological and psychiatric differences exist between those who meet these two case definitions. Additionally, researchers should continue to operationalize current criteria to reduce criterion variance and use more sophisticated analytic techniques to identify the critical dimensions of these illnesses (Jason et al., 2012).

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Table 1

Summary of Case Definition Criteria: Fukuda et al. CFS (1994) and ME-ICC (Carruthers et al., 2011)

Fukuda et al. CFS (1994) Criteria:

- Chronic fatigue of at least 6 months in duration
- At least 4 of the following symptoms:
  - Impaired memory / concentration
  - Sore throat
  - Tender cervical or axillary lymph nodes
  - Muscle pain
  - Multi-joint pain
  - New headaches
  - Unrefreshing sleep
  - Post-Exertional malaise

Myalgic Encephalomyelitis International Consensus Criteria (Carruthers et al., 2011):

- 50% reduction in premorbid activity level
- Post-exertional neuroimmune exhaustion
- Neurological impairments (symptoms from at least 3 of the following categories)
  - Neurocognitive impairments
  - Pain
  - Sleep disturbance
  - Neurosensory, perceptual, and motor disturbances
- Immune, gastro-intestinal, and genitourinary impairments (symptoms from at least 3 of the following categories)
  - Flu-like symptoms
  - Susceptibility to viral infections with prolonged recovery periods
  - Gastro-intestinal tract symptoms
  - Genitourinary symptoms
  - Sensitivities to foods, medications, odors, or chemicals
- Energy production / ion transportation impairments (symptoms from at least 1 of the following categories)
  - Cardiovascular symptoms
  - Respiratory symptoms
  - Loss of thermostatic ability
  - Intolerance of extremes of temperature

Table 2

Demographics, Psychiatric Characteristics, and Onset Issues

	DePaul Sample			Newcastle Sample		
	CFS	ME	Sig.	CFS	ME	Sig.
	M (*SD*)	M (*SD*)		M (*SD*)	M (*SD*)	
Age	54.0 (*11.4*)	49.8 (*10.9*)	*	46.4 (*14.4*)	45.6 (*13.2*)	
Other Demographic Information:	N (%)	N (%)	Sig.	N (%)	N (%)	Sig.
Gender						
Male	14 (19)	17 (15)		7 (26)	10 (17)	
Female	59 (81)	95 (85)		20 (74)	48 (83)	
Race						
Caucasian	71 (96)	109 (98)		27 (100)	57 (98)	
Asian / Pacific Islander	0 (0)	1 (1)		0 (0)	0 (0)	
Other	3 (4)	1 (1)		0 (0)	1 (2)	
Marital status						
Married / Living with partner	41 (55)	63 (58)		15 (56)	30 (52)	
Separated	1 (1)	0 (0)		0 (0)	2 (3)	
Divorced	18 (24)	14 (13)		4 (15)	8 (14)	
Never married	14 (19)	31 (29)		8 (30)	18 (31)	
Work status						
On disability	38 (51)	65 (59)		9 (35)	20 (34)	
Student	1 (1)	5 (5)		2 (8)	2 (3)	
Homemaker	4 (5)	5 (5)		0 (0)	1 (2)	
Retired	14 (19)	8 (7)		3 (12)	11 (19)	
Unemployed	7 (9)	15 (14)		0 (0)	5 (9)	
Working part-time	7 (9)	8 (7)		7 (27)	11 (19)	
Working full-time	3 (4)	5 (5)		5 (19)	8 (14)	
Educational level						
Less than high school	0 (0)	0 (0)		1 (4)	1 (2)	
Some high school	0 (0)	0 (0)		4 (15)	3 (6)	

High school	3 (4)	10 (9)		1 (4)	11 (20)	
Partial college	10 (14)	23 (21)		8 (31)	11 (20)	
Standard college degree	23 (31)	42 (38)		6 (23)	18 (33)	
Graduate / Professional degree	38 (51)	36 (32)		6 (23)	10 (19)	
	DePaul Sample			Newcastle Sample		
	CFS	ME	Sig.	CFS	ME	Sig.
Psychiatric and Onset Issues:	N (%)	N (%)		N (%)	N (%)	
Lifetime psychiatric diagnosis						
Yes	31 (42)	48 (43)		11 (41)	24 (41)	
No	43 (58)	64 (57)		16 (59)	34 (59)	
Time period of illness onset						
Within 24 hours	20 (27)	27 (24)		0 (0)	6 (11)	
Over 1 week	11 (15)	17 (15)		2 (8)	7 (13)	
Over 1 month	10 (14)	13 (12)		1 (4)	2 (4)	
Over 2–6 months	14 (19)	15 (14)		10 (40)	9 (16)	
Over 7–12 months	3 (4)	7 (6)		3 (12)	7 (13)	
Over 1–2 years	9 (12)	10 (9)		2 (8)	9 (16)	
Over 3 or more years	7 (9)	22 (20)		7 (28)	15 (27)	
Cause of fatigue:						
Definitely physical	64 (89)	82 (74)	*	11 (50)	32 (59)	
Mainly physical	8 (11)	21 (19)		7 (32)	9 (17)	
Equally physical and psychological	0 (0)	8 (7)		4 (18)	12 (22)	
Mainly psychological	0 (0)	0 (0)		0 (0)	1 (2)	
Definitely psychological	0 (0)	0 (0)		0 (0)	0 (0)	

* $p < 0.05$

J Health Psychol. Author manuscript; available in PMC 2017 January 01.

Table 3

SF-36 Subscales (Higher score indicates **less** impairment)

	DePaul Sample			Newcastle Sample		
	CFS M (*SD*)	**ME M (*SD*)**	**Sig.**	**CFS M (*SD*)**	**ME M (*SD*)**	**Sig.**
Physical Functioning	34.1 (*17.5*)	26.9 (*18.6*)	**	41.9 (*30.8*)	29.3 (*23.3*)	
Role Physical	7.9 (*19.5*)	2.5 (*10.7*)	*	12.0 (*20.6*)	7.3 (*17.5*)	
Bodily Pain	50.0 (*23.8*)	35.6 (*19.9*)	***	40.0 (*26.2*)	29.5 (*21.4*)	
General Health	28.6 (*15.3*)	22.6 (*13.3*)	**	32.3 (*18.8*)	19.1 (*10.5*)	**
Social Functioning	21.2 (*21.7*)	19.5 (*18.7*)		31.0 (*24.4*)	26.5 (*19.9*)	
Mental Health	71.5 (*16.9*)	71.6 (*17.0*)		59.1 (*17.4*)	61.4 (*21.5*)	
Role Emotional	79.5 (*37.9*)	80.7 (*36.1*)		65.4 (*43.7*)	59.4 (*44.3*)	
Vitality	15.4 (*14.2*)	11.2 (*11.9*)	*	18.0 (*13.4*)	13.4 (*15.2*)	

* $p < 0.05$;

** $p < 0.01$;

*** $p < 0.001$

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Table 4

Symptoms (Higher score indicates **more** impairment)

	DePaul Sample			Newcastle Sample		
	CFS M (*SD*)	ME M (*SD*)	Sig.	CFS M (*SD*)	ME M (*SD*)	Sig.
Fatigue	78.8 (*17.0*)	80.0 (*15.1*)		75.0 (*14.6*)	80.4 (*15.7*)	
Post-exertional malaise						
Dead, heavy feeling after starting to exercise	60.5 (*31.6*)	73.2 (*26.4*)	**	62.0 (*29.4*)	73.0 (*24.5*)	
Next-day soreness after non-strenuous activities	68.6 (*22.2*)	78.8 (*18.4*)	**	61.1 (*30.5*)	75.2 (*21.2*)	*
Mentally tired after slightest effort	55.9 (*27.3*)	68.2 (*21.8*)	**	63.0 (*29.0*)	68.8 (*23.1*)	
Minimum exercise makes you tired	66.6 (*27.0*)	81.7 (*18.4*)	***	60.6 (*28.0*)	75.0 (*20.0*)	*
Physically drained / sick after mild activity	65.2 (*27.5*)	76.7 (*20.2*)	**	56.7 (*34.0*)	69.3 (*22.2*)	
Sleep						
Unrefreshing sleep	73.5 (*24.3*)	81.8 (*18.1*)		79.3 (*16.9*)	84.3 (*16.6*)	
Need to nap during each day	53.2 (*31.2*)	51.1 (*30.4*)		46.2 (*35.3*)	54.1 (*32.5*)	
Problems falling asleep	56.3 (*34.6*)	62.0 (*30.1*)		51.4 (*29.6*)	52.1 (*34.5*)	
Problems staying asleep	56.3 (*30.6*)	65.9 (*29.6*)		43.5 (*27.5*)	53.0 (*34.3*)	
Waking up early in the morning	43.4 (*30.1*)	52.6 (*34.4*)		38.9 (*27.9*)	48.4 (*34.1*)	
Sleeping all day / staying awake all night	15.2 (*26.9*)	17.5 (*27.3*)		10.6 (*18.3*)	20.4 (*27.0*)	
Pain						
Muscle pain	50.4 (*27.4*)	68.6 (*23.3*)	***	64.8 (*21.9*)	75.9 (*24.1*)	*
Pain in multiple joints	35.8 (*34.0*)	59.7 (*29.5*)	***	57.4 (*32.9*)	71.1 (*25.8*)	*
Eye pain	25.0 (*27.1*)	38.0 (*28.7*)	**	32.4 (*28.9*)	43.3 (*26.5*)	
Chest pain	18.9 (*23.3*)	30.1 (*24.8*)	**	21.2 (*24.7*)	30.5 (*25.4*)	
Bloating	30.7 (*28.3*)	53.6 (*24.3*)	***	26.4 (*27.0*)	51.3 (*30.7*)	***
Abdomen / stomach pain	24.1 (*22.7*)	47.2 (*23.8*)	***	21.0 (*25.7*)	49.4 (*30.7*)	***
Headaches	41.7 (*24.7*)	53.9 (*24.4*)	**	48.6 (*25.1*)	65.5 (*22.4*)	**
Neurocognitive						
Muscle twitches	22.4 (*20.4*)	37.6 (*26.9*)	***	27.4 (*30.2*)	42.7 (*30.1*)	*
Muscle weakness	53.9 (*29.6*)	66.6 (*24.3*)	**	55.3 (*28.3*)	71.1 (*22.6*)	**
Sensitivity to noise	54.9 (*29.8*)	66.3 (*25.7*)	**	37.5 (*33.5*)	61.6 (*29.0*)	**

	DePaul Sample			Newcastle Sample		
	CFS M (*SD*)	ME M (*SD*)	Sig.	CFS M (*SD*)	ME M (*SD*)	Sig.
Sensitivity to bright lights	46.1 (*32.1*)	65.2 (*24.0*)	***	41.3 (*30.2*)	57.3 (*28.4*)	*
Problems remembering things	60.8 (*23.8*)	68.9 (*20.4*)	*	61.5 (*24.2*)	75.2 (*20.3*)	**
Difficulty paying attention for long periods of time	64.6 (*28.2*)	77.4 (*21.5*)	**	70.0 (*21.3*)	77.8 (*20.8*)	
Difficulty expressing thoughts	54.9 (*25.5*)	67.1 (*21.3*)	**	55.8 (*27.7*)	67.2 (*23.9*)	
Difficulty understanding things	37.3 (*22.7*)	54.1 (*21.2*)	***	51.9 (*28.2*)	57.9 (*27.2*)	
Can only focus on one thing at a time	60.6 (*31.5*)	74.9 (*22.8*)	***	63.0 (*24.9*)	68.4 (*25.7*)	
Unable to focus vision / attention	38.6 (*26.2*)	56.8 (*22.4*)	***	49.0 (*29.8*)	53.4 (*24.8*)	
Loss of depth perception	14.6 (*25.3*)	31.6 (*32.8*)	***	17.9 (*32.6*)	35.0 (*32.3*)	*
Slowness of thought	51.1 (*24.3*)	63.9 (*22.0*)	***	53.4 (*26.6*)	62.3 (*24.9*)	
Absent-mindedness	52.2 (*29.1*)	65.2 (*23.6*)	**	52.4 (*28.3*)	68.5 (*25.6*)	*
Autonomic						
Bladder problems	19.1 (*26.4*)	38.1 (*34.2*)	***	15.5 (*22.6*)	35.7 (*33.8*)	**
Irritable bowel problems	29.6 (*28.9*)	56.4 (*28.5*)	***	31.7 (*29.6*)	57.0 (*34.0*)	**
Nausea	22.1 (*20.3*)	38.3 (*24.1*)	***	24.5 (*19.5*)	43.3 (*26.2*)	**
Feeling unsteady on feet	28.8 (*20.5*)	50.2 (*26.5*)	***	34.6 (*24.6*)	52.6 (*28.0*)	**
Shortness of breath	29.3 (*26.1*)	44.0 (*25.2*)	***	21.5 (*19.3*)	42.8 (*27.8*)	***
Dizziness / fainting	29.5 (*24.5*)	44.5 (*24.0*)	***	38.5 (*25.5*)	48.1 (*30.1*)	
Irregular heart beats	20.2 (*22.9*)	38.3 (*27.0*)	***	24.5 (*27.3*)	40.0 (*32.4*)	*
Neuroendocrine						
Losing / gaining weight without trying	31.6 (*35.0*)	42.6 (*33.2*)	*	38.5 (*36.0*)	51.3 (*34.1*)	
No appetite	15.9 (*18.4*)	26.3 (*25.6*)	**	15.0 (*21.9*)	34.5 (*32.0*)	**
Sweating hands	8.6 (*19.1*)	14.5 (*23.1*)		9.5 (*18.1*)	28.1 (*32.6*)	**
Night sweats	26.6 (*29.2*)	40.0 (*30.9*)	**	26.0 (*28.4*)	38.4 (*30.2*)	
Cold limbs	44.8 (*30.5*)	56.9 (*29.7*)	**	36.5 (*29.3*)	58.6 (*33.0*)	**
Chills / shivers	25.0 (*25.3*)	41.4 (*27.9*)	***	22.6 (*23.7*)	42.5 (*30.7*)	**
Feeling hot / cold for no reason	40.9 (*28.3*)	58.3 (*27.5*)	***	44.0 (*27.7*)	59.9 (*28.2*)	*
Feeling like you have a high temperature	18.9 (*26.4*)	40.4 (*29.4*)	***	27.6 (*35.0*)	47.2 (*29.9*)	*
Feeling like you have a low temperature	18.9 (*26.7*)	34.0 (*29.5*)	***	10.9 (*22.5*)	29.6 (*30.9*)	**
Alcohol intolerance	35.2 (*39.3*)	58.3 (*37.8*)	***	27.5 (*32.1*)	56.9 (*35.3*)	***

	DePaul Sample			Newcastle Sample		
	CFS M (*SD*)	ME M (*SD*)	Sig.	CFS M (*SD*)	ME M (*SD*)	Sig.
Immune						
Sore throat	29.8 (*25.1*)	39.6 (*22.5*)	**	24.0 (*22.5*)	50.2 (*28.3*)	***
Tender lymph nodes	29.4 (*26.0*)	50.6 (*28.1*)	***	20.0 (*21.0*)	46.7 (*29.3*)	***
Fever	8.1 (*15.1*)	18.9 (*21.8*)	***	11.5 (*20.4*)	27.2 (*26.8*)	*
Flu-like symptoms	36.6 (*22.7*)	63.9 (*23.5*)	***	36.5 (*30.0*)	62.5 (*21.8*)	***
Sensitivity to smells/foods/medications/chemicals	36.0 (*36.0*)	66.8 (*30.7*)	***	22.6 (*29.6*)	54.7 (*35.5*)	***

* $p < 0.05$;

** $p < 0.01$;

*** $p < 0.001$