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Contrasting Case Definitions for Chronic Fatigue Syndrome, Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and Myalgic Encephalomyelitis

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Abstract

This article uses data from patients recruited using the 1994 case definition of chronic fatigue syndrome (CFS) to contrast those meeting criteria for the Myalgic Encephalomyelitis/chronic fatigue syndrome (ME/CFS) Canadian case definition with those that did not meet these criteria. The study also contrasts those meeting criteria for Myalgic Encephalomyelitis (ME) based on criteria from Ramsay and other theorists with those that did not meet the ME criteria. The ME/CFS case definition criteria identified a subset of patients with more functional impairments and physical, mental, and cognitive problems than the subset not meeting these criteria. The ME subset had more functional impairments, and more severe physical and cognitive symptoms than the subset not meeting ME criteria. When applied to a population meeting the 1994 CFS case definition, both ME/CFS and ME criteria appear to select a more severe subset of patients.

Keywords

chronic fatigue syndrome; myalgic encephalomyelitis; myalgic encephalomyelitis/chronic fatigue syndrome; case definition; Fukuda criteria

Introduction

The first U.S. chronic fatigue syndrome (CFS) case definition was proposed by Holmes et al. (1988). According to this case definition, individuals needed to report 6 or more months of persistent or relapsing, debilitating fatigue that does not resolve with bedrest. Also, participants were required to report at least 8 of 11 minor symptoms (fever or chills, sore throat, lymph node pain, muscle weakness, muscle pain, postexertional malaise, headaches of a new or different type, migratory arthralgia, neuropsychiatric complaints, sleep disturbance, and a sudden onset of symptoms). Participants were also required to report at least a 50% impairment of daily functioning, as compared to premorbid levels. As the Holmes et al. criteria were utilized in research and practice, it became evident that there were numerous inconsistencies in interpretation and classification. Another major concern was that the requirement of eight or more minor symptoms could inadvertently select for individuals with psychiatric problems (Katon & Russo, 1992).

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A few years later an international working group developed a revised case definition for CFS (Fukuda et al., 1994), and it required a person to experience 6 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. Jason, Torres-Harding, Taylor, and Carrico (2001) compared the Fukuda et al. (1994) and Holmes et al. (1988) criteria and found that the Holmes et al. criteria selected a group of patients with higher symptomatology and functional impairment. The Fukuda et al. case definition uses a combination of criteria: a set of symptoms in which not all need to be present to make a diagnosis. For example, because the Fukuda et al. criteria only requires four symptoms out of a possible eight, critical CFS symptoms such as postexertional malaise, and memory and concentration problems are not required of all patients.

This case definition for CFS (Fukuda et al., 1994) is characterized by vaguely worded criteria that are lacking operational definitions and guidelines to assist health care professionals in their interpretation and application of the diagnostic tool (Jason et al., 1999; Reeves et al., 2003). In order to provide more guidelines and specific criteria for this case definition, the CDC developed an empiric case definition for CFS that involves assessment of symptoms, disability, and fatigue (Reeves et al., 2005). It was an approach to operationalize the 1994 Fukuda et al. case definition. Using the CFS empiric criteria, the estimated rate of CFS has increased to 2.54% (Reeves et al., 2007), which is 10 times higher than prior CDC (Reyes et al., 2003) and other investigator prevalence estimates (Jason, Richman, et al., 1999). Jason, Najar, Porter, and Reh (2009) also found that 38% of those with a diagnosis of a Major Depressive Disorder were misclassified as having CFS using the new, more broadly based CDC empiric case definition. Consequently, the CDC definition of CFS has been rarely used by investigators.

The term Myalgic Encephalomyelitis (ME) had been used prior to the term CFS (Acheson, 1959). ME was first described in literature of the 1930s, where an outbreak of Epidemic Neuromysthenia in Los Angeles County was called atypical poliomyelitis because of its resemblance to polio (Gilliam, 1938; Hyde, 2007). Then, an anonymous editorial of a 1956 issue of the Lancet coined the term benign ME (Anonymous Editorial, 1956). It was called benign because the illness did not lead to death of the patient. Later, Ramsay (1988) published a definition of this disease using the term Myalgic Encephalomyelitis (ME) and the term benign was dropped due to the seriousness of the disability created by the illness (Hyde, Goldstein, & Levine, 1992).

Based on Ramsay's concept, research criteria were developed for ME (Dowsett, Goudsmit, Macintyre, & Shepherd, 1994; Dowsett, Ramsay, McCartney, & Bell, 1990; Goudsmit, Shepherd, Dancey, & Howes, 2009) in an effort to distinguish ME criteria from that of CFS. When Jason, Helgerson, Torres-Harding, Carrico, and Taylor (2003) attempted to operationalize the ME criteria by selecting individuals with postexertional malaise, memory and concentration impairment, and fluctuation of symptoms, and then compared these patients to those meeting the current U.S. definition of CFS (Fukuda et al., 1994), the ME criteria selected a more symptomatic group of patients.

Later, a clinical case definition was developed utilizing the term ME/CFS (Carruthers et al., 2003). These criteria became known as the Canadian ME/CFS clinical case definition, and, unlike the combination method of the Fukuda et al. (1994) criteria, they required specific ME/CFS symptoms to occur. For example, it specified that postexertional malaise must occur with a loss of physical or mental stamina, rapid muscle or cognitive fatigability, usually taking 24 hours or longer to recover. Jason, Torres-Harding, Jurgens, and Helgerson (2004) compared persons meeting the Canadian clinical case definition (Carruthers et al.),

the Fukuda et al. criteria and people experiencing chronic fatigue explained by psychiatric reasons. The Canadian ME/CFS criteria, in contrast to the Fukuda et al. criteria, selected cases with less psychiatric comorbidity, more physical functional impairment, more fatigue/weakness and more neuropsychiatric and neurological symptoms. Jason et al. (2006) later used the Canadian case definition model to develop a pediatric case definition for ME/CFS. Jason, Porter, et al. (2010) found that the Fukuda et al. criteria were less sensitive than the Pediatric ME/CFS criteria in identifying pediatric ME/CFS cases.

In an effort to operationalize the Canadian criteria, Jason, Evans, et al. (2010) specified explicit rules for determining ME/CFS status using a revised Canadian case definition. In this study, we applied these criteria to a data set of patients diagnosed with CFS according to the Fukuda et al. (1994) criteria. We compared those meeting the Canadian ME/CFS criteria to those not meeting these specific criteria (Non-ME/CFS) but meeting the Fukuda et al. criteria only. Next, we operationalized criteria based on ME case definitions (Dowsett et al., 1994; Goudsmit et al., 2009; Ramsay, 1988) and applied it to our CFS sample. We compared those meeting the ME case definition to those not meeting the ME criteria (Non-ME) but meeting the Fukuda et al. criteria only. We hypothesized that both the ME/CFS and the ME case definitions would identify individuals with more serious symptoms and greater functional disability than those meeting the Fukuda criteria.

Method

Participant Recruitment

Participants were recruited from a variety of sources in the Chicago metropolitan area, including physician referrals. One hundred and fourteen individuals diagnosed with CFS according to the Fukuda et al. (1994) criteria were recruited and enrolled in the study. All data in the current study are from baseline measures of a larger, longitudinal study (Jason et al., 2007). Participants received $75 for completing the baseline interviews.

At initial screening, all participants were required to be at least 18 years of age, not pregnant, able to read and speak English, and considered physically capable of attending the scheduled sessions. Persons who used wheel-chairs and those who were bedridden or housebound were excluded due to the practical difficulties of keeping therapy appointments. Referrals to local physicians who treat ME/CFS and to support groups were offered to these individuals. After a consent form was filled out, prospective participants were initially screened using a structured questionnaire. The study was approved by the DePaul University Institutional Review Board.

Measures

The CFS questionnaire—This screening scale was initially validated by Jason et al. (1997). This scale is used to collect demographic, health status, medication usage, and symptom data, and it uses the definitional symptoms of CFS (Fukuda et al., 1994). Hawk, Jason, and Torres-Harding (2007) revised this CFS Questionnaire and administered the questionnaire to three groups (CFS, Major Depressive Disorder, and healthy controls). The revised instrument, which was used in the present study, evidences good test–retest reliability and has good sensitivity and specificity.

The CFS Questionnaire was designed to assess the diagnostic criteria for CFS as specified by Fukuda et al. (1994). For each symptom, participants were asked to indicate if the symptom had been present for 6 months or longer, if the symptom began before the onset of their fatigue or health problems, and how often (0 = *never*, 1 = *seldom*, 2 = *often/usually*, 3 = *always*) the symptom is experienced. Participants were also asked to rate the severity of

each symptom they endorsed on a scale of 0–100, where 0 = *no problem* and 100 = *the worst problem possible*. This is a numerical rating scale, which has been shown to be a consistently valid measure of symptom intensity, particularly for pain intensity (Jensen & Karoly, 1992). In assessing case definition symptoms, items were designed to measure the eight core CFS symptoms (i.e., impaired memory or concentration, sore throat, tender lymph nodes, muscle pain, multi-joint pain, new headaches, unrefreshing sleep, and postexertion malaise) as specified by the Fukuda et al. case definition.

Both the frequency and the severity of symptoms provide a more complete understanding of the impact of symptoms. Therefore, we developed a new scale combining frequency and severity ratings on the CFS Questionnaire, and the symptom data presented in this study are based on these scales. Scores were obtained by multiplying the frequency score by 33.3 so that the scale ranged from 0 to 100, which was comparable to the severity rating. Then the transposed frequency rating was multiplied by the severity rating, and the product was divided by 100 to yield a total score representing frequency and severity, that ranged from 0 to 100, with higher scores indicating more impairment.

In order to explore the potential reason for increased rates of psychiatric comorbidity in the ME/CFS (Canadian) group compared to the Fukuda CFS group, we attempted to replicate findings by Kroenke (2003), who found that patients with CFS who experienced a greater number of symptoms were more likely to have a psychiatric diagnosis. Our data set contained 13 of the 15 symptom variables used in Kroenke's study including stomach pain; pain in arms, legs, or joints; menstrual cramps or other problems with your period; headaches; chest pain; dizziness; feeling your heart pound or race; shortness of breath; pain or problems during sexual intercourse; constipation, loose bowels, or diarrhea; nausea, gas, or indigestion; feeling tired or having low energy; and trouble sleeping. Back pain and fainting spells were the two Kroenke variables not included.

Psychiatric interview—A semistructured psychiatric interview, the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (Fourth edition; *DSM-IV*; SCID; Spitzer, Williams, Gibbon, & First, 1995) was administered in order to establish Axis I psychiatric diagnoses. The professionally administered SCID allows for clinical judgment in the assignment of symptoms to psychiatric or medical categories, a crucial distinction in the assessment of symptoms that overlap between CFS and psychiatric disorders, for example, fatigue, concentration difficulty, and sleep disturbance (Friedberg & Jason, 1998). A psychodiagnostic study (Taylor & Jason, 1998) validated the use of the SCID in a sample of patients with CFS. Because CFS is a diagnosis of exclusion, prospective participants were screened for identifiable psychiatric and medical conditions that may explain CFS-like symptoms.

After the initial interview was completed, the participants' information was reviewed to ensure that they met all eligibility requirements. If an individual was eligible for the study, a medical appointment was set up. Conversely, if an individual was not eligible, we discussed with him or her alternate treatment options.

Medical assessment of CFS—The physician screening evaluation included an in-depth medical and neurological history and a general and neurological physical examination. The evaluation also included a structured instrument, a modified version of the CFS Questionnaire (Komaroff et al., 1996). This instrument assesses the signs, symptoms, and medical history to rule out other disorders. Relevant medical information was gathered to exclude possible other medical causes of chronic fatigue, including exposure histories to tuberculosis, AIDS, and non-AIDS sexually transmitted diseases. Information on prescribed and illicit drug use was also assessed and recorded. Finally, the histories of all symptoms

related to CFS were gathered. To be diagnosed with the Fukuda et al. criteria, participants were required to experience persistent or relapsing fatigue for a period of 6 or more months concurrent with at least 4 of 8 specific core symptoms that did not predate the illness. Twenty-four additional individuals who were screened were excluded for a variety of reasons (i.e., lifelong fatigue, less than 4 Fukuda symptoms, body mass index [BMI] > 45, melancholic depression or bipolar depression, alcohol or substance abuse disorder, autoimmune thryroiditis, cancer, lupus, rheumatoid arthritis).

Laboratory tests included a chemistry screen (which assesses liver, renal, and thyroid functioning), complete blood count with differential and platelet count, erythrocyte sedimentation rate, arthritic profile (which includes rheumatoid factor and antinuclear antibody), hepatitis B, Lyme disease screen, HIV screen, and urinalysis. A tuberculin skin test was also performed. The project physician performed a detailed medical examination to detect evidence of diffuse adenopathy, hepatosplenomegaly, synovitis, neuropathy, myopathy, cardiac or pulmonary dysfunction. These laboratory tests in the battery were used to rule out other illnesses (Fukuda et al., 1994); in other words, they are used as exclusionary criteria rather than as inclusionary criteria.

Functional Status

Medical outcomes study 36-item short-form health survey (SF-36) or RAND questionnaire—The SF-36 is a 36 item broadly based self-report measure of functional status related to health (Ware & Sherbourne, 1992). A higher score indicates better health or less impact of health on functioning. An example of a question on this form follows: Does your health now limit you in these activities? Walking one block (Yes, limited a lot; Yes, limited a little; No, not limited at all). Test construction studies for the SF-36 (McHorney, Ware, Lu, & Sherbourne, 1994) have shown adequate internal consistency, significant discriminate validity among subscales, and substantial differences between patient and nonpatient populations in the pattern of scores. The SF-36 has also indicated sufficient psychometric properties as a measure of functional status in a CFS population (Buchwald, Pearlman, Umali, Schmaling, & Katon, 1996).

Cognitive Test

The Trailmaking Test is a subtest included in the Halstead-Reitan Battery (Reitan & Tarshes, 1959). This test contains “parts” A and B. Both are presented on an 8” × 11” page. Part A consists of 25 circles scattered about the page, each containing a number, 1 through 25. The examinee is instructed to connect the numbers, in order, as quickly as they can, without skipping any. Part B contains circles with numbers, 1 through 13, and letters, A through L. The examinee is instructed to connect the numbers and letters in order, alternating numbers and letters (1-A-2-B, etc.), as quickly as they can. Both parts are timed, and while the participant does not lose points for making errors, they are notified when they make an error, and instructed to correct their error, thus slowing progress and increasing total time. Total time required to complete each part is recorded. Higher completion times indicate more difficulties finishing the task. This test yields information concerning the cognitive domains of attention, visual scanning with speed of eye–hand coordination, and speed of information processing. Part B also considers the ability of the individual to alternate between two sets of stimuli, an executive function requiring multitasking. Reliability coefficients of the trailmaking test have been variable, ranging from .60 to .90.

Heart Rate

As part of the medical examination, participants had their heart rate taken while lying down, and then while standing up for a period of 10 min. Heart rate recordings were taken every 2 minutes. For this study a selection of these recordings were used to reduce redundancy in the

data reported. The following three recordings were used: lying down, 2 min after standing, and 10 min after standing.

CFS Case Definition (Fukuda)

A case of CFS is defined by Fukuda et al. (1994) as the presence of the following criteria: (a) 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 (b) the concurrent occurrence of four or more of the following symptoms, all of which must have persisted or recurred during 6 or more consecutive months of illness and must not have predated the fatigue (Fukuda et al., 1994, p. 956). All 114 participants met Fukuda CFS case definition.

ME/CFS Case Definition (Canadian)

The Canadian clinical case definition (Carruthers et al., 2003) specifies that postexertional malaise must occur with a loss of physical or mental stamina, rapid muscle, or cognitive fatigability, usually taking 24 hr or longer to recover. In addition, there need to be two or more neurological/cognitive manifestations (e.g., confusion, impairment of concentration, and short-term memory). There also needs to be unrefreshing sleep or poor sleep quantity or rhythm disturbance, as well as a significant degree of arthralgia and/or myalgia. Finally, there needs to be at least one symptom from two of the following categories: autonomic manifestations (e.g., neurally mediated hypotension, light headedness), neuroendocrine manifestations (e.g., recurrent feelings of feverishness and cold extremities), and immune manifestations (e.g., recurrent sore throats).

To operationalize the Canadian clinical ME/CFS case definition, we used data from the CFS Questionnaire to assess how often the person had experienced the symptom (fatigue, postexertional malaise, etc.) over the past 6 months using the following scale: 0 = *never*, 1 = *seldom*, 2 = *often or usually*, 3 = *always*. To be counted as "persisted or recurred," the individual had to have a frequency score of 2 or higher (See Jason, Evans et al., 2010). In addition, it is important that fatigue and the other core symptoms were either moderate or severe on a 100-point scale. This "severity index" has not been well defined in previous ME/CFS criteria. We now specified that existing symptoms need to be rated at a 50 (as moderate) or higher to meet criteria. Both ratings of frequency and severity, therefore, had to be satisfied in order to qualify for each individual symptom.

ME Case Definition

We created a revised case definition for ME based on past case definitions, which include the Ramsay (1988) definition, the Dowsett, Goudsmit, Macintyre, and Shepherd (1994) "London" criteria, the Hyde (2007) Nightingale definition, and the Goudsmit, Shepherd, Dancey, and Howes (2009) criteria. Specifically, we used past case definitions to create a revised criteria based on the cardinal features of ME. The revised definition stipulates that ME had an acute onset that could be categorized into three categories: ME—viral (ME was precipitated by a virus), ME—infectious nonviral (ME was precipitated by a nonviral infection such as a tick bite), and ME—other (ME was precipitated by trauma or chemical exposure). These categorizations were based upon patients self-report. Additionally, patients had been asked to categorize their onset as sudden or gradual. In addition, they were asked: "Over what period of time did your fatigue related illness develop?" The responses included the following answers: within 24 hr, over 1 week, over 1 month, over 2–6 months, and so on. To meet ME sudden onset criteria, patients needed to indicate a sudden onset and the illness developed either over 1 week or within 24 hr.

The major symptom categories of ME in the revised case definition included: postexertional malaise, neurological manifestation, and autonomic dysfunction. Postexertional malaise was described as prolonged restoration of muscle power following either mental or physical exertion with recovery often taking 2–24 hr or longer. Neurological manifestations, which included at least one of the following symptoms: short-term memory loss, loss of powers of concentration, cognitive dysfunction, increased irritability, confusion, and perceptual difficulties. Autonomic dysfunction included at least one of the following: neutrally mediated hypotension, postural orthostatic tachycardia, delayed postural hypotension, palpitations with or without cardiac arrhythmias, dizziness, feeling unsteady on ones feet, disturbed balance, cold extremities, hypersensitivity to climate change, cardiac irregularity, Raynaud's phenomenon, circulating blood volume decrease, and shortness of breath. Secondary features of ME included: pain, endocrine manifestations, immune manifestations, and sleep dysfunction. To meet full criteria of ME, patients must have had an acute onset and qualify for the three major ME symptom categories (postexertional malaise, neurological manifestations, and autonomic manifestations). To be counted as “persisted or recurred,” the individual had to indicate a frequency score of 2 or higher. In addition, symptoms had to be rated at a 50 (as moderate) or higher to meet severity criteria. Both ratings of frequency and severity, therefore, had to be satisfied in order to qualify for each individual symptom. The ME group was not made up of all individuals from the ME/CFS group, as the ME group required Autonomic symptoms, whereas the ME/ CFS group only required 2 of the 3 of the Other criteria to be met.

Results

Demographics

Table 1 presents demographic data for the ME/CFS ($n = 57$) versus Fukuda CFS who did not meet the ME/CFS criteria (Fukuda CFS[a]; $n = 56$) conditions, and for the ME ($n = 27$) versus Fukuda CFS who did not meet the ME criteria (Fukuda CFS[b]; $n = 87$) conditions. Due to missing data, one participant could not be classified using the ME/CFS criteria and was excluded from the ME/CFS versus Fukuda CFS[a] comparison. There were no significant demographic differences between these groups. However, as expected, the ME condition had significantly more reports of sudden onset and were more likely to think that the cause was definitely or mainly physical when compared to the Fukuda CFS condition. The ME/CFS condition had significantly higher current psychiatric comorbidity rates (58%) than the Fukuda CFS[a] condition, 20%; $\chi^2(1, N = 113) = 17.38$, $p < .05$.

Functional Status

Table 2 presents data from the SF-36. Using a multivariate analysis of variance (MANOVA), the ME/CFS group was significantly different than the Fukuda CFS[a] group, Wilks's $\lambda = .78$, $F(8, 100) = 3.53$, $p = .01$, and the ME group was significantly different from the Fukuda CFS[b] group, Wilks's $\lambda = .85$, $F(8, 101) = 2.20$, $p = .03$. Upon examination of the univariate tests, the ME/CFS condition had significantly worse scores than the Fukuda CFS[a] group on the following seven subscales: Physical functioning, $F(1, 107) = 13.27$, $p < .01$; Bodily pain, $F(1,107) = 15.18$, $p < .01$; General health, $F(1, 107) = 5.94$, $p = .02$; Vitality, $F(1, 107) = 4.82$, $p = .03$; Social functioning, $F(1, 107) = 7.80$, $p = .01$; Role emotional, $F(1, 107) = 5.65$, $p = .02$; and Mental health, $F(1, 107) = 4.99$, $p = .03$. A significant difference between the ME/CFS and Fukuda CFS[a] groups was not found for the role physical subscale.

The ME group had worse scores than the Fukuda CFS[b] group on the following five subscales: Physical functioning, $F(1, 108) = 10.87$, $p < .01$; Bodily pain, $F(1, 108) = 6.03$, $p = .02$; General health, $F(1, 108) = 6.07$, $p = .02$; Vitality, $F(1, 108) = 5.72$, $p = .02$; and

Social functioning, $F(1, 108) = 5.44$, $p = .02$. No significant differences were found between the ME and Fukuda CFS[b] groups for the role physical, role emotional, and mental health subscales.

Of interest was that the role emotional and mental health subscales were only significantly different for the ME/CFS versus Fukuda CFS[a] comparisons. For all other subscales, the ME criteria had directionally worse scores when compared to the ME/CFS criteria.

Symptoms

Table 3 lists the Fukuda et al. (1994) symptoms, as well as the ME/CFS Canadian and ME symptoms. The symptoms are categorized into the following groups: Fatigue, Postexertional Malaise, Pain, Neurological, Autonomic, Neuroendocrine, and Immune and use the combined frequency × severity 0–100 scale. The items in these tables specify the ME/CFS criteria (and also include the ME and CFS core symptoms). As is evident, the ME/CFS criteria had significantly worse scores on 34 items, and most items were significant at the $p < .01$ level. For those few items that were not significantly different, the ME/CFS group had directionally worse scores than the Fukuda CFS[a] group. The ME group had significantly worse scores than the Fukuda CFS[b] group on 11 items at the $p < .05$ level; however, only 5 were significant at the $p < .01$ level. Given the number of comparisons and risk of Type I error, differences found at the $p < .01$ level can be interpreted with more confidence than those at the $p < .05$ level.

Heart Rate and Cognitive Measure

Table 4 presents data on heart rate lying down and standing, and the Trailmaking A and B cognitive measure. Findings from a MANOVA revealed a significant overall effect of ME/CFS versus Fukuda CFS[a] group on the three heart rate measures, Wilks's $\lambda = .93$, $F(3, 108) = 2.81$, $p = .04$. Univariate findings indicate that the ME/CFS group had significantly higher heart rates than the Fukuda CFS[a] group when lying down, $F(1, 110) = 5.71$, $p = .02$; two minutes after standing, $F(1, 110) = 7.46$, $p < .01$; and 10 min after standing, $F(1, 110) = 7.92$, $p < .01$.

A second MANOVA revealed a significant overall effect of ME vs. Fukuda CFS[b] group on the three heart rate measures, Wilks's $\lambda = .90$, $F(3, 109) = 3.91$, $p = .01$. Univariate findings indicate that the ME group had significantly higher heart rates than the Fukuda CFS[b] group when lying down, $F(1, 111) = 10.73$, $p < .01$, 2 min after standing, $F(1, 111) = 6.99$, $p = < .01$, and 10 min after standing, $F(1, 111) = 8.55$, $p < .01$.

For the Trailmaking A and B test, a significant overall effect was found for ME/CFS versus Fukuda CFS[a] group on the two measures, Wilks's $\lambda = .94$, $F(2, 110) = 3.29$, $p = .04$. The ME/CFS group had significantly higher completion times on the Trailmaking A, $F(1, 111) = 5.56$, $p = .02$ and B $F(1, 111) = 5.08$, $p = .03$ tests. A significant overall effect was also found for ME versus Fukuda CFS[b] group on the Trailmaking test measures, Wilks's $\lambda = .93$, $F(2, 111) = 4.30$, $p = .02$. The ME group had significantly higher completion times on the Trailmaking A, $F(1, 112) = 6.21$, $p = .02$, and B, $F(1, 112) = 7.57$, $p < .01$ tests than the Fukuda CFS group[b].

Symptoms and Psychiatric Comorbidity

When we examined those individuals with five or fewer of these 13 Kroenke symptoms, 13 of the 48 (27%) individuals had a current psychiatric diagnosis, whereas among those individuals with 6 or more symptoms, 31 of the 65 (48%) had a current psychiatric diagnosis, $\chi^2(1, N = 113) = 4.93$, $p < .05$. Those who met the ME/CFS classification had 7.3 of these Kroenke symptoms, whereas those that met the Fukuda CFS[a] criteria had

significantly fewer with only 5.1 symptoms, $t(95.1) = -5.38$, $p < .01$]. In addition, if we consider all ME/CFS symptoms in Table 3, the ME/CFS group had 26.4 symptoms whereas the Fukuda CFS[a] group had significantly fewer with only 16.2 symptoms, $t(91.7) = -9.03$, $p < .01$.

For the ME versus Fukuda CFS[b] groups, there was also a significant differences with the ME group having 8.1 of the 13 Kroenke (2003) symptoms, while the Fukuda CFS[b] group had 5.6 symptoms, $t(111) = -5.14$, $p < .01$. In addition, when examining all the symptoms in Table 3, there was a significant difference, with the ME group having 25.6 symptoms versus 19.8 for the Fukuda CFS[b] group, $t(104) = -3.56$, $p < .01$.

Discussion

There has been considerable debate about what case definition to use with the illness commonly known as CFS. The present study suggests that the initial definitions of ME (Dowsett et al., 1994; Goudsmit et al., 2009; Ramsay, 1988) and later on the Canadian criteria of ME/CFS (Carruthers et al., 2003) appear to select a group of patients that have more severe functional impairments, and physical and cognitive symptoms. The ME/CFS criteria appear to identify more impairments in symptoms, whereas the ME criteria appear to identify more impairment in functional status, except for emotional and mental health domains.

Table 2 indicates that both the ME/CFS and the ME groups had more impairment than the comparison Fukuda CFS groups. In addition, the most impairment on physical issues involved the ME group. We did not directly contrast the ME/CFS and ME groups, but in general, impairment was significant for both groups. In addition, the ME group appears to have less mental health issues than the ME/CFS group. It does appear that requiring specific criteria, such as what occurs in the ME and ME/CFS case definitions, does select individuals with more functional disabilities.

In the original Canadian ME/CFS criteria (Carruthers et al., 2003), symptoms could be rated as mild, moderate or severe, but it was unclear whether symptoms needed to meet specific frequency and severity levels to be counted. In other words, it was possible to count just whether symptoms occurred in order to meet the ME/CFS criteria. Had just occurrence of symptoms been employed (rather than needing to meet cutoff scores for frequency and severity of symptoms) for the core ME/CFS Canadian criteria symptoms in Table 3, 105 of the individuals in the current sample (over 90%) would have met ME/CFS criteria. However, when using the symptom frequency and severity cutoff points as specified by Jason et al. (2010), only 50% met the ME/CFS criteria. It is clear that these individuals with ME/CFS had more severe functional disability and symptoms than the Fukuda CFS[a] group.

Jason et al. (2004) previously compared a sample that met the Canadian criteria for ME/CFS to two other groups, those that only met the Fukuda et al. (1994) criteria and those that had psychiatric reasons for their chronic fatigue. There were many statistically significant symptom differences between the ME/CFS group and the group that had psychiatric reasons for their fatigue. In contrast, there were a small number of significant symptom differences between the ME/CFS and CFS groups. This prior study utilized a community-based sample of participants, rather than a tertiary care sample as utilized in the present study, and in general, tertiary care samples have more severe symptoms (Jason, Plioplys, Torres-Harding, & Corradi, 2003). In addition, the Jason, Evans, et al. (2010) study used occurrence data rather than the cutoff points specified in Jason et al. (2010) Jason, Porter, et al. (2010) to select the ME/CFS group. Therefore, the present study involved a group of tertiary patients

with more severe and frequent symptoms than the Jason et al. (2004) study of a community-based sample.

In the present study, we found significantly higher current psychiatric comorbidity rates for those with ME/CFS versus Fukuda CFS[a] (58% vs. 20%). In the prior study, using just symptom occurrence to classify patients, Jason et al. (2004) found that the ME/CFS group had significantly lower current psychiatric rates (48%) than the Fukuda et al. (1994) CFS group (75%). It is probable that the current study selected a more seriously impaired group of patients with ME/CFS and that their impairments were across a broad array of both physical and mental health areas. Katon and Russo (1992) have argued that a requirement of more symptoms to meet criteria could inadvertently select for individuals with psychiatric problems. Similarly, Kroenke (2003) found similar results examining 15 variables within a fatigued sample. Upon examination of 13 of these 15 variables in our sample, we found that a greater number of symptoms was associated with increased psychiatric comorbidity as well as an ME/CFS diagnosis. It is certainly possible that the larger number of symptoms of higher frequency and severity among patients meeting the ME/CFS criteria versus Fukuda CFS[a], accounts for the higher levels of psychiatric comorbidity and more functional impairments on the Role Emotional and Mental Health SF-36 subscales among the ME/CFS criteria group.

In contrast, the ME criteria required four versus the seven ME/CFS symptoms to meet its case definition. Of interest, there were no significant psychiatric rate differences for the ME versus Fukuda CFS[b] groups (44% vs. 37%). There were also no significant differences between the ME and Fukuda CFS[b] groups on the SF-36 scales measuring Role Emotional and Mental Health areas. In a prior study, our group had contrasted the ME criteria, the Fukuda et al. (1994) criteria, and chronic fatigue due to psychiatric reasons (Jason et al., 2003), and also found no significant differences between the ME group (53%) and the CFS group (56%). Yet that prior study also dealt with occurrence of symptoms rather than the required frequency and severity criteria within the present study. When we examined the 13 Kroenke (2003) symptoms and other symptoms, we found that the ME group had significantly more symptoms than the Fukuda CFS[b] group. These findings would suggest that the number of symptoms probably accounts for some of the differences between the ME and Fukuda CFS[b] groups on Table 3, and yet there were far fewer significant differences at the .01 level than the ME/CFS versus the Fukuda CFS[a] groups. But the lack of differences on the psychiatric items suggests that the ME criteria selects individuals with less psychiatric comorbidity and mental health issues than the ME/CFS group. It is possible that sudden onset, postexertional malaise, a neurocognitive and autonomic symptom identify individuals with fewer emotional and mental health problems, but when additional symptoms are required, this selects both more physical and mental problems.

It should also be noted that in previous studies that have found more disability/symptoms causing psychiatric problems, there were confounds, with symptoms counting for psychiatric diagnoses. In addition, there might be a number of reasons for a higher rate of psychiatric disorders associated with more symptoms and/or disability. For example, it could be more “depressing” to have more symptoms and/or disability interfering with what one can do. Perhaps similarly, one might be more anxious about how one might be able to cope in the future. Across medical conditions, illnesses/diseases that are more disabling and/or have more symptoms associated with them/interfere with life more are associated with higher rates of psychiatric problems.

Some have argued that an ME case definition should focus on those with a sudden, viral onset, rather than just a sudden onset. Among the group of 36 individuals with a sudden onset, we found 13 with a viral onset, 5 with an infectious onset, and 18 with other types of

onsets (only 27 of these individuals met all the ME criteria). Of interest, when we examined whether there was a current psychiatric disorder among those with a viral onset, only 3 of the 13 (23%) had a disorder (which was considerably below 39%, which was the overall mean for the entire sample), suggesting that this viral onset group might be different from the other onset type groups, and surely more research is needed to explore this possibility with larger sample sizes.

With an acute onset, people notice at the time, and might be more likely to get instrumental support and also be able to pace one's activity by listening to one's body. In contrast, for those who are not sure what precipitated their illness, it may take longer to get diagnosed and instrumental support may not be available for a long period of time. Such individuals might be more inclined to not pace themselves, and this could cause more flare ups which could cause both depression and anxiety.

For the symptoms on Table 3, it is clear that the ME/CFS group had more significant differences with the comparison groups than the ME group. For 27 items, the ME/CFS group had worse scores than the ME group, and for 12 items, the ME group had directionally worse scores than the ME/CFS group. Of interest, the ME group had worse scores than the ME/CFS group on all four Autonomic manifestation items and 4 of the 6 of the Pain items.

Table 4 indicates that patients with ME/CFS and ME do have higher pulse rates at resting and standing than those that do not meet these criteria. Such findings might indicate that these patients have a greater likelihood of having Orthostatic Intolerance. This is also supported by the self-report symptoms from the Autonomic category within Table 3. Of interest, the ME group had directionally more impairment than the ME/CFS group for the autonomic measures in Table 3. In addition, on the Trailmaking test, which assesses for cognitive domains of attention, visual scanning with speed of eye–hand coordination, and information processing, the ME/CFS and ME groups had significantly poorer performance than the Fukuda CFS[a] and Fukuda CFS[b] groups, with the ME group having the worst scores.

Had there been a larger data set, with more individuals in both the ME and the ME/CFS groups, it might have been possible to directly compare these two groups. However, the sample sizes would have been too small to compare those with pure ME, those with pure ME/CFS, and those not meeting ME or ME/CFS criteria. Another limitation in this study is that a questionnaire developed to assess ME/CFS and ME symptoms had not yet been developed when these data were collected, and therefore for several of the items, we had to make approximations to estimate severity or frequency data. Clearly, there is a need to replicate these results with questionnaires specifically designed to assess these symptoms (Jason, Evans, et al., 2010), and this work is currently ongoing. Additionally, other researchers may apply the various case definitions used in this article differently, and to heterogeneous patient populations. Therefore, these findings may be difficult to replicate. In addition, definitions will perform differently depending on the population studied and how participants were screened prior to enrolment. Our study design used the 1994 criteria as basis for enrolment, so applying other definitions to the population that require additional symptoms would of course mean that those patients meeting the more restrictive criteria would be more symptomatic. Finally, as this article was being finalized for publication, a new International ME case definition was published (Carruthers et al, 2011), and this case definition now requires eight symptoms, which is one more than what had been required in the ME/CFS Canadian criteria (Carruthers et al., 2003). It is unclear how this new case definition compares to the ME criteria described in the current study or to the older Fukuda et al. (1994) criteria.

The current CFS case definition of Fukuda et al. (1994) has been used internationally by researchers for over 15 years. It is possible that some patients meeting these criteria do not have core symptoms such as postexertional malaise or memory/concentration problems. By specifying seven symptoms as with the ME/CFS criteria or by specifying four symptoms with the ME criteria, it may be possible to identify a more homogenous and impaired group of patients. The current study suggests that the ME and ME/CFS criteria might be used to identify patients with possibly more homogenous and severe symptomatology and functional impairment. Some might conclude that the ME/CFS definition requires too many symptoms that may at the upper ends select for psychiatric disorder. Others might feel that we should just expect higher levels of a variety of both medical and psychiatric disorders if this definition is utilized. Still others might feel that the severity dimension be relaxed as in the previous ME/CFS study (Jason, Torres-Harding, Jurgens, & Helgerson, 2004) that did not require such a high level of symptom severity.

The present study suggests that the initial definitions of ME (Dowsett et al., 1994; Goudsmit et al., 2009; Ramsay, 1988) and later on the Canadian criteria of ME/CFS (Carruthers et al., 2003) appear to select a group of patients that have more severe functional impairments, and physical and cognitive symptoms. The ME/CFS criteria appear to identify more impairments in symptoms, whereas the ME criteria appear to identify more impairment in functional status, except for emotional and mental health domains.

It would be premature to make any definitive conclusion at this time concerning which explanation is more valid. Certainly, there is a need for more research on this topic, with larger data sets. We are currently collecting more data on this issue, and we hope in the future to be able to offer more definitive interpretations of the findings reported in the current study.

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Table 1

Demographics, Psychiatric Characteristics, and Onset Issues

	ME/CFS[1]	Fukuda CFS[a2]	Sig.	ME[3]	Fukuda CFS[b4]	Sig.
	N (%)	*N* (%)		*N* (%)	*N* (%)	
Gender						
Male	9 (16)	10 (18)	0.77	4 (15)	15 (17)	0.77
Female	48 (84)	46 (82)		23 (85)	72 (83)	
Ethnicity						
Caucasian	50 (89)	48 (86)	0.7	24 (88)	75 (87)	0.99
African American	3 (5)	2 (4)		1 (4)	4 (5)	
Latino	2 (4)	3 (5)		1 (4)	4 (5)	
Asian American	1 (2)	3 (5)		1 (4)	3 (3)	
Marital status						
Married/living together	24 (43)	32 (57)	0.3	11 (41)	45 (52)	0.33
Single	20 (36)	16 (29)		12 (44)	25 (29)	
Divorced/separated	12 (21)	8 (14)		4 (15)	16 (19)	
Work status						
Disability	18 (32)	9 (16)	0.06	5 (19)	23 (26)	0.07
Unemployed	l6 (28)	11 (20)		5 (19)	22 (25)	
Working part-time	9 (16)	14 (25)		5 (19)	18 (21)	
Working full-time	6 (11)	16 (29)		5 (19)	17 (20)	
Retired	3 (5)	4 (7)		4 (14)	3 (4)	
Part-time student	4 (7)	1 (2)		2 (7)	3 (4)	
Full-time student	0 (0)	1 (2)		0 (0)	1 (1)	
Working part-time on disability	1 (2)	0 (0)		1 (3)	0 (0)	
Educational level						
Standard college degree	25 (44)	29 (52)	0.47	14 (52)	40 (46)	0.58
Graduate/professional degree	11 (19)	14 (25)		5 (18)	20 (23)	
Partial college	15 (26)	9 (16)		4 (15)	20 (23)	
High school degree or less	6 (11)	4 (7)		4 (15)	7 (8)	
Current psychiatric diagnosis						

	ME/CFS[1]	Fukuda CFS[a][2]	Sig.	ME[3]	Fukuda CFS[b][4]	Sig.
	N (%)	*N* (%)		*N* (%)	*N* (%)	
Yes	33 (58)	11 (20)	.00	12 (44)	32 (37)	0.48
No	24 (42)	45 (80)		15 (56)	55 (63)	
Mode of illness onset						
Sudden (less than 1 month)	22 (41)	3 (24)	0.06	27 (100)	9 (11)	.00
Gradual	32 (59)	42 (76)		0 (0)	74 (89)	
Virus caused illness						
Agree	15 (28)	7 (33)	0.77	2 (44)	21 (26)	0.19
Neutral	24 (45)	20 (39)		8 (30)	36 (46)	
Disagree	14 (26)	15 (29)		7 (26)	22 (28)	
Cause of fatigue						
Definitely/mainly physical	36 (64)	35 (65)	0.95	22 (81)	50 (60)	0.04
Other	20 (36)	9 (35)		5 (19)	34 (40)	
	M (*SD*)	*M* (*SD*)	Sig.	*M* (*SD*)	*M* (*SD*)	Sig.
Age	43.6 (11.9)	43.9 (11.5)	0.9	44.4 (11.7)	43.6 (11.6)	0.75

[1] *N* = 53–57.

[2] *N* = 52–56.

[3] *N* = 27.

[4] *N* = 79–87.

Table 2

SF-36 Subscales

	ME/CFS[1] *M* (*SD*)	Fukuda CFS[a][2] *M* (*SD*)	Sig.	ME[3] *M* (*SD*)	Fukuda CFS[b][4] *M* (*SD*)	Sig.
SF-36 subscales						
Physical functioning	38.0 (21.9)	53.8 (23.4)	.00	32.9 (19.5)	49.8 (23.8)	.00
Role physical	2.3 (8.8)	6.4 (14.6)	0.08	1.9 (6.8)	5.1 (13.3)	0.25
Bodily pain	32.2 (20.0)	48.0 (22.1)	.00	30.8 (18.8)	42.8 (22.8)	0.02
General health	28.5 (16.0)	36.5 (18.3)	0.02	24.9 (13.7)	34.5 (18.3)	0.02
Vitality	14.8 (12.0)	20.9 (16.6)	0.03	11.9 (10.1)	19.6 (15.4)	0.02
Social functioning	34.0 (22.7)	46.6 (24.2)	0.01	30.8 (22.1)	43.2 (24.1)	0.02
Role emotional	42.6 (42.2)	61.8 (42.3)	0.02	56.4 (45.0)	51.2 (42.5)	0.59
Mental health	59.6 (18.0)	67.1 (16.6)	0.03	60.8 (19.4)	64.3 (17.0)	0.38

[1] $N = 54$.

[2] $N = 55$.

[3] $N = 26$.

[4] $N = 84$.

Table 3

Symptoms

	ME/CFS[1] *M* (*SD*)	FukudaCFS[a][2] M (SD)	Sig.	ME[3] M (SD)	Fukuda CFS[b][4] M (SD)	Sig.
Fatigue	72.5 (19.3)	61.2 (19.3)	.00	70.5 (20.0)	65.8 (20.0)	0.3
Postexertional malaise	67.6 (21.9)	53.3 (26.4)	.00	67.6 (22.9)	58.2 (25.6)	0.08
Sleep						
Unrefreshing sleep	78.4 (23.3)	63.8 (27.8)	.00	72.0 (28.3)	70.8 (26.1)	0.84
Need to nap during each day	50.3 (33.6)	38.3 (30.2)	0.05	44.9 (37.8)	43.5 (30.7)	0.86
Difficulty falling asleep	47.7 (38.0)	29.4 (35.0)	0.01	35.1 (34.7)	39.1 (38.6)	0.61
Difficulty staying asleep	51.3 (35.0)	40.0 (35.7)	0.1	53.0 (33.8)	43.1 (36.1)	0.2
Waking up early in the morning	43.3 (36.7)	32.8 (35.4)	0.13	42.3 (38.6)	36.4 (35.6)	0.49
Pain						
Muscle pain	58.3 (30.3)	40.6 (28.0)	.00	54.0 (28.4)	48.0 (31.0)	0.36
Pain in multiple joints	50.7 (30.0)	22.9 (28.1)	.00	40.5 (30.7)	35.6 (32.6)	0.48
Headaches	41.3 (27.6)	29.6 (25.9)	0.02	44.8 (27.5)	32.5 (26.7)	0.05
Chest pain	14.2 (19.1)	4.1 (10.3)	.00	15.6 (19.4)	6.9 (14.3)	0.04
Abdomen pain	25.9 (28.0)	10.9 (19.5)	.00	35.3 (32.7)	12.7 (19.4)	.00
Eye pain	20.4 (28.4)	5.8 (13.8)	.00	28.5 (34.3)	7.5 (14.9)	.00
Neurological						
Impaired memory and concentration	57.8 (24.5)	42.9 (25.7)	.00	53.6 (26.4)	49.4 (26.1)	0.48
Abnormal sensitivity to light	42.8 (36.5)	15.3 (24.6)	.00	35.8 (37.4)	26.3 (32.4)	0.25
Slowness of thought	47.2 (29.3)	29.2 (26.4)	.00	42.9 (31.5)	36.2 (28.5)	0.34
Confusion/disorientation	30.4 (28.4)	13.9 (20.4)	.00	26.3 (29.1)	20.7 (24.9)	0.37
Difficulty finding the right word	45.4 (27.3)	25.5 (21.1)	.00	44.6 (28.6)	32.1 (25.1)	0.05
Difficulty comprehending information	32.8 (27.1)	13.1 (18.2)	.00	26.2 (28.4)	21.7 (23.9)	0.47
Need to have to focus on one thing at a time	48.7 (33.3)	23.9 (27.4)	.00	50.1 (35.6)	31.2 (30.6)	0.02
Frequently lose train of thought	43.6 (27.8)	21.2 (26.2)	.00	36.9 (30.0)	30.4 (28.9)	0.33
Trouble expressing thoughts	36.2 (25.9)	17.3 (20.5)	.00	34.4 (29.2)	24.1 (23.3)	0.11
Difficulty retaining information	46.8 (29.3)	22.9 (22.5)	.00	43.2 (33.2)	32.0 (26.8)	0.13
Poor hand to eye coordination	24.0 (27.5)	3.6 (11.4)	.00	22.8 (29.4)	11.1 (20.6)	0.06
Autonomic						

	ME/CFS[1] *M* (*SD*)	FukudaCFS[a][2] M (SD)	Sig.	ME[3] M (SD)	Fukuda CFS[b][4] M (SD)	Sig.
Racing Heart	16.3 (22.0)	6.5 (14.2)	0.01	20.8 (25.8)	8.2 (15.2)	0.02
Shortness of breath	27.1 (22.2)	11.8 (20.0)	.00	30.9 (23.4)	15.4 (20.8)	.00
Dizziness	31.0 (27.3)	14.4 (17.9)	.00	36.1 (28.6)	18.2 (21.3)	0.01
Feel unsteady on feet	32.1 (27.8)	13.3 (17.5)	.00	35.5 (27.9)	18.2 (22.5)	0.01
Neuroendocrine						
Sensitivity to alcohol	19.7 (34.1)	13.0 (24.9)	0.25	18.9 (33.3)	15.4 (28.3)	0.62
Night sweats	21.9 (26.8)	7.8 (15.8)	.00	18.4 (25.6)	13.7 (22.2)	0.39
Chills or shivery	32.0 (26.8)	12.9 (20.1)	.00	30.2 (29.9)	20.1 (23.6)	0.12
Hot or cold spells	34.0 (27.6)	9.6 (18.4)	.00	31.9 (31.3)	18.6 (23.9)	0.05
Feeling like you have a temperature	25.5 (28.4)	10.1 (17.2)	.00	25.4 (33.6)	15.2 (20.4)	0.15
Temperature lower than normal	26.1 (30.4)	7.3 (15.6)	.00	22.5 (27.5)	14.7 (25.0)	0.22
Immune						
Sore throat	18.4 (18.0)	10.1 (16.7)	0.01	18.5 (17.5)	13.6 (18.5)	0.21
Tender/sore lymph	27.0 (26.3)	6.1 (9.5)	.00	25.1 (22.3)	13.4 (21.4)	0.02
Fever and chills	31.5 (26.9)	12.8 (21.4)	.00	22.6 (25.7)	21.8 (26.1)	0.89
Chemical sensitivity	28.5 (34.4)	18.6 (28.3)	0.11	29.8 (37.1)	20.9 (29.3)	0.27
New sensitivities to food/drug	33.5 (40.7)	17.8 (30.0)	0.03	27.7 (39.6)	24.3 (35.2)	0.71

[1] *N* = 50–57.

[2] *N* = 51–56.

[3] *N* = 25–27.

[4] *N* = 78–87.

Table 4

Heart Rate (HR) and Cognitive Measures

	ME/CFS[1] *M* (*SD*)	Fukuda CFS[a][2] *M* (*SD*)	Sig.	ME[3] *M* (*SD*)	Fukuda CFS[b][4] *M* (*SD*)	Sig.
HR lying down	80.7 (14.8)	74.5 (11.1)	0.02	84.4 (16.4)	75.4 (11.4)	.00
HR standing minute two	94.2 (17.1)	85.7 (14.6)	.00	96.9 (18.9)	87.7 (14.9)	.00
HR standing minute ten	94.6 (14.5)	86.2 (13.6)	.00	97.8 (14.4)	88.1 (13.9)	.00
Trailmaking A-time	32.9 (13.6)	26.8 (9.9)	0.02	35.3 (15.8)	28.2 (10.3)	0.02
Trailmaking B-time	56.1 (25.1)	46.8 (14.9)	0.03	61.2 (28.3)	48.5 (17.3)	.00

[1] *N* = 55–57.

[2] *N* = 53–55.

[3] *N* = 27.

[4] *N* = 82–86.