Published in final edited form as:

Fatigue. 2016 ; 4(1): 1–23. doi:10.1080/21641846.2015.1124520.

Case definitions integrating empiric and consensus perspectives

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Abstract

Background—There has been considerable controversy regarding how to name and define the illnesses known as myalgic encephalomyelitis (ME) and chronic fatigue syndrome (CFS). The IOM report has proposed a new clinical criteria and name for this illness, but aspects of these recommendations have been scrutinized by patients and scientists.

Purpose—It is possible that both empiric and consensus approaches could be used to help settle some of these diagnostic challenges. Using patient samples collected in the United States, Great Britain, and Norway (N=556), the current study attempted to categorize patients using more general as well as more restricted case definitions.

Results—Overall, the outcomes suggest that there might be four groupings of patients, with the broadest category involving those with chronic fatigue (N=62), defined by 6 or more months of fatigue which cannot be explained by medical or psychiatric conditions. A second category involves those patients that have chronic fatigue that can be explained by a medical or psychiatric condition (N=47). A third category involves more specific criteria that have been posited both by

the IOM report, a Canadian Clinical Case criteria, a ME-ICC criteria and a more empiric approach. These efforts have specified domains of substantial reductions of activity, post-exertional malaise, neurocognitive impairment, and sleep dysfunction (N=346). Patients with these characteristics were more functionally impaired than those meeting just chronic fatigue criteria, $p < .05$. Finally, those meeting even more restrictive ME criteria proposed by Ramsay, identified a smaller and even more impaired group, $p < .05$.

Discussion—The advantages of using such empirical and consensus approaches to develop reliable classification and diagnostic efforts are discussed.

Keywords

myalgic encephalomyelitis; chronic fatigue syndrome; case definition

Chronic fatigue syndrome (CFS) has been defined by 20 case definitions, and the large number of case definitions provide both researchers and clinicians challenges in both diagnosing and treating patients. [1] The Fukuda et al. [2] case definition of CFS has been the most frequently used, and epidemiologic studies can provide clues for approaches to categorize patients. According to one community-based epidemiologic study by Jason et al. [3], about 4% of the population experience 6 or more months of fatigue. Within this group, 19% meet Fukuda et al. criteria, 27% do not meet these Fukuda et al. criteria, and 54% of this group have a medical or psychiatric (melancholic depression, bipolar disorders, anorexia nervosa or bulimia nervosa, psychotic disorders, drug or alcohol related disorders) exclusionary illness.

Unfortunately, the Fukuda et al. [2] criteria have been assessed with different instruments and operationalized differently. As a result, the rates of CFS prevalence in community-based samples have ranged widely, from .004 to .0087%, .24%, and .42% to 2.54% of the population. [3–6] For example, Reeves et al. [7] attempted to operationalize the Fukuda et al. [2] criteria, but this effort resulted in broadening of the case definition. [8] In addition, the polythetic criteria of Fukuda et al. [2] have been criticized as not requiring fundamental symptoms including post-exertional malaise. [9] As a reaction to these criticisms, the Clinical Canadian ME/CFS criteria [10] developed by a group of researchers and clinicians, which required seven symptoms including post-exertional malaise and neurocognitive impairment. Later, the Myalgic Encephalomyelitis International Consensus criteria (ME-ICC) [11] were developed and they required eight symptoms.

The history of this illness began with an outbreak of epidemic neuromyasthenia in L.A. County [12–13] In a 1956 editorial in the *Lancet*, the term “benign myalgic encephalomyelitis” was coined. [14] Later, Ramsay [15] published a definition of this illness using the term “myalgic encephalomyelitis” (ME) and the term “benign” was dropped due to the seriousness of the disability. [16] There were later efforts to operationalize Ramsay’s [15] ME case definition with what are now known as the London criteria. [17–19]

In one community-based study, these London ME criteria were found to select a smaller and more symptomatic group of patients than the CFS Fukuda et al [2] criteria. [20] In an effort to better operationalize these ME criteria based on the work of a number of theorists and

practitioners, Jason, Damrongvachiraphan, et al. [21] used more precise frequency and severity criteria of symptoms for post-exertional malaise, neurological manifestation, and autonomic dysfunction. Patients also needed to have an acute onset to meet this ME criteria. When Jason, Brown et al. [22] applied these revised ME criteria to a data set of patients in a tertiary sample diagnosed with CFS using the Fukuda et al. [2] criteria, only 24% met these ME criteria, and they were more functionally impaired than those that just met the Fukuda et al. criteria. Later, Jason, Evans, Brown, Sunnquist, and Newton [23] found that 29.6% of a CFS sample in the US, and 17.7% of a CFS sample in England met these ME criteria. The more restrictive ME criteria appear to select a smaller group of patients than the Fukuda et al. [2] criteria, and those selected with ME are more impaired.

The Canadian Clinical ME/CFS Criteria [10] in contrast to the Fukuda et al. [2] criteria has been found to select cases with less psychiatric comorbidity, more physical functioning impairment, more fatigue or weakness, and more neuropsychiatric and neurological symptoms [24], and comparable findings emerged in another study by Jason, Brown, et al. [25]. When Jason, Brown, Evans, Sunnquist, and Newton [26] utilized three different samples of patients, each collected through a different case ascertainment method, 87 to 96% of the samples met the Fukuda et al. [2] case definition criteria, whereas only 73 to 77% met the Canadian ME/CFS criteria. Unfortunately, a study by Johnston, Brenu, Staines, and Marshall-Gradisnik's [27] found that only one study reported prevalence rates according to these Canadian Consensus criteria.

The more recently developed ME-ICC criteria [11] also identified a group of patients with more functional impairments and physical, mental, and cognitive problems than the larger group of patients who met the Fukuda et al. criteria. [28] In a larger study with samples from the US and Great Britain, Jason, Sunnquist, Brown, Evans, and Newton [29] found from 57 to 58% met the ME-ICC case definition, whereas the Fukuda et al. criteria identified a larger group of patients. Johnston, Brenu, Hardcastle, Huth, Staines, and Marshall-Gradisnik [30] also found that patients fulfilling the ME-ICC criteria reported significantly lower scores for physical functioning, role physical, bodily pain, social functioning as well as greater disability than those who met the Fukuda et al. [2] criteria.

These different definitions and criteria provide substantial problems for investigators, because if case definitions have different symptoms, which are measured in different ways, then criterion variance is introduced. If diagnostic categories are unreliable, then this will have problematic consequences for estimating prevalence rates or finding biological markers. Empirical approaches might help specify which symptoms and domains have both the needed sensitivity and specificity for the case definitions. More empirical methods have been used to identify symptoms that differentiate CFS samples from controls. [31–32] For example, Jason, Kot, et al. [33] used data mining techniques to separate patients with CFS from controls. Outcomes from these analyses suggest that individuals identified using fewer, but empirically selected, symptoms (i.e., fatigue or extreme tiredness, physically drained/sick after mild activity, difficulty finding the right word to say or expressing thoughts, and unrefreshing sleep) could accurately identify patients and controls. Hawk, Jason and Torres-Harding [34] also found these domains were able to successfully differentiate patients with CFS from Major Depressive Disorder. Although a moderate percentage of the CFS group

reports other important symptoms within pain, autonomic, immune, and neuroendocrine domains, they are less prominent.

Using factor analytic approaches, Brown and Jason [35] found a three-factor solution: Neuroendocrine, Autonomic, and Immune Dysfunction; Neurological/Cognitive Dysfunction; and Post-Exertional Malaise. In a more recent study with a large data set of 788 patients, Jason, Sunnquist et al. [36] found a 4-factor solution. Three of these factors, cognitive dysfunction, post-exertional malaise, and sleep, fit well with previous literature indicating that these are cardinal symptom clusters. A combined factor involving neuroendocrine, autonomic and immune dysfunction symptoms suggests that neuroendocrine, autonomic, and immune areas that occur at lower rates than the more core domains might be better thought of as subtypes of the illness. These investigators next used an exploratory factor analysis to examine solely the items within this heterogeneous factor. The results indicate that circulatory/neuroendocrine impairment, orthostatic intolerance, and gastro-intestinal distress could be thought of as subtypes.

A new name for CFS and a new clinical criteria has recently been proposed by the Institute of Medicine [37] in the US. The new name is Systemic Exertion Intolerance Disease (SEID), and the new clinical criteria requires the following four symptoms: substantial reduction or impairment in the ability to engage in pre-illness levels of occupational, educational, social, or personal activities; post-exertional malaise; unrefreshing sleep; and at least one of the two following symptoms: cognitive impairment or orthostatic intolerance. SEID is clinical criteria and was designed for clinicians who may require less rigor in their diagnostic assessment of patients with CFS. Jason, Sunnquist, and Brown et al. [38] analyzed archival samples from tertiary care settings which included seven hundred and ninety-six patients from the USA, Great Britain, and Norway. If investigators begin to compare and contrast the SEID criteria with other existing criteria, it would be of some importance for the scientific community to be informed of the consequences. For example, our findings indicated that the SEID criteria identified 88% of participants in the samples analyzed, which was comparable to the 92% that met the Fukuda criteria. However, the samples selected had already been screened for exclusionary illnesses. Because the SEID criteria have few exclusionary conditions, when other data sets were examined that had other illness groups, a study by Jason, Sunnquist et al. [39] found that the SEID prevalence rate would be 2.8 times as great as the rate found when the Fukuda et al. [2] criteria were applied. In addition, the erroneous inclusion of individuals with primary psychiatric conditions in SEID samples would have detrimental consequences for the interpretation of epidemiologic, etiologic, and treatment efficacy findings for people with this illness. For example, 47% of a sample of individuals with melancholic depression met SEID criteria. It should be noted that these studies were not prospective, and the SEID criteria were not directly assessed in these patients; instead, symptoms meant to represent the criteria were examined in a cohort that was diagnosed using different diagnostic criteria.

In the large sample described by Jason, Sunnquist et al. [39], the four-item empiric criteria [40] identified only 61% of patients whereas ME criteria identified even fewer at 20%. It appears that the Fukuda et al. [2] criteria includes more patients, with fewer being identified

with the Canadian ME/CFS[10], ME-ICC criteria [11], or empiric criteria [40], with still fewer meeting the London ME criteria described by Jason, Damrongvachiraphan, et al. [21].

The present study classified patients into four groupings of patients. The exclusionary condition is composed of patients that have chronic fatigue which can be explained by a medical or psychiatric factor. At the Chronic Fatigue Syndrome Advisory Committee (CFSAC) in August of 2015, a recommendation was voted on and approved regarding treating exclusionary illnesses as has occurred with other case definitions, which is a departure from the IOM report. [2, 10, 37] A second grouping is chronic fatigue, which involves 6 or more months of fatigue which cannot be explained by a medical or psychiatric factor. A third category involves more specific criteria that have been posited both by the IOM report, a Canadian Clinical Case criteria, a ME-ICC criteria and a more empiric approach [10–11, 40] specifying domains of post-exertional malaise, neurocognitive impairment, and sleep dysfunction, as well as substantial reductions in activity; we hypothesized that this group was more functionally impaired than those meeting just chronic fatigue criteria. Finally, those meeting more restrictive ME criteria proposed by Ramsay [15] and the London criteria [17] were hypothesized to identify a smaller more impaired group.

Method

Research Participants

DePaul Sample—An international convenience sample of adults self-identifying as having CFS, ME/CFS, or ME was recruited. To be eligible, an individual needed to be at least 18, capable of reading and writing English, and have a self-reported, current diagnosis of ME, CFS, or ME/CFS. Following approval from DePaul University's Institutional Review Board, participants were recruited from a variety of sources: postings on internet forums, support group visits, re-contacting individuals who had participated in the DePaul research team's studies in the past, and contacting individuals who had emailed the team in the past with interest in future studies.

Participants were given three options for completing study measures: an electronic survey, a hard-copy survey, or a verbal survey over the telephone. All participants were given the opportunity to complete these surveys at home or in person at DePaul University. Participants were not given a timeline for survey completion, as this illness can be unpredictable and result in a rapid decline of functioning on any given day. The first one hundred individuals who completed the survey received a \$5.00 gift card to Amazon.com for their participation. Of the 217 individuals who participated, 216 were included in the present study; one participant was excluded due to incomplete data.

Demographically, the sample was 84.2% female and 15.8% male. This sample was predominantly (97.7%) Caucasian, while 0.5% identified as Asian, and the remaining 1.9% selected 'Other' as their race. Only 13.5% of the sample was working full- or part-time, and 56.7% of the sample was on disability. With regard to educational level, 40.5% of the sample held a graduate or professional degree; 34.4% held a standard college degree; 18.1% had attended college for at least one year; and 7.0% completed high school or had a GED. The mean age of the sample was 52.0 ($SD = 11.3$).

Newcastle Sample—Participants in the Newcastle sample had been referred for a medical assessment at the Newcastle-upon-Tyne Royal Victoria Infirmary clinic due to a suspected diagnosis of CFS. An experienced physician performed a comprehensive medical history and examination, and individuals who met eligibility criteria completed a written informed consent process. A total of one hundred participants completed study measures by hard copy, but three were excluded due to incomplete data.

The Newcastle sample was 99.0% Caucasian and 1.0% multiracial, and 82.5% of participants were female. Of this sample, 37.5% of participants were working either part- or full-time, and 30.2% were on disability. With regard to education level, 20.9% had a graduate or professional degree; 29.7% had a college degree; 24.2% had completed at least one year of college; 14.3% had a high school degree; and 11.0% had not completed high school. The average age of the sample was 45.6 ($SD = 14.0$).

Norway Sample 1—Individuals with CFS were invited to participate in a randomized controlled trial of a CFS self-management program. Participants were recruited from four mid-sized towns in southern Norway, two suburbs of Oslo, and some surrounding communities. Recruitment sources included: healthcare professionals, the waiting list for a patient education program, and CFS patient organizations. Information about the study was disseminated through brochures and personal communication. In addition, study announcements for participants were placed on the Oslo University Hospital website.

Participants were required to be older than 18 years of age and diagnosed with CFS by a physician or medical specialist. In addition, participants could not be pregnant and needed to be physically able to attend the self-management program. Those who were interested in participation were given additional information by telephone. Participants completed a consent form that provided permission to request confirmation of their CFS diagnosis from their physician or medical specialist. The study gained approval from the Regional Committee for Medical Research Ethics (Health Region North) and the Privacy Ombudsman for Research at Oslo University Hospital. Of the 176 participants, 175 were included in this study; one participant was excluded due to missing data.

This sample was 86.8% female and 13.2% male. Almost all participants were Caucasian (99.4%); one participant selected 'Other' when asked about race. Only 9.7% of participants were working, while 84.0% were on disability. Regarding education, 9.9% of participants had a graduate or professional degree, 40.1% a standard college degree, 41.9% a high school degree, and the remainder had not completed high school. The mean age of the sample was 43.4 years ($SD = 11.7$).

Norway Sample 2—Participants were recruited from an inpatient medical ward for severely ill patients as well as from the outpatient clinic at a multidisciplinary CFS/ME Center. To be eligible for inclusion, participants needed to be between 18 and 65 years old and capable of reading and writing Norwegian. Individuals with a suspected diagnosis of CFS were referred for evaluation and completed the study measures. All participants took part in a comprehensive medical history interview and a detailed medical examination conducted by experienced consultant physicians and a psychologist. The examinations were

conducted to rule out exclusionary medical and psychiatric conditions. Participants completed a written informed consent, and the study measures were completed by hard copy. The project gained approval from the Privacy Ombudsman for research at Oslo University Hospital. Of the 64 total participants, 63 were included in this study; one was excluded due to missing data.

This sample was 82.5% female and 17.5% male. The majority of the sample identified as Caucasian, but 1.6% identified as Asian, and 3.3% as 'Other.' Most participants (76.2%) were on disability, while 19.0% were working. With regard to education, 11.1% held a graduate or professional degree; 25.4% held a standard college degree; 46.0% had a high school degree; and 17.5% had not completed high school. The mean age of the sample was 34.9 years ($SD = 11.6$).

Measures

The DePaul Symptom Questionnaire

All participants completed the DePaul Symptom Questionnaire (DSQ), a self-report measure of ME and CFS symptomatology, demographics, and medical, occupational and social history. [41] This measure was developed to classify individuals by a variety of ME and CFS case definitions, but the list of 54 symptoms was based upon a revised approach to the Clinical Canadian criteria. [10] Participants 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 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. Frequency and severity scores were multiplied by 25 to create 100-point scales. The 100-point frequency and severity scores for each symptom were averaged to create one composite score per symptom. The DSQ has evidenced good test-retest reliability among both patient and control groups. [42] A factor analysis of these symptoms resulted in a three-factor solution, and these factors evidenced good internal consistency. [35] The DSQ is available in the shared library of Research Electronic Data Capture (REDCap) [43], hosted at DePaul University: <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 measures the impact of participants' health on physical and mental functioning. [44] The measure results in eight subscales: Physical Functioning, Role Physical, Bodily Pain, General Health, Social Functioning, Mental Health, Role Emotional, and Vitality. Higher subscale scores indicate less impairment. The SF-36 evidences strong psychometric properties, including good internal consistency and discriminant validity. [45]

Case Definitions

Chronic Fatigue (CF)—The first category refers to those with chronic fatigue, which involves 6 or more months of fatigue but cannot be explained by an exclusionary medical or psychiatric factors, and does not include individuals classified by the three categories below.

Neuroendocrineimmune Dysfunction Syndrome (NDS)—A second category involves more specific criteria that have been posited both by the IOM report, a Canadian Clinical Case criteria, a ME-ICC criteria and a more empiric approach specifying domains of post-exertional malaise, neurocognitive impairment, and sleep dysfunction. [10–11, 37, 40] The diagnosis NDS is a general term that could represent findings that been suggested by several groups of researchers. But it should not be thought as of representing the IOM report, as those criteria had considerable fewer exclusionary conditions, and tended to prefer the use of comorbidities (in this article, we have made a separate category for the illnesses that had been considered exclusionary by prior case definitions). We decided to use the term NDS rather than CFS or SEID, as neither of these names were recommended by the CFSAC at the meeting in August of 2015. The term ME/CFS has been suggested as well, but such a term can be confusing as the Canadian criteria has used this particular diagnostic label. [10] The NDS label was initially proposed at the CFSAC in 2003 by the Name Change workgroup. Post-exertional malaise items included: soreness after mild activity, feeling drained or sick after mild activity, minimum exercise makes you tired, muscle weakness, a dead or heavy feeling after exercise, and feeling mentally tired after the slightest effort. Neurocognitive items included: difficulty paying attention, difficulty expressing thoughts, problems remembering, absent-mindedness, can only focus on one thing at a time, slowness of thought, and difficulty understanding. We did not include Orthostatic Intolerance (OI), as our prior work found that almost all patients who met the cognitive dysfunction domain would include those with OI. Sleep dysfunction symptoms included: unrefreshing sleep, problems staying asleep, problems falling asleep, waking up early, and need to nap daily. Frequency and severity criteria as recommended by the IOM report were used. Finally, these patients must have had a substantial reduction in functioning as measured by meeting at least two of the three following criteria on the SF-36: Role Physical score ≤ 50 , Social Functioning score ≤ 62.5 , and Vitality score ≤ 35 .

Myalgic Encephalomyelitis (ME)—ME criteria proposed by Ramsay [15] were operationalized by Jason, Damrongvachiraphan, et al. [21] based on past case definitions. This included Ramsay's definition, Dowsett et al.'s "London" criteria, Hyde's Nightingale definition, and Goudsmit et al.'s criteria. [13, 17, 19] Patients also categorized their onset as sudden or gradual, and were asked: "Over what period of time did your fatigue related illness develop?" The responses included the following answers: within 24 hours, 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 that their illness developed either within 24 hours or over 1 week. The major symptom categories of ME in the revised case definition included: post-exertional malaise, neurological manifestations, and autonomic dysfunction. Post-exertional malaise was described as prolonged restoration of muscle power following either mental or physical exertion with recovery often taking 2–24 hours or longer. Neurological manifestations included at least one of the following symptoms: short-term memory loss, loss 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 (post-exertional malaise, neurological manifestations, and autonomic manifestations).

Exclusions—The fourth category refers to those with chronic fatigue that can be explained by a number of medical or psychiatric factors, as indicated by other case definitions such as Fukuda et al. Methods of obtaining this information did vary by sample, as for samples with a physician diagnosis (Newcastle and Norway) would be obtained after a medical examination, whereas with those who just completed the DSQ for the DePaul sample, symptoms were obtained by self-report.

Results

Demographic Characteristics

Table 1 provides a comparison of the demographic characteristics of the patient in each diagnostic category. There were no significant differences on any of the demographic characteristics between illness groups, $p > .05$.

Illness Groups

Symptom Presence—Table 2 provides a comparison of the presence of symptoms and symptom domains of the patients in each illness group with at least moderate severity and presence at least half of the time in the past six months. Significance of χ^2 tests are displayed in the table. Symptoms were significantly more likely to be present in the NDS, ME, and Exclusion groups as compared to the CF group. The ME group was more likely to have pain [$\chi^2 (1) = 4.02, p < .05$] and orthostatic intolerance [$\chi^2 (1) = 4.05, p < .05$] present compared to the NDS group.

Mean Composites—Table 3 provides a comparison of the mean and standard deviations of symptom and domain composites for patients in each illness group. There were significant effects of illness groups on mean composite scores ($p < .05$) in each domain and individual symptom, with the exception of the low temperature symptom. Using the Games-Howell post hoc comparison, it was determined that the CF group differed significantly from the Exclusions, NDS, and ME groups with regard to the symptom severity and frequency. The analyses determined the CF group experiences less severe, less frequent symptoms compared to the other three groups.

SF-36—Table 4 provides a comparison of the means and standard deviations for each illness group on the SF-36 subscales. The CF group has significantly higher scores in the physical functioning, role physical, bodily pain, general health, social functioning, and vitality subscales compared to the other three groups indicating these patients have better overall functioning. Additionally, patients in the NDS group have significantly higher scores on the physical functioning subscale compared to the ME group, $p < .05$. This indicates that the ME group has worse physical functioning compared to the NDS group.

Illness Characteristics—Table 5 provides a comparison of illness characteristics between each illness group. As shown in this table, the ME group has been sicker significantly longer than the NDS group, $p < .001$. The ME group was also more likely to indicate an infectious illness occurred prior to the onset of becoming ill compared to the NDS group [$\chi^2 (1) = 4.95, p < .05$] and the CF group [$\chi^2 (1) = 4.82, p < .05$]. Additionally, the NDS and Exclusions groups reported having symptoms predating their illness significantly more than the ME group, $p < .05$.

Discussion

Our study suggests that there might be different groupings of patients who have significant limitations in energy and endurance. The most consistent finding was that those with CF were the most differentiated from the other three groups on both symptoms and functional limitations. Although the differences in symptoms are not too surprising as the CF group did not have ratings of frequency or severity of symptoms to meet the NDS and ME criteria. Among the NDS, ME and exclusionary group, the latter had directionally more functional limitations and had the highest percent of patients who were bedbound. However, this group is rather diverse, as it is composed of individuals with multiple types of medical and psychiatric illnesses. The ME group had more functional limitations than the NDS group, and fewer symptoms that predated their fatiguing illness. Overall, this investigation suggests that both consensus efforts to differentiate illness groups as well as more empiric efforts does appear to have some validity.

The study suggests that the term CF could be used to designate a broad criteria, as has been used in the US and Britain. The term NDS (or ME/CFS as proposed by the CFSAC at the August 2015 meeting) has comparable symptoms to the SEID criteria, and these core symptoms are also within the Canadian ME/CFS criteria, the ME-ICC criteria or the more empirically based ME criteria. [10–11, 37, 40] The ME criteria identify a much smaller percent of patients with more sudden onset of infectious symptoms, with fewer predating symptoms. In addition, whereas the Fukuda et al. [2] CFS criteria, the ME/CFS Canadian criteria [10] and the ME-ICC criteria [11] excluded other medical and psychiatric conditions that might have produced the fatigue and other symptoms, the new IOM [37] criteria regarded most other illnesses as comorbid rather than exclusionary. [39] This issue is still being debated, but the CFSAC meeting of August 2015 has recommended maintaining the exclusionary criteria, somewhat comparable to previous case definitions. The CFSAC is represented by scientists, patients, and government officials and makes recommendations on CFS and ME to the Secretary of Health and Human Resources.

The differences in CF and NDS might also help us better understand why tertiary care samples appear to be more impaired than those from community-based samples. [46] In a CDC community-based epidemiology study in Wichita, Kansas [5], Nisenbaum et al. [47] provided percentages of symptoms for 65 individuals classified as having CFS. Unusual fatigue post-exertion was found in 78.5%, and difficulty thinking/concentrating or memory problems was found in 76.9%. The percentages of these classic CFS symptoms tend to be low, suggesting an identified CFS group with fewer core symptoms. In Wessely et al.'s [48] British community based sample, 36 individuals were diagnosed as having CFS. Among this

group, only 64% had sleep disturbances and 63% had post-exertional malaise. These percentages are again rather low, as both symptoms are critical features of CFS. It is quite possible that these individuals have CF rather than NDS, and this is reflected in other findings as well suggesting less impairment. For example, in the CDC study, 58 patients with CFS were brought back for a two day inpatient study that occurred from December 2002 to July 2003, and only 16 (28% of the original group diagnosed with CFS) had a current diagnosis of CFS. But within tertiary care settings, less than 10% of patients with CFS recovery, so it is very possible that some of the patients within the community-based samples had CF rather than NDS. [5, 47, 49–50]

It is also possible that because those with CF are less impaired than those with NDS, they might be more likely to benefit from the non-pharmacologic interventions. In addition, those with psychiatric reasons for their fatigue might also be more likely to benefit from the non-pharmacologic interventions. In support of this proposition, Jason et al. [51] found that those with the most severe immune baseline characteristics tended to be non-improvers within non-pharmacologic interventions. Jason et al. [52] also found that patients with CFS with normal baseline cortisol evidenced improvements on a number of immunologic and self-report measures, whereas patients most impaired on hypothalamic-pituitary-adrenal (HPA) functioning at baseline were least able to improve when provided rehabilitation interventions. If those with a more severe illness, such as having NDS and ME, are mixed with those with CF and those with exclusionary illnesses, it might be more difficult to determine therapeutic outcomes for clinical studies.

There is a need for more studies to use the new criteria of the IOM. [37] The present study used some of these criteria, except for one symptom involving cognitive impairment or orthostatic intolerance (but similar results would have been found if we had used this criteria). In addition, the IOM criteria regard most other illnesses as comorbid rather than exclusionary, and as this issue is still being debated. Our current study suggests that the exclusionary group might be different in some important ways from those with just the other IOM criteria, and perhaps for the research criteria that are developed, eliminating patients with these exclusionary illnesses very likely would reduce subject heterogeneity.

The current study has several limitations. Most notably, the patient samples merged were from convenience samples as well as from samples that were evaluated by a medical specialist. We have published another paper that suggests that there are differences between our British and US samples. [53] We did analyze the Norway, Great Britain, and US samples separately, and found comparable results, although reduced power did affect some significant findings. In general, we felt that it was important to merge samples for the current study, and demographic differences as well as differences in ways cases were ascertained provided us a more generalizable data set, increasing external validity.

The IOM diagnostic criteria are clinical rather than research criteria. Even though the IOM SEID was developed to be a clinical diagnostic criteria, and not a research criteria, as we know, the Fukuda et al. CFS criteria tended to be used both for research and clinical purposes, although that was not the original intention of it. In addition, when the Canadian clinical criteria were developed, they have also been used for both purposes. So, when only

one type of criteria is announced and disseminated, there is always the possibility of it being used for both clinical and research purposes. Clearly, what is needed is both a research and clinical criteria, and there would probably be less confusion had both been worked on and disseminated at the same time. We do need both a research and clinical criteria, and hopefully this will occur in the future.

Of course one might criticize the use of self-report in the DePaul sample for making the diagnosis of a psychiatric exclusion, however, research [54] has found that physicians are likely to report high rates of overdiagnosis and misdiagnosis as well. That said, having all patients complete a structured clinical interview is best practice and the absence of this type of interview is a study limitation.

Our scientific enterprise depends on valid methods of classifying patients into diagnostic categories, and this basic research has important implications for research in areas such as etiology, pathophysiology, and treatment. It is only through ongoing data collection that we can provide the perspectives and analyses that can be used by gatekeepers representing scientists, patients and government groups to make the types of recommendations that will provide a sturdier foundation for identifying cases. We continue to believe that cardinal factors including cognitive dysfunction, post-exertional malaise, and sleep help us identify those with more severe illness versus those with milder CF. [29, 55] In addition, even within this broader NDS category, there might very well be those who represent either a separate illness category or are more severe cases, and such individuals might represent those within what Ramsay [15] called ME. Those with more general criteria of NDS could represent a clinical criteria, which is what the IOM attempted to identify, whereas those with a more research criteria could be represented by either the Canadian criteria, which was recommended by the CFSAC at their August 2015 meeting, or a more sudden onset ME group that was described in the current study. [10, 15, 37] Whatever diagnostic system that is ultimately specified, it is critical that scientists world-wide develop consensus on how to identify and classify patients using clinical and research criteria, and one day develop subtypes within such categories.

Acknowledgments

The authors appreciate the funding provided by NIAID (grant numbers AI 49720 & AI 055735).

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Table 1

Demographic information for patients in each illness subtype (N=556)

	CF (N=62)		Exclusions (N=47)		NDS (N=346)		ME (N=101)	
	M	(SD)	M	(SD)	M	(SD)	M	(SD)
Age	44.18	(16.2)	49.09	(13.3)	45.83	(12.9)	47.83	(11.9)
	%	(N)	%	(N)	%	(N)	%	(N)
Gender								
Male	24.19	(15)	14.89	(7)	13.66	(47)	19.80	(20)
Female	75.81	(47)	85.11	(40)	86.34	(297)	80.20	(81)
Race								
White	96.72	(59)	97.87	(46)	97.97	(338)	100.00	(100)
Asian or Pacific Islander	0.00	(0)	0.00	(0)	0.59	(2)	0.00	(0)
Other	3.28	(2)	2.13	(1)	1.48	(5)	8.00	(8)
Ethnicity								
Non-Hispanic	100.00	(59)	97.87	(46)	98.81	(331)	99.00	(99)
Hispanic	0.00	(0)	2.13	(1)	1.19	(4)	1.00	(1)
Marital Status								
Married	42.37	(25)	50.00	(23)	57.89	(198)	54.00	(54)
Separated	0.00	(0)	4.35	(2)	1.75	(6)	1.00	(1)
Widowed	0.00	(0)	0.00	(0)	1.17	(4)	1.00	(1)
Divorced	8.47	(5)	17.39	(8)	11.70	(40)	19.00	(19)
Never Married	49.15	(29)	28.26	(13)	27.49	(94)	25.00	(25)
Education								
High School	55.56	(25)	14.75	(9)	30.97	(105)	27.27	(27)
Partial College	17.78	(8)	14.75	(9)	9.44	(32)	13.13	(13)
College Degree	33.33	(15)	22.95	(14)	35.40	(120)	37.37	(37)
Graduate Degree	28.89	(13)	21.31	(13)	24.19	(82)	22.22	(22)
Work Status								
On Disability	40.98	(25)	70.21	(33)	64.06	(221)	70.00	(70)
Student	8.20	(5)	4.26	(2)	4.06	(14)	1.00	(1)

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	CF (N=62)		Exclusions (N=47)		NDS (N=346)		ME (N=101)	
	M	(SD)	M	(SD)	M	(SD)	M	(SD)
	%	(N)	%	(N)	%	(N)	%	(N)
Age	44.18	(16.2)	49.09	(13.3)	45.83	(12.9)	47.83	(11.9)
Homemaker	3.28	(2)	0.00	(0)	2.03	(7)	3.00	(3)
Retired	11.48	(7)	6.38	(3)	8.70	(30)	7.00	(7)
Unemployed	6.56	(4)	2.13	(1)	4.93	(17)	8.00	(8)
Working Part-Time	21.31	(13)	8.51	(4)	11.59	(40)	8.00	(8)
Working Full-Time	8.20	(5)	8.51	(4)	4.64	(16)	3.00	(3)

Table 2

Percentage of patients with each symptom present at 2/2 threshold or above (N=556)

	CF (N=62)			Exclusions (N=47)			NDS (N=346)			ME (N=101)			
	%	N		%	N		%	N		%	N	Sig.	
Post-Exertional Malaise	72.6	(45)	abc	97.9	(46)	ad	100.0	(346)	bd	100.0	(101)	c	**
Soreness after mild activity	61.3	(38)	abc	91.5	(43)	a	88.7	(307)	b	92.1	(93)	c	**
Drained/sick after mild activity	59.7	(37)	abc	89.4	(42)	a	87.3	(302)	b	88.1	(89)	c	**
Minimum exercise makes tired	54.8	(34)	abc	89.4	(42)	a	87.9	(304)	b	92.1	(93)	c	**
Muscle weakness	41.9	(26)	abc	85.1	(40)	a	74.9	(259)	b	73.3	(74)	c	**
Dead/heavy feeling after exercise	37.1	(23)	abc	83.0	(39)	a	79.5	(275)	b	83.2	(84)	c	**
Mentally tired after slightest effort	37.1	(23)	abc	91.5	(43)	ade	79.2	(274)	bd	78.2	(79)	ce	**
Sleep	82.3	(51)	abc	95.7	(45)	ad	100.0	(346)	bd	99.0	(100)	c	**
Unrefreshing sleep	75.8	(47)	ab	89.4	(42)	c	96.2	(333)	ac	95.0	(96)	b	**
Problems staying asleep	43.5	(27)	abc	74.5	(35)	a	67.6	(234)	b	67.3	(68)	c	**
Problems falling asleep	41.9	(26)	abc	78.7	(37)	ad	63.3	(219)	bd	68.3	(69)	c	**
Waking up early	35.5	(22)	a	53.2	(25)		49.7	(172)	a	45.5	(46)		
Need to nap daily	33.9	(21)	abc	72.3	(34)	a	61.6	(213)	b	61.4	(62)	c	**
Neurocognitive	100.0	(62)	abc	93.6	(44)	ad	100.0	(346)	bd	100.0	(101)	c	**
Difficulty paying attention	38.7	(24)	abc	87.2	(41)	a	92.8	(321)	b	93.1	(94)	c	**
Difficulty expressing thoughts	33.9	(21)	abc	80.9	(38)	a	80.6	(279)	b	77.2	(78)	c	**
Problems remembering	30.6	(19)	abc	78.7	(37)	a	88.4	(306)	b	84.2	(85)	c	**
Absent-mindedness	30.6	(19)	abc	83.0	(39)	a	77.2	(267)	b	71.3	(72)	c	**
Can only focus on one thing at a time	27.4	(17)	abc	83.0	(39)	a	77.2	(267)	bd	87.1	(88)	cd	**
Slowness of thought	22.6	(14)	abc	72.3	(34)	a	72.0	(249)	b	74.3	(75)	c	**
Difficulty understanding	12.9	(8)	abc	70.2	(33)	a	58.7	(203)	b	58.4	(59)	c	**
Immune	33.9	(21)	abc	72.3	(34)	a	76.0	(263)	b	79.2	(80)	c	**
Flu-like symptoms	29.0	(18)	abc	70.2	(33)	a	64.7	(224)	b	72.3	(73)	c	**

	CF (N=62)			Exclusions (N=47)			NDS (N=346)			ME (N=101)			Sig.
	%	N		%	N		%	N		%	N		
Sore throat	14.5	(9)	abc	40.4	(19)	a	39.9	(138)	b	36.6	(37)	c	**
Tender lymph nodes	12.9	(8)	abc	46.8	(22)	a	40.2	(139)	b	45.5	(46)	c	**
Fever	4.8	(3)	ab	17.0	(8)	a	15.6	(54)	b	12.9	(13)		
Neuroendocrine/Circulatory	59.7	(37)	abc	83.0	(39)	a	83.5	(289)	b	78.2	(79)	c	**
Feeling hot/cold for no reason	46.8	(29)	ab	74.5	(35)	a	69.1	(239)	b	62.4	(63)		**
Cold limbs	41.9	(26)	abc	66.0	(31)	a	67.6	(234)	b	58.4	(59)	c	**
Chills/shivers	33.9	(21)	a	40.4	(19)		52.9	(183)	a	42.6	(43)		*
Low temperature	25.8	(16)		29.8	(14)		33.2	(115)		32.7	(33)		
Pain	46.8	(29)	abc	87.2	(41)	a	82.9	(287)	bd	91.1	(92)	cd	**
Joint pain	41.9	(26)	abc	76.6	(36)	a	69.7	(241)	b	69.3	(70)	c	**
Muscle pain	38.7	(24)	abc	83.0	(39)	a	78.6	(272)	bd	88.1	(89)	cd	**
Gastrointestinal	40.3	(25)	abc	80.9	(38)	a	72.0	(249)	b	74.3	(75)	c	**
Bloating	30.6	(19)	abc	61.7	(29)	a	55.8	(193)	b	62.4	(63)	c	**
Stomach pain	29.0	(18)	abc	57.4	(27)	a	56.4	(195)	b	56.4	(57)	c	**
Irritable bowel problems	22.6	(14)	abc	57.4	(27)	a	46.2	(160)	b	43.6	(44)	c	**
Orthostatic Intolerance	41.9	(26)	abc	83.0	(39)	a	72.3	(250)	bd	82.2	(83)	cd	**
Unsteady on feet	21.0	(13)	abc	68.1	(32)	ade	39.6	(137)	bd	45.5	(46)	ce	**
Shortness of breath	19.4	(12)	abc	59.6	(28)	ad	41.9	(145)	bd	42.6	(43)	c	**
Dizziness/fainting	17.7	(11)	abc	42.6	(20)	a	42.5	(147)	b	43.6	(44)	c	**
Irregular heart beats	16.1	(10)	abc	42.6	(20)	ad	28.0	(97)	bd	37.6	(38)	c	**
Chest pain	8.1	(5)	abc	27.7	(13)	a	22.3	(77)	b	26.7	(27)	c	*

Similar letters denote significance

* p < .05

** p < .01

Table 3
Mean composite scores of symptoms in each domain for patients in each illness subtype (N=556)

	CF		Exclusions		NDS		ME	
Post-Exertional Malaise	47.3	abc	78.3	a	71.7	b	72.9	c
Drained/sick after mild activity	52.7	abc	81.6	a	73.6	b	75.3	c
Minimum exercise makes tired	51.8	abc	82.5	a	77.5	b	79.8	c
Soreness after mild activity	51.5	abc	80.0	a	73.3	b	77.5	c
Dead/heavy feeling after exercise	47.9	abc	77.8	a	75.0	b	74.4	c
Muscle weakness	42.0	abc	74.1	a	64.5	b	64.1	c
Mentally tired after slightest effort	36.9	abc	73.8	a	65.8	b	66.8	c
Sleep	43.3	abc	66.9	a	61.6	b	61.7	c
Unrefreshing sleep	64.0	abc	82.8	a	83.5	b	83.5	c
Problems falling asleep	44.9	abc	69.1	a	59.0	b	62.9	c
Problems staying asleep	41.1	abc	68.4	a	60.7	b	61.9	c
Need to nap daily	36.6	ade	69.8	abc	57.0	bd	54.8	ce
Waking up early	29.8	ab	45.0		47.4	a	45.8	b
Neurocognitive	30.2	abc	67.2	a	65.6	b	64.2	c
Problems remembering	38.4	abc	69.1	a	72.6	b	65.9	c
Difficulty expressing thoughts	36.3	abc	69.4	a	65.3	b	62.4	c
Difficulty paying attention	35.4	abc	74.4	a	78.0	b	76.6	c
Absent-mindedness	32.7	abc	68.1	a	63.7	b	61.8	c
Slowness of thought	26.2	abc	64.4	a	60.4	b	59.5	c
Can only focus on one thing at a time	25.6	abc	69.4	a	67.7	b	72.0	c
Difficulty understanding	15.5	abc	55.9	a	51.5	b	51.3	c
Immune	18.3	abc	44.1	a	39.2	b	39.8	c
Flu-like symptoms	25.0	abc	59.1	a	57.4	b	59.2	c
Tender lymph nodes	19.6	acd	50.3	ab	36.9	bc	42.4	d
Sore throat	19.0	abc	42.5	a	40.0	b	39.3	c

	CF	Exclusions	NDS	ME	
Fever	8.9 abc	24.7 a	22.1 b	18.0 c	**
Neuroendocrine/Circulatory	34.2 ab	48.7 a	49.1 b	43.6	**
Feeling hot/cold for no reason	39.6 ab	60.9 a	57.7 b	51.9	**
Cold limbs	39.3 ab	58.8 a	58.8 b	52.5	**
Chills/shivers	29.8 a	43.1	48.1 ab	37.6 b	**
Low temperature	27.7	31.9	31.7	32.4	
Pain	37.5 abc	69.8 a	63.1 b	62.4 c	**
Muscle pain	38.7 abc	72.2 a	66.0 b	69.2 c	**
Joint pain	36.0 abc	67.5 a	60.3 b	55.5 c	**
Gastrointestinal	22.1 abc	55.0 a	47.8 b	47.7 c	**
Bloating	23.2 abc	53.1 a	49.3 b	47.9 c	**
Irritable bowel problems	22.6 abc	62.5 a	50.4 b	51.9 c	**
Stomach pain	20.1 abc	49.7 a	43.8 b	43.3 c	**
Orthostatic Intolerance	19.1 abc	45.8 a	37.7 b	38.6 c	**
Dizziness/fainting	23.5 abc	50.0 a	43.2 b	42.1 c	**
Shortness of breath	22.0 abc	48.1 a	40.7 b	39.3 c	**
Unsteady on feet	21.1 acd	55.6 ab	42.4 bc	46.3 d	**
Irregular heart beats	14.9 abc	41.6 a	34.3 b	35.1 c	**
Chest pain	13.4 abc	33.4 a	27.6 b	30.1 c	**

Similar letters denote significant differences

* p < .05

** p < .01

Table 4

MANOVA results for mean (SD) differences on SF-36 Subscales between illness subtypes (N=524)

	CF (N=47)		Exclusions (N=45)		NDS (N=334)		ME (N=98)						
Physical Functioning	58.92	(25.6)	acd	25.89	(18.6)	ab	36.52	(22.1)	bce	29.61	(19.3)	de	**
Role Physical	25.89	(37.7)	abc	2.22	(7.2)	a	5.61	(15.4)	b	2.55	(10.5)	c	**
Bodily Pain	55.98	(22.3)	abc	30.27	(23.8)	a	38.79	(23.6)	b	35.87	(21.4)	c	**
General Health	40.73	(18.9)	acd	19.73	(13.3)	ab	28.19	(16.6)	bc	25.34	(13.8)	d	**
Social Functioning	51.86	(33)	abc	21.11	(22.6)	a	24.96	(20.1)	b	20.15	(20)	c	**
Vitality	31.38	(22.2)	abc	14.00	(15)	a	17.17	(14.5)	b	16.43	(15)	c	**
Mental Health	75.02	(14.7)	a	68.07	(20.5)		68.73	(18.2)	a	72.82	(16.3)		*
Role Emotional	81.56	(36)		71.11	(39.9)		72.85	(41.3)		80.27	(35.8)		

* Similar letters denote significant differences

* p < .05

** p < .01

Table 5

Illness characteristics of patients in each subtype (N=556)

	CF (N=62)		Exclusions (N=47)		NDS (N=346)		ME (N=101)	
	M	(SD)	M	(SD)	M	(SD)	M	(SD)
Illness Duration	7.3	(7.7)	10.6	(8.8)	6.8	(7.0)	11.0	(8.6)
Current Hours Spent on Activities								
Household activities	8.6	(9.1)	7.3	(7.4)	6.1	(6.2)	6.9	(6.6)
Social/recreational activities	6.2	(11.9)	a	3.1	(3.2)	3.9	(5.9)	2.9
Family related activities	6.0	(10.9)		4.0	(5.6)	4.8	(6.4)	4.2
Work related activities	11.1	(15.3)	abc	3.6	(10.1)	a	5.3	(11.1)
Total hours spent	34.4	(28.1)	abc	18.8	(14.6)	a	20.3	(17.0)
Past Hours Spent on Activities								
Household activities	12.0	(8.1)		12.2	(8.8)		12.6	(8.8)
Social/recreational activities	14.9	(10.0)		12.8	(13.7)		12.9	(8.9)
Family related activities	10.2	(7.0)		13.8	(13.1)		10.8	(8.8)
Work related activities	38.8	(11.4)		35.6	(18.7)		38.1	(13.7)
Total hours spent	75.5	(18.5)		73.0	(29.8)		75.3	(21.4)
Total Hours Spent on Activities - Reduction	41.1	(25.6)	ab	54.3	(29.9)		55.0	(24.4)
	%	(N)	%	(N)	%	(N)	%	(N)
Functional Status								
Bedbound	16.7	(10)	a	41.3	(19)	ab	21.5	(73)
Light housework	41.7	(25)		37.0	(17)	ab	55.0	(187)
Able to work	41.7	(25)	abc	21.7	(10)	a	23.5	(80)
Event Prior to Illness								
Infectious illness	61.0	(36)	a	63.0	(29)		66.3	(222)
Accident	5.0	(3)		8.7	(4)		4.5	(15)
Trip or vacation	6.7	(4)		4.3	(2)		6.8	(23)
Immunization	13.3	(8)		10.9	(5)		10.9	(37)
Surgery	15.0	(9)		17.4	(8)		9.7	(33)
Severe Stress	25.0	(15)	a	28.3	(13)		39.5	(134)

	CF (N=62)		Exclusions (N=47)		NDS (N=346)		ME (N=101)	
	M	(SD)	M	(SD)	M	(SD)	M	(SD)
Onset								
Within 24 hours	8.6	(5)	11.4	(5)			51.5	(52)
Over 1 week	6.9	(4)	6.8	(3)	3.7	(12)	58.4	(49)
Over 1 month	15.5	(9)	9.1	(4)	12.2	(40)	0.0	(0)
Over 2–6 months	24.1	(14)	20.5	(9)	26.2	(86)	0.0	(0)
Over 7–12 months	6.9	(4)	2.3	(1)	10.1	(33)	0.0	(0)
Over 1–2 years	12.1	(7)	4.5	(2)	18.3	(60)	0.0	(0)
Over 3 years	24.1	(14)	45.5	(20)	27.4	(90)	0.0	(0)
Predating Symptoms								
Headaches	11.5	(7)	46.8	(22)	26.5	(91)	16.2	(16)
Unrefreshing sleep	31.1	(19)	61.7	(29)	44.5	(153)	23.2	(23)
Impaired memory and concentration	24.6	(15)	48.9	(23)	32.0	(110)	13.3	(13)
Sore throat	37.7	(23)	68.1	(32)	42.2	(145)	30.3	(30)
Muscle pain	24.6	(15)	59.6	(28)	36.3	(125)	22.2	(22)
Prolonged fatigue following physical or mental exertion	27.9	(17)	53.2	(25)	33.4	(115)	21.2	(21)
Tender/sore lymph nodes	45.9	(28)	59.6	(28)	45.6	(157)	23.2	(23)
Joint pain	21.3	(13)	48.9	(23)	32.7	(112)	19.4	(19)

* Similar letters denote significant differences

* p < .05

** p < .01