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Chronic Fatigue Syndrome versus Systemic Exertion Intolerance Disease

Leonard A. Jason,
DePaul University

Madison Sunnquist,
DePaul University

Abigail Brown,
DePaul University

Julia L. Newton,
Newcastle University

Elin Bolle Strand, and
Oslo University Hospital

Suzanne D. Vernon
Solve ME/CFS Initiative

Abstract

Background—The Institute of Medicine has recommended a change in the name and criteria for Chronic Fatigue Syndrome (CFS), renaming the illness Systemic Exertion Intolerance Disease (SEID). The new SEID case definition requires substantial reductions or impairments in the ability to engage in pre-illness activities, unrefreshing sleep, post-exertional malaise, and either cognitive impairment or orthostatic intolerance.

Purpose—In the current study, samples were generated through several different methods and were used to compare this new case definition to previous case definitions for CFS, Myalgic Encephalomyelitis (ME-ICC), Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), as well as a case definition developed through empirical methods.

Methods—We used a cross-sectional design with samples from tertiary care settings, a biobank sample, and other forums. 796 patients from the US, Great Britain, and Norway completed the DePaul Symptom Questionnaire.

Results—Findings indicated that the SEID criteria identified 88% of participants in the samples analyzed, which is comparable to the 92% that met the Fukuda criteria. The SEID case definition was compared to a four item empiric criteria, and findings indicated that the four item empiric criteria identified a smaller, more functionally limited and symptomatic group of patients.

Conclusion—The recently developed SEID criteria appears to identify a group comparable in size to the Fukuda et al. criteria, but a larger group of patients than the Canadian ME/CFS and ME criteria, and selects more patients who have less impairment and fewer symptoms than a four item empiric criteria.

Keywords

Systemic Exertion Intolerance Disease; Myalgic Encephalomyelitis; chronic fatigue syndrome; case definitions

Brurberg, Fønhus, Larun, Flottorp, and Malterud [1] identified 20 chronic fatigue syndrome (CFS) case definitions, with the Fukuda et al. CFS [2] criteria as the most frequently applied. The Fukuda et al. CFS [2] criteria only require four symptoms out of a possible eight, so it is possible that some individuals who meet these diagnostic criteria do not have core symptoms of the illness, such as post-exertional malaise, memory/concentration problems, or unrefreshing sleep. This factor might have contributed to wide variability in CFS prevalence rates (.004 to .0087% [3], .24% [4], .42% [5], and 2.54% [6]).

Another consensus clinical case definition has been called the Canadian Clinical Criteria, and has been referred to as ME/CFS [7]. This ME/CFS case definition specified core symptoms, including post-exertional malaise, impairment of memory and concentration, unrefreshing sleep, arthralgia and/or myalgia; and several autonomic, neuroendocrine, and immune manifestations. In an effort to better operationalize the ME/CFS criteria [7], Jason et al. [8] specified explicit rules for determining ME/CFS status, and in particular, using severity and frequency criteria as opposed to just the presence of symptoms. In addition, the International Consensus Criteria for Myalgic Encephalomyelitis (ME-ICC) criteria [9] was recently developed, and to meet these criteria, a person needed to have symptoms from the following four domains: Post-Exertional Neuroimmune Exhaustion; Neurological Impairments; Immune, Gastro-intestinal, and Genitourinary Impairments; and Energy Production/Transportation Impairments. Rather than 4 symptoms required by the Fukuda et al. CFS [2] criteria, the ME/CFS criteria [7] required 7 symptoms whereas the ME-ICC criteria [9] required 8 symptoms. Unfortunately, with the increase of symptoms from 4 to 7 or 8, criteria could identify individuals with higher rates of psychiatric co-morbidity [10].

Using a more empirical approach, Jason et al. [11] used several methods (i.e., continuous scores of symptoms, theoretically and empirically derived cut off scores of symptoms) to identify core symptoms best differentiating patients from controls. Data mining with decision trees was used to identify core that were most effective at accurately classifying participants as patient or control. Decision trees consist of a series of successive binary choices (branch points) that result in an accurate classification of participants. SPSS Statistics software was used to build our decision tree models. To build the models, a Classification and Regression Tree (CART) algorithm was applied to a training set consisting of 66% of the cases, stratified to reflect the distribution of patient and control groups. The value of the model was measured by evaluating its classification performance when applied to cases reserved for testing (34% of the data), allowing this technique the ability to be generalized to new data. Because data mining is best conducted with similar

numbers of participants in groups, we took a random sample of 80 ME patients along with the 80 Controls. We created 100 sets of analyses. For most analyses, only 3–5 variables were needed to classify participants.[11] Outcomes from these analyses suggest that individuals with CFS could be accurately identified using only 4 empirically selected symptoms: fatigue or extreme tiredness, physically drained/sick after mild activity, difficulty finding the right word to say or expressing thoughts, and unrefreshing sleep.

Recently, the Institute of Medicine [12] issued a report that proposed a new case definition [13] that included the following 4 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. As with the Jason et al. [8,11] studies, the IOM authors recommended using frequency and severity ratings with clear cut off points.[12] This new case definition, newly named Systemic Exertion Intolerance Disease (SEID), has never been compared to other consensus based criteria, nor to the four item empiric criteria [11]. The current study is one of the first to compare this SEID criteria [12] to other diagnostic criteria.

Method

Research Participants DePaul sample—An international convenience sample of adults self-identifying as having CFS, ME/CFS, or ME was recruited (96.3% reported a diagnosis from a medical doctor). The majority (90%) of participants were from the United States. 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 by DePaul University's Institutional Review Board, participants were recruited from a variety of sources including postings on internet forums, support group visits, re-contacting of individuals who have participated in the DePaul Research Team's studies in the past and have indicated interest in future studies, and contacting of individuals who have emailed the team's address in the past with interest in future studies.

Most (94%) of participants completed the electronic version of the survey, while the remainder completed and mailed hard copies. Most (94%) of participants completed the electronic version of the survey, while the remainder completed and mailed hard copies. Participants were given three options for completion of the surveys: an electronic survey, a hardcopy 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. 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 100 individuals who completed the survey received a \$5.00 gift card to Amazon.com for their participation.

Of the 216 participants, 84.2% were female and 15.8% male. 97.7% of the sample identified as Caucasian, 0.5% as Asian, and the remaining 1.9% identified as 'Other.' 57.2% of the sample stated that they were currently on disability, with only 13.0% of the sample working part or full-time. With regards to educational level, 40.2% of the sample held a professional

degree, 34.6% held a standard college degree, 18.2% attended college for at least one year, and 7.0% completed high school or had a GED. The mean age was 52.0 ($SD = 11.3$).

SolveCFS BioBank Sample—A separate sample of individuals was collected by the Solve ME/CFS Initiative. This patient data originated from the SolveCFS BioBank, a resource with clinical information and blood samples on a sample of individuals diagnosed by a licensed physician specializing in CFS, ME/CFS, and ME. The sample used in the present study included only those over 18. Participants were recruited by the Solve ME/CFS Initiative through physician referral. All participants who met eligibility criteria completed a written informed consent process. Participants completed the study measures electronically or by hard copy. The data was de-identified and shared with the DePaul research team following submission and peer review of a research protocol to the Solve ME/CFS Initiative.

Of the 239 patients who participated, 99.2% were Caucasian, and 0.8% were Asian or Pacific Islander. With regards to gender, 73.1% of the sample was female. Only 10.5% of the sample was working full- or part-time, with 65.3% on disability. Regarding education level, 24.7% of the sample held a graduate or professional degree; 42.3% had completed college; 20.5% had completed some college; and 11.3% had a high school degree or GED. The average age of the sample was 49.7 ($SD = 12.9$).

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 100 participants completed study measures by hard copy.

The Newcastle sample was 99.0% Caucasian and 1.0% multiracial, and 81.0% of participants were female. Of this sample, 36.7% of participants were working either part- or full-time, and 30.6% were on disability. With regard to education level, 20.4% had a graduate or professional degree; 29.0% had a college degree; 24.7% had completed at least one year of college; 14.0% had a high school degree; and 11.9% had not completed high school. The average age of the sample was 45.8 ($SD = 13.9$).

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, 86.3% were female and 13.7% male. Almost all participants were Caucasian (99.4%); one participant selected 'Other' when asked about race. Only 9.7% of participants were working, while 83.5% were on disability. Regarding education, 9.8% of participants had a graduate or professional degree, 39.9% a standard college degree, 42.2% a high school degree, and the remainder had not completed high school. The mean age of the sample was 43.6 years ($SD = 11.9$).

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, 81.3% were female and 18.8% male. The majority of the sample identified as Caucasian, but 1.6% identified as Asian, and 3.2% as 'Other.' Most participants (76.6%) were on disability, while 18.8% were working. With regard to education, 12.5% held a graduate or professional degree; 25.0% held a standard college degree; 45.3% had a high school degree; and 17.2% had not completed high school. The mean age of the sample was 35.3 years ($SD = 11.9$).

Measures

The DePaul Symptom Questionnaire—All participants completed the DePaul Symptom Questionnaire (DSQ) [8], a self-report measure of symptomatology, demographics, and medical, occupational, and social history. Participants were asked to rate each of the symptom's frequency and severity over the past six months on a 5-point Likert scale. Symptom frequency was rated: 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, severity was rated: 0=symptom not present, 1=mild, 2=moderate, 3=severe, and 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 [14] with factors evidencing good internal consistency [15]. The DSQ is available at REDCap's [16] shared library: <https://redcap.is.depaul.edu/surveys/?s=tRxxtSPVVw>

Functional status

Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36 or RAND Questionnaire)—The SF-36 is a 36-item self-report measure of functional status related to health. [17] 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 have shown adequate internal consistency, significant discriminant validity among subscales, and substantial differences between patient and non-patient populations in the pattern of scores.[18]

Case Definitions

Fukuda et al. [2] CFS Case Definition—A case of chronic fatigue syndrome is defined by Fukuda et al. [2] as the presence of the following criteria: (1) clinically evaluated, unexplained, persistent or relapsing chronic fatigue of six or more months that is of new or definite onset (has not been lifelong); is not the result of ongoing exertion; is not substantially alleviated by rest and results in substantial reduction in previous levels of occupational, educational, social, or personal activities, and (2) the concurrent occurrence of four or more core symptoms (memory or concentration problems, sore throat, tender lymph nodes, muscle pain, joint pain, headaches, unrefreshing sleep, and post-exertional malaise), all of which must have persisted or recurred during six or more consecutive months of illness and must not have predated the fatigue.[2] Because frequency and severity criteria were not specified for the symptoms required in this case definition, participants needed to report frequency and severity scores of at least 1 for a symptom to be counted toward the four required symptoms. Participants with morbid obesity, lifelong fatigue, or medical or psychiatric conditions that could explain fatiguing symptoms were excluded from analysis of this case definition.

Canadian ME/CFS Case Definition [7]—The Canadian clinical ME/CFS consensus case definition (ME/CFS) specifies that post-exertional malaise must occur with a loss of physical or mental stamina, rapid muscle or cognitive fatigability, usually taking 24 hours or longer to recover.[7] In addition, two or more neurological/cognitive manifestations must be present (e.g., confusion, impairment of concentration and short-term memory). Unrefreshing sleep or poor sleep quantity or rhythm disturbance must be reported, as well as a significant degree of arthralgia and/or myalgia. Finally, one symptom from two of the following categories must be present: autonomic manifestations (e.g., neurally mediated hypotension, light headedness), neuroendocrine manifestations (e.g., recurrent feelings of feverishness, cold extremities), and immune manifestations (e.g., recurrent sore throats). Exclusionary criteria included morbid obesity, lifelong fatigue, and other medical or psychiatric conditions that could explain fatigue.

ME-ICC Case Definition [9]—The International Consensus Criteria for ME (ME-ICC) [9] state that symptom severity must result in a 50% or greater reduction of a patient's premorbid activity level for a diagnosis. Additionally, symptoms from four major groupings are required. First, to meet criteria, a person must experience Post-Exertional Neuroimmune Exhaustion. Within the Neurological Impairment symptom grouping, a patient must have at

least one symptom from three of the following four symptom categories (1) neurocognitive impairments (e.g., difficulty processing information, short-term memory loss), (2) pain, (3) sleep disturbance, and (4) neurosensory, perceptual and motor disturbances (e.g. inability to focus vision, sensitivity to light, feeling unsteady on feet). The third category is Immune, Gastro-intestinal and Genitourinary Impairments, and individuals must have at least one symptom from three of the following five symptom categories: (1) flu-like symptoms, (2) susceptibility to viral infections with prolonged recovery periods (3) gastro-intestinal tract symptoms (e.g., nausea, abdominal pain), (4) genitourinary symptoms (e.g., urinary urgency), and (5) sensitivities to food, medications, odors, or chemicals. The final category is Energy Production/Transportation Impairments, and at least one symptom from one of the following four symptom categories must be present: (1) cardiovascular (e.g. orthostatic intolerance), (2) respiratory (e.g. labored breathing), (3) loss of thermostatic stability (e.g. subnormal body temperature), and (4) intolerance of extremes of temperature. Participants needed to report frequency and severity scores of at least 2 for a symptom to meet criteria. Individuals with morbid obesity or medical or psychiatric conditions that could explain fatigue were excluded from meeting this case definition.

Four item empiric criteria [11]—Data mining analyses indicated the selection of four symptoms: fatigue or extreme tiredness, difficulty finding the right word to say or expressing thoughts, physically drained/sick after mild activity, and unrefreshing sleep [11]. In particular, these were all symptoms that appeared in a majority of the 100 classification trees. Individuals with medical or psychiatric conditions that could explain fatigue were excluded from analysis when applying this case definition.

Systemic Exertion Intolerance Disease [12]—Our group developed operationalized the SEID criteria [12] in the following way: a patient needed to have 6 or more months of illness (For how long have you had problems with fatigue or energy?) To meet the requirement regarding substantial reduction from previous levels of functioning, a patient needed to meet 2 of the following 3 criteria: role physical < 50, social functioning < 62.5, or vitality < 35. To meet the post-exertional malaise criteria, a patient would need to have a frequency and severity ≥ 2 on at least one of five post-exertional malaise items. To meet the unrefreshing sleep criteria, frequency and severity ≥ 2 were required for at least one of the following items: unrefreshing sleep, problems falling asleep, problems staying asleep, needing to nap daily, or sleeping all day and staying awake all night. Additionally, participants needed to report either cognitive impairment or orthostatic intolerance. In order to meet the cognitive impairment criteria, a patient would need a frequency and severity score of ≥ 2 on at least 1 of the following cognitive or orthostatic intolerance items: problems remembering, difficulty paying attention, difficulty expressing thoughts, difficulty understanding things, difficulty focusing on more than one thing, slowness of thought, absent-mindedness. To meet the orthostatic intolerance criteria, we did not have items related to lightheadedness or spatial orientation, but we assessed this domain through the following items (at least 1 item; frequency and severity ≥ 2): feeling unsteady on feet, shortness of breath, dizziness or fainting, or irregular heartbeats. While the questionnaire used in this study was not able to assess for lightheadedness or problems with spatial orientation, two symptoms that were included in the IOM [12] report's suggestions for

operationalizing orthostatic intolerance, almost all individuals who reported orthostatic intolerance symptoms also reported cognitive impairment, so it is unlikely that the absence of these two items precluded many participants from meeting criteria. No medical or psychiatric conditions were considered exclusionary for the SEID criteria, as the IOM criteria state that conditions are only exclusionary if they explain all of an individual's symptoms. Only 17 participants (2% of the sample) were eligible for exclusion based on medical or psychiatric conditions, as the samples were in general carefully selected to reduce these types of exclusionary illnesses. Our analyses below for the SEID criteria are based on including these individuals, but when these participants were excluded and therefore classified as not meeting the SEID criteria, similar overall results were found.

Results

Table 1 displays the percentage of participants who met various case definitions. The SEID case definition captures 88% of participants in the samples analyzed, which is comparable to the 92% that met the Fukuda criteria [2]. Fewer individuals met the ME/CFS [7] criteria, and still fewer met the ME-ICC [9], and four item empiric criteria [11]. Of those who met the SEID criteria [12], 98% met the CFS Fukuda criteria [2], 85% met the ME/CFS criteria [7], 66% met the ME-ICC criteria [9], and 66% met the a four item empiric criteria [11].

Table 2 displays the percentage of participants in the overall sample who met each requirement of the SEID criteria [12]. Approximately 93% to 97% of participants reported substantial reductions in functioning, post-exertional malaise, unrefreshing sleep, and cognitive impairment; however, just 67% reported orthostatic intolerance.

We next wanted to compare those who met the SEID criteria to a group that was more restricted, and we selected a four item empiric criteria [11]. Two groups were created for comparison: in one group were individuals who met a four item empiric criteria and in the other group those that met the SEID criteria but not the four item empiric criteria. There are more individuals in the four item empiric group because almost all those meeting this criteria also met the SEID criteria. Table 3 displays information on demographics and history of psychiatric diagnosis for those who meet the SEID [12] and a four item empiric criteria [11]. The only demographic differences between the groups were related to level of education [$p = 0.048$, two-tailed Fisher's exact test] and occupational status [$\chi^2(5, n = 707) = 11.67, p = 0.04$]. The SEID group included individuals with higher levels of education, and the four item empiric criteria included more individuals on disability. As work status could be treated as an outcome variable related to level of functioning, only educational level was considered as a covariate in the subsequent analyses.

A multivariate analysis of variance (MANOVA) was conducted to compare the SF-36 scores of the SEID and four item empiric groups (Table 4). Five of the eight subscales showed significant differences: Physical Functioning [$F(1, 685) = 19.12, p < 0.001$], Role Physical [$F(1, 685) = 4.97, p = 0.03$], Bodily Pain [$F(1, 685) = 20.71, p < 0.001$], Social Functioning [$F(1, 685) = 24.07, p < 0.001$], and Vitality [$F(1, 685) = 17.82, p < 0.001$]. To ensure that educational level was not contributing to these differences, a subsequent analysis

was conducted to control for education; all subscales that had showed significant differences in the previous analysis remained significant.

Table 5 compares the symptom scores of the SEID and the four item empiric groups. An ANOVA indicated that fatigue scores were significantly different between these two groups [$F(1, 708) = 69.23, p < 0.001$]. Seven symptom groups were created, and MANOVAs were conducted on each group. All MANOVAs were significant: PEM [$F(5, 660) = 30.69, p < 0.001$], Sleep [$F(6, 652) = 12.29, p < 0.001$], Pain [$F(7, 673) = 5.32, p < 0.001$], Neurocognitive [$F(13, 622) = 23.25, p < 0.001$], Autonomic [$F(7, 668) = 6.77, p < 0.001$], Neuroendocrine [$F(10, 641) = 3.43, p < 0.001$], and Immune [$F(5, 665) = 7.38, p < 0.001$]. Tests of between-subjects effects indicated that the groups had significantly different scores for all symptoms except: headaches, irregular heartbeats, alcohol intolerance, sore throat, and tender lymph nodes. Results were replicated when controlling for level of education.

Discussion

Consistent findings across the four data sets suggest that slightly fewer individuals meet the SEID [12] case definition than the Fukuda et al [2] CFS criteria; still fewer meet the ME/CFS [7] criteria, and an even smaller group are identified by the four item empiric criteria [11] and the ME-ICC [9] case definition [9]. In addition, the current study found that the four item empiric criteria [11] identified a more impaired group than the SEID [12] criteria, suggesting that the former might select a more homogenous group for research purposes, whereas the latter group might be broader and represent a broader group for clinical diagnosis.

Across the various case definitions, differences occur in three areas: (1) whether criteria require specific symptoms (e.g. drained/sick after mild activity in the four item empiric criteria [11]) or broader domains of symptoms (e.g. post-exertional malaise in the ME-ICC criteria [9]); (2) how many symptoms or domains are required; and (3) whether criteria are polythetic (i.e., requiring a certain number of a larger possible list of symptoms, such as the Fukuda et al. [2] CFS criteria) or require all identified symptoms to be present. Exploring the advantages and disadvantages of each of these approaches is an important activity for the future. When criteria require domains instead of specific symptoms, a variety of symptoms can fulfill criteria for a certain domain; thus, more patients are eligible for meeting domain criteria. Alternatively, when specific symptoms are required, such as the four item empiric criteria's [11] requirement of feeling physically drained/sick after mild activity (related to post-exertional malaise), fewer individuals will meet criteria. Additionally, criteria that require larger numbers of symptoms, such as the 8 symptom domains required by the ME-ICC [9], will select fewer patients; however, Katon and Russo [10] have found that requiring larger numbers of somatic symptoms can increase rates of psychiatric co-morbidity. Finally, polythetic case definitions select more heterogeneous groups, as patients who meet criteria can have different combinations of symptoms.

Both the SEID criteria [12] and the four item empiric criteria [11] consist of 4 requirements; however, the SEID criteria [12] uses domains, while the four item empiric criteria [11] requires specific symptoms. The SEID criteria [12] identified more individuals than the four

item empiric criteria [11], even though there was considerable overlap between types of symptoms required by the two sets of criteria. However, the criteria differed in that the SEID criteria [12] state that patients could have either cognitive impairment or orthostatic intolerance, whereas the four item empiric criteria [11] require cognitive impairment but not orthostatic intolerance. The SEID criteria [12] identify individuals who are impaired, but the four item empiric criteria [11] identified individuals with even more impairment. Although the ME-ICC [9] criteria also identify a comparable percentage of patients, the four item empiric criteria [11] require fewer symptoms compared to the 8 ME-ICC domains. In addition, the four item empiric criteria [11] consist of specific, core symptoms, as opposed to the polythetic method used by the Fukuda et al. [2] CFS criteria. In other words, using just 4 core symptoms, the four item empiric criteria select a more homogenous and impaired group of patients than the other case definitions discussed. Given these findings, the SEID [12] or CFS [2] criteria could be used as a broad clinical criteria, whereas the narrower ME/CFS [7] criteria, or the even more selective ME/ICC [9] or four item empiric [11] criteria could be used in research to identify a smaller, more seriously impaired group.

On the other hand, it is possible to argue that there is no established precedent for using one case definition in research and another for clinical care. Many research papers use a common broad definition as inclusion criteria, but decide to focus on a specific subgroup of participants (e.g. HIV patients who have immune cell counts of less than 200) based on the researchers' interests. Currently, there is no "clinical case definition" and "research case definition" for HIV.

There are several limitations in the present study. First, outcome measures were self-reported. For example, operationalizing post-exertional malaise remains a difficult activity, and there needs to be more research on how best to capture this phenomena through self-report questionnaires. In the future, it would be important to replicate the self-report findings with additional biological markers, such as those associated with two day exercise challenges. In addition, several different data sets were used, some of which were more carefully selected through physicians and others that relied on patient report of diagnosis. However, the fact that such disparate sources of data yielded comparably similar results suggests that our methods for operationalizing and testing the SEID criteria were generalizable.

Regarding the SEID case definition, there are a number of possible conceptual problems with the criteria. First, prevalence rates of orthostatic intolerance are not as high as the other proposed core symptoms, nor is there any clear justification for the option of having either cognitive impairment or orthostatic intolerance. In fact, in the current sample, the option of having orthostatic intolerance instead of cognitive impairment enabled just 2% more participants to meet SEID criteria than had the definition simply required cognitive impairment. In addition, lack of clarity regarding recommendations for with exclusionary illnesses, such as psychiatric disorders and medical illnesses, could lead to a more heterogeneous group of patients and higher prevalence rates in the general population [19]. This issue was not really dealt with in our study as our samples of patients, for the most part, had been screened to meet the Fukuda et al. [2] criteria, and using these criteria, these samples were screened to exclude those with exclusionary illnesses.

At the present time, there is considerable debate among scientists regarding which case definition to use for clinical and research purposes. Likewise, patients are concerned about the case definition, as well as the name of the illness. As indicated in the IOM report [12], limited funding has resulted in an inadequate number of studies that have focused on case definition reliability and validity. With the release of this report, it is hoped that more research will be stimulated and supported. Empirical methods can be used to evaluate criteria and develop a consensus among gatekeepers (scientists, clinicians, patients, government) in deciding which case definition to use. In addition, researchers need to use operationally explicit structured interview schedules to ensure the necessary information is elicited from an interview. Finally, there needs to be consensus on how to determine when a symptom reaches a threshold at which it can be considered a problem. These activities could be accomplished by providing support for structural capacities that facilitate ongoing data collection and interactive feedback, one that is vetted by broad based gatekeepers representing scientists, patients and government groups.

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Table 1

Percentage of Participants who Meet Various Case Definitions

Sample	SEID ¹²	Fukuda ²	ME/CFS ⁷	Four item empiric ¹¹	ME-ICC ⁹
DePaul (n = 216)	91%	96%	77%	60%	57%
BioBank (n = 239)	88%	93%	73%	61%	N/A ^a
Newcastle (n = 100)	82%	87%	73%	51%	58%
Norway (n = 240)	88%	90%	77%	67%	62%
Overall Sample	88%	92%	76%	61%	60% ^a

^aThe BioBank sample was collected prior to a revision of the DePaul Symptom Questionnaire that included additional items to assess all symptoms of the ME-ICC; thus, the percentage of participants who met the ME-ICC definition cannot be computed for the BioBank sample.

Table 2

Percentage of Participants Who Meet Components of SEID Criteria (n = 795)

Domain:	Percentage who Meet Criteria:
Substantial Reduction	95%
Post-Exertional Malaise	96%
Unrefreshing Sleep	97%
Cognitive Impairment OR Orthostatic Intolerance	95%
<i>Cognitive Impairment</i>	93%
<i>Orthostatic Intolerance</i>	67%
Overall SEID Criteria	88%

Table 3

Demographic Comparison

	Four Item Empiric <i>n</i> = 475	SEID <i>n</i> = 239	
	M (SD)	M (SD)	Sig.
Age	47.2 (12.7)	47.0 (13.6)	
Other Demographic Information:	% (n)	% (n)	Sig.
Gender			
Female	81 (385)	80 (192)	
Male	19 (88)	20 (47)	
Race			
Caucasian	98 (464)	98 (233)	
Asian / Pacific Islander	1 (3)	0 (1)	
Other	1 (5)	1 (3)	
Marital status			
Married / Living with partner	57 (270)	53 (125)	
Never married	26 (123)	31 (72)	
Divorced	14 (67)	14 (33)	
Separated	2 (8)	0 (1)	
Widowed	1 (5)	2 (4)	
Work status			*
On disability	71 (334)	59 (138)	
Working	11 (54)	18 (42)	
Retired	7 (34)	11 (26)	
Unemployed	4 (21)	4 (10)	
Student	4 (19)	4 (10)	
Homemaker	2 (11)	3 (8)	
Educational level			*
Less than high school	4 (20)	1 (3)	
Some high school	1 (5)	1 (2)	
High school	22 (103)	17 (39)	
Partial college	15 (69)	13 (30)	
Standard college degree	36 (168)	40 (95)	
Graduate / Professional degree	22 (102)	28 (67)	
History of Psychiatric Diagnosis ^a			
Yes	35 (117)	35 (59)	
No	65 (213)	65 (112)	

*
 $p < 0.05$

^aData not available for BioBank Sample

Table 4**SF-36 Comparison**

	Four Item Empiric <i>n</i> = 475	SEID <i>n</i> = 239	
SF-36 Subscale	M (SD)	M (SD)	Sig.
Physical Functioning	32.1 (20.4)	39.6 (23.4)	***
Role Physical	3.4 (12.9)	5.8 (14.2)	*
Bodily Pain	36.6 (22.6)	45.1 (23.7)	***
General Health	25.2 (15.5)	27.2 (15.8)	
Vitality	14.0 (13.5)	18.7 (14.5)	***
Social Functioning	21.6 (20.3)	29.9 (22.2)	***
Role Emotional	71.1 (41.7)	75.5 (38.8)	
Mental Health	67.7 (19.1)	70.5 (17.0)	

***
 $p < 0.001$;

*
 $p < 0.05$

Higher scores indicate **less** impairment

Table 5

Symptom Comparison from the DePaul Symptom Questionnaire

	Four Item Empiric <i>n</i> = 475	SEID <i>n</i> = 239	
Symptom	M (SD)	M (SD)	Sig.
Fatigue	83.6 (13.1)	73.7 (17.9)	***
Post-exertional malaise			
Dead, heavy feeling after starting to exercise	79.9 (22.4)	64.3 (28.7)	***
Next-day soreness after non-strenuous activities	78.2 (19.5)	66.0 (24.9)	***
Mentally tired after slightest effort	71.5 (22.5)	53.2 (25.2)	***
Minimum exercise makes you tired	82.9 (18.1)	68.7 (25.5)	***
Physically drained / sick after mild activity	80.8 (16.5)	61.5 (28.7)	***
Sleep			
Unrefreshing sleep	86.6 (14.9)	75.8 (21.2)	***
Need to nap during each day	60.5 (31.3)	53.2 (32.8)	**
Problems falling asleep	63.1 (31.3)	55.4 (31.8)	**
Problems staying asleep	62.7 (30.5)	53.9 (31.3)	**
Waking up early in the morning	49.3 (33.1)	39.6 (32.2)	***
Sleeping all day / staying awake all night	20.2 (28.3)	12.6 (23.9)	**
Pain			
Muscle pain	70.5 (25.9)	60.0 (27.8)	***
Pain in multiple joints	63.5 (31.1)	52.6 (32.4)	***
Eye pain	37.5 (29.1)	28.3 (27.0)	***
Chest pain	29.7 (25.6)	24.7 (22.8)	*
Bloating	48.8 (29.5)	40.5 (27.8)	***
Abdomen / stomach pain	45.1 (29.3)	37.7 (29.4)	**
Headaches	53.7 (27.5)	50.3 (25.1)	
Neurocognitive			
Muscle twitches	36.4 (26.7)	26.2 (24.1)	***
Muscle weakness	70.5 (24.0)	55.7 (28.0)	***
Sensitivity to noise	67.5 (27.4)	55.2 (28.0)	***
Sensitivity to bright lights	63.8 (28.3)	48.8 (27.1)	***
Problems remembering things	76.2 (20.1)	58.9 (24.1)	***
Difficulty paying attention for long periods of time	77.2 (20.4)	60.3 (26.5)	***
Difficulty expressing thoughts	74.4 (16.5)	46.4 (25.5)	***
Difficulty understanding things	56.5 (24.8)	39.5 (24.6)	***
Can only focus on one thing at a time	72.2 (25.1)	56.0 (28.6)	***
Unable to focus vision / attention	52.5 (26.3)	35.3 (24.9)	***
Loss of depth perception	28.5 (32.2)	18.9 (27.2)	***
Slowness of thought	66.0 (22.4)	48.0 (25.4)	***
Absent-mindedness	68.4 (24.8)	51.7 (26.4)	***
Autonomic			

	Four Item Empiric <i>n</i> = 475	SEID <i>n</i> = 239	
Symptom	M (SD)	M (SD)	Sig.
Bladder problems	35.6 (35.0)	25.3 (30.4)	***
Irritable bowel problems	54.2 (32.9)	42.3 (32.2)	***
Nausea	38.8 (27.8)	31.0 (24.0)	***
Feeling unsteady on feet	46.4 (27.4)	34.8 (25.1)	***
Shortness of breath	44.3 (28.9)	35.4 (27.2)	***
Dizziness / fainting	45.1 (27.3)	34.7 (25.3)	***
Irregular heart beats	34.5 (27.9)	30.3 (25.4)	
Neuroendocrine			
Losing / gaining weight without trying	45.1 (36.3)	33.9 (33.2)	***
No appetite	27.7 (26.8)	21.4 (25.3)	**
Sweating hands	17.8 (26.4)	12.2 (22.7)	**
Night sweats	39.5 (31.1)	31.7 (29.6)	**
Cold limbs	55.1 (31.6)	48.5 (29.9)	*
Chills / shivers	42.9 (30.1)	35.1 (27.7)	**
Feeling hot / cold for no reason	40.9 (32.9)	45.3 (28.1)	***
Feeling like you have a high temperature	41.1 (33.0)	30.6 (26.8)	***
Feeling like you have a low temperature	31.2 (31.0)	25.1 (25.7)	*
Alcohol intolerance	42.9 (39.5)	38.9 (36.4)	
Immune			
Sore throat	40.0 (27.1)	36.2 (24.7)	
Tender lymph nodes	41.4 (29.7)	37.3 (28.9)	
Fever	21.6 (24.7)	15.6 (22.6)	**
Flu-like symptoms	59.5 (26.8)	46.8 (27.2)	***
Sensitivity to smells/foods/medications/chemicals	50.2 (36.0)	43.0 (36.2)	*

*
 $p < 0.05$

**
 $p < 0.01$

***
 $p < 0.001$

Higher scores indicate **more** impairment, and scores range from 0–100.