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Myalgic encephalomyelitis and chronic fatigue syndrome case definitions: effects of requiring a substantial reduction in functioning

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Abstract

Background: Current case definitions for myalgic encephalomyelitis (ME) and chronic fatigue syndrome (CFS) require an individual to report a ‘substantial reduction’ in activity levels, when compared to premorbid functioning. However, little guidance is provided on how to measure these reductions, as well as what level of reduction should be deemed ‘substantial,’ leading to inconsistencies in how this criterion is applied across research settings.

Purpose: The current study examined the influence of substantial reduction criterion on case definitions.

Method: The current study analyzed an international convenience sample of 1002 individuals with ME or CFS, 53 healthy controls, and 260 controls with other chronic illnesses.

Results: Findings indicated that the utility of the substantial reduction criterion varied by case definition, with more stringent case definitions not needing this criterion to identify cases.

Conclusion: These results suggest that the requirement of a substantial reduction in functioning may be redundant when case definitions specify that individuals must endorse a set of core symptoms at specified frequency and severity levels.

Keywords

Myalgic encephalomyelitis; chronic fatigue syndrome; case definitions; substantial reduction; functional impairment

Myalgic encephalomyelitis (ME) and chronic fatigue syndrome (CFS) are characterized by debilitating fatigue, severe exhaustion after mental or physical exertion, sleep dysfunction, and cognitive impairment [1]. Since 1988, multiple case definitions have been developed with varying diagnostic criteria [1–4]. Most ME and CFS case definitions require that

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individuals demonstrate a substantial reduction in activity level or functioning, although the wording of this criterion varies.

The Fukuda et al. CFS criteria [3], one of the most widely applied CFS case definitions, requires that fatigue, ‘results in substantial reduction in previous levels of occupational, educational, social, or personal activities’ [3,p.956]. Similarly, the Canadian ME/CFS criteria [4] require, ‘fatigue that substantially reduces activity level’ [4,p.11]. The first criterion of the recently developed Institute of Medicine [1] clinical criteria states, ‘A substantial reduction or impairment in the ability to engage in pre-illness levels of occupational, educational, social, or personal activities.’

Despite the ubiquity of the ‘substantial reduction’ criterion, case definitions provide limited guidance on how to measure activity reductions and, importantly, what level of reduction should be deemed, ‘substantial.’ Variation in the application of this criterion may lead to diagnostic inconsistencies and heterogeneous research samples, perpetuating challenges in replicating findings across research settings. A recent study demonstrated that individuals’ perceptions of activity reductions are subjective to the individual and can vary by age [5].

Researchers have explored various instruments’ ability to validly and reliably measure reductions in functioning [6,7]. A number of studies have proposed using the Medical Outcomes Study 36-Item Short Form Health Questionnaire (SF-36) to operationalize this criterion among individuals with ME and CFS [8]. The SF-36 is a self-report measure that assesses an individual’s current mental and physical functioning. The instrument consists of eight subscales: Physical Functioning, Role Physical, Bodily Pain, General Health Functioning, Social Functioning, Role Emotional, Vitality, and Mental Health Functioning. Lower scores are indicative of greater disability [8].

Reeves and colleagues [6] utilized the SF-36 to operationalize substantial reductions in functioning; they specified that patients must score at or below the 25th percentile of the general population on at least one of the following subscales: Physical Functioning, Role Physical, Social Functioning, or Role Emotional. The selection of the Role Emotional subscale was criticized, as researchers demonstrated that a majority of individuals with Major Depressive Disorder (MDD) would meet the empiric disability criterion, decreasing diagnostic specificity [9]. In further support of this critique, Jason and colleagues [9] applied ROC analysis to the SF-36 scores of individuals with ME or CFS and healthy controls; the Role-Emotional subscale had the lowest sensitivity and specificity out of all of the subscales.

Subsequent studies sought to identify which SF-36 subscales would best measure substantial reductions in functioning. Jason and colleagues [10] further examined the SF-36 subscale scores of individuals with CFS and healthy controls who were recruited through a community-based study and a tertiary care setting. ROC curve analysis suggested that the Vitality, Social Functioning, and Role Physical subscales evidenced the highest sensitivity and specificity across both samples, indicating that these subscales best differentiated patients from healthy controls. As a result of these findings, Jason and colleagues [10] recommended that individuals should meet the ‘substantial reduction’ criterion if they

scored score at or below empirically-identified cut-off points on two of three subscales: Vitality (≤ 35), Role-Physical (≤ 50), or Social Functioning (≤ 62.5).

To further validate the use of these subscales, Schafer and colleagues [11] examined the relationship between the SF-36 subscale scores of individuals with ME or CFS and their reports of current and pre-illness hours spent on occupational, social, and household activities [11]. Results suggested that past and current hours of occupational activity were positively associated with the SF-36 subscale scores. These findings suggest that current functioning, as measured by the SF-36, is indicative of both current and past occupational functioning; however, this study did not explicitly measure reductions in activity.

To address this limitation, a study conducted by Thorpe and colleagues [12] compared patients' pre-illness functioning to current SF-36 functioning. Results suggested that assessing patients' current levels of functioning (as measured by the SF-36) was comparable to assessing reductions in function. However, this study noted that participants' accounts of pre-illness activity level were subject to recall bias [12]. As ME and CFS are often accompanied by cognitive impairment, this limitation is important to consider in interpreting findings.

While several researchers have attempted to specify measurement rules for assessing substantial reductions in functioning, no study has explicitly examined the diagnostic utility of this criterion. Its inclusion in case definitions may have been inspired by psychiatric literature, as diagnostic criteria for other chronic medical illnesses do not include criteria related to activity reductions from premorbid functioning [e.g. 13–16]. In contrast, this requirement has been included in psychiatric diagnostic criteria within the Diagnostic and Statistical Manual of Mental Disorders (DSM), in versions that predate the first ME and CFS case definitions (e.g. the DSM-III-R) [17]. In the latest version of the manual, the DSM-5 [18], the following phrase is included as a diagnostic criterion for numerous disorders: 'symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.' As individuals with ME and CFS often report experiences during which others suggest that their symptoms are psychological [19], using a criterion associated with psychiatric diagnoses could perpetuate their experiences of stigma.

The 'substantial reduction in functioning' criterion, while present in most ME and CFS case definitions, has several limitations: measurement guidelines have not been defined; recall bias will affect patients' reports, particularly those with cognitive impairment or longer illness durations; and the criterion may be rooted in psychiatric diagnoses and further experiences of stigma. Due to these limitations, the current study aimed to examine the diagnostic utility of requiring a substantial reduction in functioning.

Method

Participants

Data were aggregated from participants at five research settings. All participants completed a written, informed consent process, and study procedures were approved by institutional

review boards. Each site's procedures are described below, followed by a summary of the full, combined sample.

Chronic illness sample—Individuals diagnosed with ME or CFS, lupus, multiple sclerosis (MS), post-polio syndrome (PPS), gulf war illness (GWI), HIV/AIDS, or cancer were recruited through national foundations, support groups, research forms, and social media platforms. Individuals who were 18 years or older, had access to the internet, and could read and write in English were eligible to participate. All study measures were completed online. Individuals with chronic illnesses (other than ME or CFS) were included in this study's 'Ill Control' group; those with ME or CFS were included in the ME/CFS group.

Solve ME/CFS Initiative BioBank sample—Individuals with a physician-confirmed diagnosis of ME or CFS were referred to the Solve ME/CFS Initiative. The initiative collects clinical and medical information on individuals diagnosed with ME or CFS. Participants had to be 18 years or older to be eligible to participate in the study. Questionnaires were administered online. Upon arrival, participants completed a paper consent form and answered study measures on computer or paper. Additionally, this site recruited healthy individuals to complete study measures; these individuals were included in this study's 'Healthy Control' group.

Newcastle sample—Primary care physicians referred individuals with suspected diagnoses of CFS to experienced physicians at the Newcastle-upon-Tyne Royal Victoria Infirmary clinic. Individuals needed to be 18 years of age or older, capable of providing a comprehensive medical history, and willing to undergo a comprehensive physical exam in order to participate.

Norway sample 1—Individuals with a physician-confirmed diagnosis of CFS were invited to participate in a randomized CFS self-management trial program. Participants (18 years of age or older) were recruited through brochures posted in CFS patient groups, education programs, and physician referrals. Participants completed study measures upon arrival to the program.

Norway sample 2—Individuals with ME or CFS were recruited from an outpatient CFS center and inpatient medical ward for the severely ill. Participants were eligible if they were between the ages of 18 and 65 years old and capable of reading and writing in Norwegian. Participants completed study measures and underwent a full medical and psychiatric review to rule out any exclusionary conditions that could explain their fatigue.

Combined sample—In summary, this study analyzed data from 1002 individuals with ME or CFS, 260 Ill Controls, and 53 healthy controls. Demographic information for each of these groups is provided in Table 1.

Measures

Depaul Symptom Questionnaire (DSQ)—The DSQ is a self-report measure that includes questions related to demographics, symptomatology, health history, and

functioning. The questionnaire assesses the frequency and severity of 54 symptoms of ME and CFS. Participants rate the frequency and severity of each symptom on 5-point Likert scales. The frequency scale ranges from 0 (*none of the time*) to 4 (*all of the time*); the severity scale ranges from 0 (*symptom not present*) to 4 (*very severe*). The DSQ has demonstrated good test-retest reliability [20], construct validity [21], and the ability to differentiate individuals with ME and CFS from healthy controls and individuals with other chronic illnesses [e.g. 22,23]. The DSQ can also be used to determine whether participants meet criteria for various ME and CFS case definitions. Detailed descriptions of the DSQ and its case definition algorithms can be found in Jason and Sunnquist [24]. The DSQ is freely available on REDCap [25]: <https://redcap.is.depaul.edu/surveys/?s=QQufxrgRFN>.

Medical outcomes study-short form-36 (SF-36)—The SF-36 is a self-report measure consisting of eight subscales which assess an individual's overall current functioning. Subscale scores range from 0 to 100, with lower scores indicating worse functioning. The present study used the three subscales (Role-Physical, Social Functioning, and Vitality) recommended by Jason and colleagues [10] to measure substantial reductions in functioning for case definition fulfillment. The SF-36 has demonstrated good internal consistency and discriminant validity among subscales [26], as well as strong internal reliability and convergent validity among ME and CFS samples [27].

Case definitions

Responses to study measures were utilized to determine which participants fulfilled three commonly-used case definitions: the Fukuda et al. [3] CFS criteria, the Canadian ME/CFS criteria [4], and the Institute of Medicine [5] criteria. Detailed scoring rules are provided in Jason and Sunnquist [24], and the symptoms required by each case definition are summarized below. All of the following case definitions require participants to report a substantial reduction in functioning. The Jason et al. [10] criteria were utilized to assess this criterion; participants needed to meet two of the following SF-36 criteria: Vitality 35, Role-Physical 50, or Social Functioning 62.5.

Fukuda et al. CFS [3]—To meet this case definition, participants must report six or more months of fatigue and four of the following symptoms: post-exertional malaise, memory or concentration problems, headaches, unrefreshing sleep, muscle pain, joint pain, sore throat, or tender lymph nodes.

Canadian ME/CFS [4]—Participants must report six or more months of fatigue, post-exertional malaise, sleep dysfunction, pain, neurocognitive impairment (at least 2 symptoms), and symptoms from at least two of the following domains: autonomic, neuroendocrine, or immune.

Institute of Medicine [1]—Participants needed to report post-exertional malaise, unrefreshing sleep, and either cognitive impairment or orthostatic intolerance. Symptoms must be present for six or more months.

Results

Demographic Comparison

Table 1 displays the demographic characteristics of the ME/CFS group, Ill Control group, and Healthy Control group. Although these groups are not directly compared in subsequent analyses, their demographic differences were statistically examined in order to allow for robust characterizations of each group. The ME/CFS group was somewhat younger than the other two groups [Welch's $F(2,129.6) = 18.83, p < 0.001$], although the difference in mean ages across all groups was fewer than seven years. The Healthy Control group had a slightly lower proportion of females [66%, compared to 81%]; $\chi^2(2,1) = 8.34, p = 0.02$. All groups were predominantly white, but the Ill Control group included slightly more participants who identified as another race [Fisher's exact statistic = 13.97, $p = 0.01$]. The Healthy Control group included fewer individuals without a college degree [Fisher's exact statistic = 93.77, $p < 0.001$]. Finally, as would be expected, the ME/CFS and Ill Control groups had a higher percentage of participants who were on disability [56% and 21%, respectively, compared to 0%; $\chi^2(8,1) = 232.87, p < 0.001$].

Functional status

The percentage of participants in the ME/CFS, Ill Control, and Healthy Control groups who met the substantial reduction criterion (as defined by Jason and colleagues in 2011) was calculated. Almost all participants (97.7%) in the ME/CFS group met this criterion, as did the majority (80.9%) of the Ill Control group. A minority (13.2%) of the Healthy Control group met this requirement.

Case definition fulfillment

Table 2 displays the percent of participants who met the Fukuda et al. [3] CFS criteria, the Canadian ME/CFS criteria [4] and the Institute of Medicine [1] criteria. Case definition fulfillment was calculated in two ways: (1) as the case definitions were written, requiring a substantial reduction in functioning, and (2) eliminating the substantial reduction requirement (i.e. the case definition criteria were altered such that participants were not required to endorse a substantial reduction in functioning).

The majority of the ME/CFS group met the Fukuda et al. CFS criteria, regardless of whether a substantial reduction in functioning was required. However, removing the substantial reduction requirement increased the percentage of Ill Control and Healthy Control participants who met this case definition. When the substantial reduction criterion was required, 72.7% of Ill Controls met the Fukuda et al. CFS criteria; when a substantial reduction was not required, 91.5% of Ill Controls met the Fukuda et al. CFS criteria. Similarly, the percentage of Healthy Controls who met the Fukuda et al. CFS criteria increased from 5.7% to 24.5% when participants were not required to have a substantial reduction in functioning.

In contrast, across all groups, the percentage of participants who met the Canadian ME/CFS and Institute of Medicine criteria remained relatively stable when the substantial reduction

requirement was eliminated. An additional 0.3% to 6.5% of participants met criteria when a substantial reduction in functioning was not required.

Discussion

Research has highlighted the complexity in understanding and measuring substantial reductions in functioning among individuals with ME and CFS [6,10–11]. Specifically, little guidance is provided on how to measure reductions in functioning, and on how to determine whether a reduction is ‘substantial.’ Furthermore, this criterion is subject to recall bias, particularly among individuals with cognitive impairment (a common ME and CFS symptom) and longer illness durations. Finally, this type of criterion is not utilized to diagnose other chronic medical conditions, and this concept appears to have been derived from psychiatric literature, further contributing to stigma against patients. Due to these significant concerns, the present study evaluated the utility of this criterion by examining the impact of its removal from three commonly-used case definitions.

In analyzing participants’ fulfillment of the Fukuda et al. [3] criteria, a small increase in the percentage of participants with ME or CFS who met criteria was observed when the substantial reduction requirement was removed. However, the removal of this criterion resulted in a substantial increase in the percentage of Ill Controls and Healthy Controls who fulfilled this case definition. This large increase would suggest that the substantial reduction criterion improves this case definition’s diagnostic specificity, as the Fukuda et al. [3] CFS criteria include several symptoms may be more commonly experienced by the general population. Furthermore, this case definition’s criteria are polythetic, such that participants’ symptom presentations could vary widely; this method of diagnosis has shown in past studies to be problematic in diagnosing individuals with ME and CFS [9].

However, the Canadian ME/CFS [4] and Institute of Medicine [1] criteria were less affected by the elimination of the substantial reduction requirement. Results indicated that the elimination of the substantial reduction criterion led to minor increases in the percentage of participants in all three groups who met criteria. This finding suggests that the substantial reduction criterion does not significantly improve diagnostic specificity when utilizing these two case definitions, and requiring a reduction in functioning may be redundant when case definitions require specific, cardinal symptoms of ME and CFS that would inherently be debilitating.

Diagnostic criteria for other medical illnesses with similar symptomatology to ME and CFS do not require individuals to show reductions in activity; instead, criteria emphasize objective, biological measures unique to each illness. For example, when diagnosing multiple sclerosis, physicians use magnetic resonance imaging (MRI) to identify lesions [15]. When diagnosing lupus, physicians run blood tests to assess for antinuclear antibodies and look for other clinical signs, such as oral ulcers and serositis [14]. If patients present a number of clinical signs and have positive blood tests, they fulfill case definition criteria.

The current study has several limitations. To achieve a large sample, data from multiple research settings were collected and aggregated; however, each setting utilized different

recruitment methods and procedures, resulting in a heterogeneous sample; however, findings may be more generalizable to the overall patient population. Similarly, the Ill Control group includes individuals with several different chronic illnesses; while this sample is also heterogeneous, the purpose of this group was to assess diagnostic specificity, so homogeneity within this group was not imperative. Finally, there were several demographic differences among the ME/CFS, Ill Control, and Healthy Control group. However, only within-group comparisons were examined for the purposes of this study.

Standard, consistently operationalized case definitions are imperative to furthering research on ME and CFS. Examining the purpose and utility of each criterion can assist in refining and improving diagnostic processes. Given the ambiguous nature of the substantial reduction criterion, as well as its potentially stigmatizing association with psychiatric diagnosis, future research should continue to evaluate this criterion's inclusion in case definitions, as results of this study suggest that the criterion is redundant when case definitions require specific, cardinal symptoms of ME and CFS.

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Table 1.

Demographic information by group.

	ME/CFS <i>n</i> = 1002		III Controls <i>n</i> = 260		Healthy Controls <i>n</i> = 53		
	<i>M</i>	(<i>SD</i>)	<i>M</i>	(<i>SD</i>)	<i>M</i>	(<i>SD</i>)	Sig.
Age	51.8	(13.1)	58.2	(15.8)	56.1	(13.0)	***
	%	(<i>n</i>)	%	(<i>n</i>)	%	(<i>n</i>)	Sig.
Gender							
Male	18.6	(183)	19.4	(48)	34.0	(18)	*
Female	81.4	(802)	80.6	(199)	66.0	(35)	
Race							
White	98.3	(967)	93.8	(243)	100.0	(52)	**
Other Race	1.7	(17)	6.2	(16)	0.0	(0)	
Education Level							
High School or Less	36.1	(353)	30.4	(79)	11.3	(6)	***
College Degree	48.3	(472)	33.5	(87)	88.7	(47)	
Graduate Degree	15.6	(153)	36.2	(94)	0.0	(0)	
Work Status							
On Disability	55.7	(546)	21.2	(55)	0.0	(0)	***
Working	18.8	(184)	37.3	(97)	66.7	(34)	
Retired	11.4	(112)	35.0	(91)	27.5	(14)	
Unemployed	9.1	(89)	2.7	(7)	0.0	(0)	
Student/Homemaker	5.1	(50)	3.8	(10)	5.9	(3)	

*
p < 0.05;**
p < 0.01;***
p < 0.001.

Table 2.

Case definition fulfillment (with and without the substantial reduction criterion).

Measurement method	ME/CFS		III Controls		Healthy Controls	
	%	(n)	%	(n)	%	(n)
Fukuda et al. [3]						
Substantial Reduction Required	94.9	(952)	72.7	(189)	5.7	(3)
Substantial Reduction <u>Not</u> Required	98.0	(983)	91.5	(238)	24.5	(13)
Canadian ME/CFS (2003)						
Substantial Reduction Required	71.7	(719)	34.2	(89)	5.7	(3)
Substantial Reduction <u>Not</u> Required	72.0	(722)	35.8	(93)	9.4	(5)
Institute of Medicine [1]						
Substantial Reduction Required	86.8	(871)	41.2	(107)	3.8	(2)
Substantial Reduction <u>Not</u> Required	87.8	(881)	47.7	(124)	5.7	(3)

Note: Valid percentages are displayed (i.e. denominator is less than the total sample size), as a small percentage of participants did not respond to certain items.