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A reexamination of the cognitive behavioral model of chronic fatigue syndrome

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Abstract

Objective—The cognitive behavioral model of chronic fatigue syndrome (CFS) suggests that cognitions and reduced activity level perpetuate the fatigue and impairment that individuals with CFS experience. The two empirical evaluations of this model resulted in conflicting findings. The current study examines the influence of case definition fulfillment on the applicability of this model to CFS.

Method—A moderated mediation analysis was conducted on 990 individuals with CFS to reexamine the behavioral pathway of this model. Case definition fulfillment was entered as a moderator.

Results—Findings were generally inconsistent with the cognitive behavioral model of CFS. Case definition fulfillment significantly moderated the relation between activity level and physical impairment ($\beta = -0.08$, $p = 0.03$); individuals who met more stringent case definitions demonstrated a weaker relation between activity level and impairment.

Conclusions—This model may not accurately represent the experience of individuals with CFS, particularly those who fulfill more stringent case definitions.

Keywords

case definition; chronic fatigue syndrome; cognitive behavioral model; graded exercise; myalgic encephalomyelitis

1 Introduction

Chronic fatigue syndrome (CFS) is an enervating illness characterized by symptoms such as post-exertional malaise, unrefreshing sleep, cognitive dysfunction, and fatigue (Fukuda et al., 1994). Various names and case definitions have been used to describe constellations of these symptoms, including myalgic encephalomyelitis (ME; Carruthers et al., 2011; Ramsay, 1988), ME/CFS (Carruthers et al., 2003), CFS (Fukuda et al., 1994; Sharpe et al., 1991), and systemic exertion intolerance disease (SEID; Institute of Medicine, 2015). Unfortunately, these case definitions select different groups of individuals (e.g., Brown, Jason, Evans, & Flores, 2013; Jason, Brown, Evans, Sunnquist, & Newton, 2013; Johnston et al., 2014), and

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the same case definitions are applied inconsistently across research settings (McManimen, Jason, & Williams, 2015). Perhaps due to heterogeneity in the diagnostic process, neither biological markers nor curative treatments have yet been discovered.

Although no curative treatments exist, researchers have developed and investigated several rehabilitative strategies that attempt to attenuate the illness's impact (Chambers, Bagnall, Hempel, & Forbes, 2006). One such strategy, cognitive behavioral therapy (CBT), was suggested under the presumption that thoughts and behaviors perpetuate fatigue and other illness symptoms through a purported deconditioning process, regardless of the original cause of the illness (Wessely, Butler, Chalder, & David, 1991). Specifically, this therapeutic technique attempts to counteract cognitions related to activity avoidance while gradually increasing an individual's level of activity (Wessely, David, Butler, & Chalder, 1989).

In recognition of the need for data-driven research to support the cognitive theory of CFS, Vercoulen and colleagues (1998) sought to empirically develop a model that explains the role of cognitive and behavioral factors in perpetuating fatigue. The study applied structural equation modeling (SEM) to 51 individuals with CFS. An initial model examined relationships among the following variables: causal attribution (i.e., how strongly an individual believes in a physical or psychological cause for his or her illness), sense of control over symptoms, depression, physical activity, impairment, and fatigue. The model was subsequently adjusted three times until adequate fit statistics were obtained. The final model indicated that causal attribution was associated with fatigue and impairment via activity level; focusing on symptoms was directly related to fatigue and impairment; and sense of control over symptoms was directly associated with fatigue (see Figure 1). Though these results appear to coalesce with the cognitive behavioral framework, the study's limitations warrant further scrutiny.

Since the publication of this study, several more stringent and specific case definitions have been developed. The Vercoulen et al. (1998) study utilized the Oxford CFS case definition (Sharpe et al., 1991) as inclusion criteria; this case definition requires the presence of unexplained fatigue of six or more months' duration. A community-based prevalence study (Jason et al., 1999) indicated chronic fatigue (i.e., fatigue that has persisted for six or more months) was reported by 2.7% to 4.1% of the population. However, thorough medical and psychiatric examinations revealed that over half of individuals with chronic fatigue had psychiatric or medical reasons (other than CFS) for their fatigue; just 0.42% of the population met the Fukuda et al. (1994) criteria for CFS. In addition to chronic fatigue, the Fukuda et al. (1994) criteria require a substantial reduction in functioning and four of the following eight symptoms: post-exertional malaise, unrefreshing sleep, memory or concentration difficulties, headaches, joint pain, muscle pain, sore throat, or tender lymph nodes. Further, medical and psychiatric diagnoses that could explain fatigue must be ruled out before a diagnosis can be made. The Oxford criteria (Sharpe et al., 1991) may select a heterogeneous group of individuals, and some of these individuals may have chronic fatigue for reasons other than CFS. Given the potential heterogeneity of the sample examined in the Vercoulen et al. (1998) study, further research is needed to determine whether its cognitive behavioral model displays adequate fit for individuals who meet more stringent CFS case definitions.

In addition, the Vercoulen et al. (1998) study's sample size may have been too small for SEM. Though no firm sample size guidelines exist for SEM, some literature recommends an absolute minimum of 100 cases (Kline, 2011), and evidence from simulated data indicates that a higher sample size to parameter ratio is associated with more accurate fit statistics (Jackson, 2003). The Vercoulen et al. (1998) study applied SEM to a sample of 51 individuals. Although the article did not explicitly state whether error covariances were estimated, the final model consisted of at least six parameters, or approximately 8.5 cases per parameter. This ratio is lower than ideal (Kline, 2011); thus, the model may lack robustness.

Finally, the Vercoulen et al. (1998) study stated that utilizing SEM allowed the relationships in the final model to be interpreted as causal. In describing the final model, the articles states, "*Attributing complaints to a somatic cause produced low levels of physical activity, which in turn had a causal effect on fatigue severity.*" Though SEM could be used as a tool to demonstrate causality in a highly controlled, prospective, longitudinal experimental design, the Vercoulen et al. (1998) study does not demonstrate three requisite tenets of causality: temporal precedence of cause from effect, covariance of cause and effect variables, and rejection of all plausible alternative causes for the effect (Shadish, Cook, & Campbell, 2002).

Given these limitations, a subsequent investigation (Song & Jason, 2005) utilized a community-based sample to further examine the Vercoulen et al. (1998) model of CFS. This follow-up study assessed the model's fit for six groups: individuals who met the Fukuda et al. (1994) CFS criteria, individuals with chronic fatigue from psychiatric disorders (e.g., depression with melancholic features), individuals with chronic fatigue from medical conditions (e.g., untreated hypothyroidism), individuals with chronic fatigue from a substance use disorder, individuals with unexplained chronic fatigue who did not fulfill the Fukuda et al. (1994) CFS criteria, and healthy control participants. To ensure accurate diagnostic classification, participants received a medical and psychological evaluation and were diagnosed by a panel of physicians. Results indicated that the Vercoulen et al. (1998) model displayed adequate fit for the group of individuals with chronic fatigue due to psychiatric reasons; however, model fit statistics for the remaining five groups were inadequate. These findings suggest that the CFS case definition applied by the Vercoulen et al. (1998) study may have captured individuals with chronic fatigue due to psychiatric illness. As cognitive therapy was originally developed to treat psychiatric disorders (Beck, 1997), individuals with a primary psychiatric diagnosis may experience the associations among cognitions, behaviors, and fatigue illustrated in the Vercoulen et al. (1998) model. However, like the Vercoulen et al. (1998) study, the groups analyzed in the Song and Jason (2005) study included fewer than 50 participants, so these results may not be generalizable.

As the two extant data-driven studies of the cognitive behavioral model of CFS reported discrepant results, the current study seeks to reexamine the Vercoulen et al. (1998) model using a sample of 990 individuals with CFS and determine whether case definition fulfillment influences results. This study will specifically investigate the model's "behavioral pathway": causal attribution's relation to activity level and activity level's relation to fatigue and impairment (see Figure 1). This pathway is used as justification for the prescription of

graded exercise therapy (GET) to individuals with CFS (Bavinton, Darbishire, & White, 2004). The current study hypothesizes that: (1) consistent with the Song and Jason (2005) study, casual attribution of illness will not be significantly associated to activity level or impairment; (2) activity level and impairment will correlate with one another, such that individuals with lower levels of activity will report greater impairment, and; (3) case definition fulfillment will moderate the relation between activity level and impairment, such that individuals who meet the Canadian Clinical ME/CFS case definition (Carruthers et al., 2003) or the ME Ramsay case definition (Jason et al., 2012) will have a weaker association between activity level and impairment than individuals who meet the less stringent Oxford CFS criteria (Sharpe et al., 1991).

2 Method

2.1 Research participants

This study examined a sample of individuals with ME or CFS who were recruited from five settings. All sites obtained ethics board approval, and all participants completed a written, informed consent process. Participants subsequently completed self-report questionnaires that assessed their symptomatology, medical and psychiatric history, and impairment. Each sample is described in Table 1, and sample-specific demographics are presented in Table 2. The resulting data allowed researchers to determine whether participants met criteria for three ME and CFS case definitions and to conduct the analyses described above.

2.1.1 Sample comparison—The DePaul University and BioBank samples were significantly older than all other samples, and the Newcastle sample was significantly younger ($F[4, 1042] = 56.82, p < 0.001$). Additionally, the DePaul University and Solve ME/CFS Initiative BioBank samples had a higher proportion of participants with college or graduate degrees ($\chi^2[4, n = 1,041] = 60.47, p < 0.001$). A larger proportion of the Norway 1 and Norway 2 samples were on disability ($\chi^2[20, n = 1,048] = 212.32, p < 0.001$), while a larger proportion of the Newcastle sample was working. Due to these differences, sample source was entered as a covariate in all subsequent analyses.

2.2 Materials

2.2.1 DePaul symptom questionnaire—The DePaul symptom questionnaire (DSQ) collects information on demographics, ME/CFS symptomatology, illness history, and functioning in personal, social, and work domains. The current study utilized data from the DSQ to measure causal attribution of illness, activity level, and case definition fulfillment.

To assess illness attribution, participants selected what they believed to be the cause of their problems with fatigue or energy from the following options: definitely physical, mainly physical, equally physical or psychological, mainly psychological, or definitely psychological. This item has evidenced strong test-retest reliability, with 92% agreement between at test and retest time points, $K = 0.76, p < 0.001$ (Jason, So, Brown, Sunnquist, & Evans, 2015). To evaluate activity level, participants reported the average number of hours per week they spent on household, social, family, and work related activities over the past

month. These items have also demonstrated strong test-retest reliability, $r = 0.70 - 0.93$, $p < 0.01$ (Jason, So, et al., 2015).

To assess for case definition fulfillment, DSQ symptom ratings were used. The DSQ contains items that measure the frequency and severity of 54 ME and CFS symptoms over the past six months (e.g., fatigue, sore throat, difficulty expressing thoughts, etc.). Symptom frequency is measured on a five-point Likert Scale ranging from 0 (*none of the time*) to 4 (*all of the time*). Likewise, symptom severity is measured on a five-point Likert Scale ranging from 0 (*symptoms not present*) to 4 (*very severe*). These frequency and severity ratings are used to determine whether participants fulfill the following case definitions: Oxford CFS (Sharpe et al., 1991), Canadian Clinical ME/CFS (Carruthers et al., 2003), and ME Ramsay (Jason et al., 2012). Criteria are described in more detail below. DSQ symptom ratings have evidenced adequate test-retest reliability, $r = 0.40-0.96$, $p < 0.05$ (Jason, So, et al., 2015), and strong internal consistency reliability (Brown & Jason, 2014).

2.2.2 Medical outcomes study 36-Item short form health questionnaire—The short form health questionnaire (SF-36) is a measure of physical and mental functioning given current health status. The current study utilized the Physical Functioning subscale to measure impairment. Items on this subscale ask participants to rate how much their health limits them in a variety of physical activities on a three-point scale: yes, limited a lot; yes, limited a little; no, not limited at all. Activity prompts range from dressing oneself to engaging in vigorous activities, such as running. Responses are aggregated to obtain a composite score that ranges from 0 to 100. Lower physical functioning scores indicate that current health is impeding an individual's ability to engage in these physical tasks. Three additional subscales, Role Physical, Social Functioning, and Vitality, were utilized to operationalize the “substantial reduction” criterion of the case definitions described below. The SF-36 has shown strong internal consistency for individuals with a variety of health conditions (McHorney, Ware, Lu, & Sherbourne, 1994). Furthermore, the Physical Functioning subscale can accurately differentiate individuals with chronic illness from those with severe psychiatric conditions, and its scores correlate with the severity of various physical illnesses (McHorney, Ware, & Raczek, 1993).

2.3 Case definitions

This study examined three case definitions: the Oxford criteria (Sharpe et al., 1991), the Canadian ME/CFS criteria (Carruthers et al., 2003), and the ME Ramsay criteria (conceptualized by: Dowsett, Ramsay, McCartney, & Bell, 1990; Goudsmit, Shepherd, Dancey, & Howes, 2009; Ramsay, 1988; operationalized by Jason et al., 2012). The Oxford criteria were selected for further analysis due to their application in the original Vercoulen et al. (1998) study. The Canadian ME/CFS criteria were selected due to recommendations to the US Department of Health and Human Services by the CFS Advisory Committee (Chronic Fatigue Syndrome Advisory Committee, 2015). Finally, the ME Ramsay criteria were selected, as prior research has demonstrated that these criteria select a smaller, more impaired group of individuals than other case definitions (Jason et al., 2012). Table 3 specifies how each case definition was operationalized using participants' DSQ and SF-36 data.

2.3.1 Case definition classification—As these case definitions are not mutually exclusive, individuals may meet more than one case definition. Guidelines from past research (Jason et al., 2013; Jason, Evans, Brown, Sunnquist, & Newton, 2015) were used to create four independent groups: all individuals who fulfilled the ME Ramsay criteria ($n = 224$) were included in the “ME” group; individuals who met the Canadian Clinical ME/CFS criteria but did not meet the ME Ramsay criteria comprised the “ME/CFS” group ($n = 474$); individuals who met the Oxford CFS criteria ($n = 242$) who did not meet the other two case definitions constituted the “CFS” group; individuals who met none of these three case definitions were included in the “No Case Definition” group ($n = 131$).

2.4 Statistical analyses

2.4.1 Moderated mediation—Moderated mediation, also termed conditional process analysis (Hayes, 2013), allows for the simultaneous investigation of factors that explain why an independent variable is associated with a dependent variable (mediation) and factors that alter the strength of the mediation pathway (moderators). The current study employed the PROCESS macro for SPSS (Hayes, 2012) to analyze second-stage conditional process models. The PROCESS macro generates regression coefficients, standard errors, confidence intervals, and significance levels for each model pathway. The conditional process model examined activity level as a mediator of illness attribution's association with impairment; case definition fulfillment was examined as a moderator of the association between activity level and impairment. Sample source was entered as a covariate.

3 Results

3.1 Preliminary analyses

After excluding participants with significant amounts of missing data ($n = 67$) or responses considered outliers (2.2 times the interquartile range, $n = 14$), 990 individuals remained in the sample for analysis. Little's missing completely at random (MCAR) test was not significant, $\chi^2(2) = 3.92$, $p = 0.14$, indicating that multiple imputation was an appropriate method to replace the remaining missing values (Schafer, 1999). As no variable was missing data for more than 5% of cases, it is unlikely that multiple imputations would significantly bias results (Schafer, 1999). Five sets of imputed data were calculated; analysis parameters presented below are the averaged parameters from the five imputed datasets (Schafer, 1999). Assumptions of linearity, homoscedasticity, and normality were met. An examination of scatterplots for each pair of continuous variables indicated that data were linearly related. Scatterplots of regression-predicted values by residuals indicated that data were homoscedastic. Skewness and kurtosis values were all within an absolute value of two, indicating that data were relatively normal.

3.2 Moderated mediation analysis

As hypothesized, causal attribution did not significantly predict activity level ($\beta = 1.48$, $t[2, 987] = 1.75$, $p = 0.08$); thus, activity level did not mediate the relation between causal attribution and impairment. Contrary to the study's hypothesis, causal attribution predicted impairment ($\beta = 5.22$, $t[5, 984] = 5.22$, $p < 0.001$), such that individuals who reported a physical illness etiology were more physically impaired than those who reported some

psychological etiology. As hypothesized, activity level was significantly related to impairment ($\beta = 0.64$, $t[5, 984] = 8.61$, $p < 0.001$), and case definition fulfillment moderated the relation between activity level and impairment ($\beta = -0.08$, $t[5, 984] = -2.15$, $p = 0.03$), such that individuals who met more stringent case definitions evidenced a weaker (though still significant) relation between activity level and impairment. Coefficients and significant levels for the full model are displayed in Figure 2. Figure 3 displays a graphical representation of the moderating influence of case definition fulfillment on the relation between activity level and impairment. Table 4 displays the means and standard deviations of activity level and impairment by case definition group.

4 Discussion

Results of the moderated mediation analysis were consistent with several of the study's hypotheses. Findings suggest that there is not a significant relation between perceptions about illness etiology and activity level among individuals with ME and CFS. Activity level was associated with impairment; however, the relation between activity level and impairment was moderated by case definition fulfillment. When individuals met more stringent case definitions, the relation between activity level and impairment was weaker. In other words, activity level is least predictive of impairment for individuals who meet more stringent case definitions and are likely the most symptomatic and physically impaired (Jason et al., 2013; Jason et al., 2015). The deconditioning hypothesis would predict a consistent relationship between activity level and impairment, regardless of case definition fulfillment or symptom severity (Wessely et al., 1991). The significant moderation effect of case definition fulfillment suggests that the most impaired individuals are overexerting themselves compared to what would be predicted by the deconditioning hypothesis. Among severely impaired individuals, this overexertion may result from the need to complete basic activities of daily living (e.g., personal hygiene tasks, preparing meals, etc.) or respond to illness demands (e.g., attending medical appointments). In addition to providing evidence against the deconditioning hypothesis, this moderation effect may partially explain the discrepant findings of the Vercoulen et al. (1998) and Song and Jason (2005) studies. As the Vercoulen et al. (1998) study included individuals who met a less stringent case definition than that applied by the Song and Jason (2005) study, the former study was more likely to find a significant relation between activity level and impairment.

Though activity level and impairment were significantly correlated, this result may simply demonstrate that these represent indicators of illness severity, as opposed to implying that activity reductions cause individuals' impairment. In order to establish causality, researchers would need to demonstrate covariance between cause (i.e., activity level) and effect variables (i.e., impairment and fatigue). Proving covariance (i.e., changes in activity level lead to changes in impairment and fatigue), requires an experimental design. Neither the Vercoulen et al. (1998) nor the current study utilized an experimental design; thus, conceptualizing these variables as indicators of a latent construct may be more methodologically appropriate, as individuals with greater illness severity likely have lower activity level, greater impairment, and more severe fatigue. Individuals who grapple with debilitating illnesses are less able to engage in activity and experience more severe symptomatology. Cross-sectional studies of individuals who have had ME and CFS for many years cannot statistically or

methodologically justify claims that reduced activity levels cause greater impairment and symptom severity.

One of the current study's hypotheses was unsupported. Contrary to prediction, causal attribution was associated with impairment; individuals who attributed their illness to physical causes reported greater impairment than those who attributed their illness to both physical and psychological factors. Though not originally hypothesized, this finding suggests that individuals hold valid perceptions related to factors that contribute to their symptoms. The measure of impairment utilized in this study assessed only physical impairment. Individuals who attributed some of their illness to psychological causes may have evidenced greater mental health or emotional impairment.

The current study added to previous literature in that it analyzed a large sample of 990 individuals with ME and CFS, examined the influence of case definition, and utilized variables that were assessed in the correct temporal order; however, several limitations may have impacted its results. This study relied upon self-report data; although the study's measures have evidenced strong psychometric properties, future research could utilize objective measures of activity and physical impairment. Additionally, participants were recruited from different sites and through different recruitment strategies; however, sample source was entered as a covariate to control for its potential effects. While these differences led to a heterogeneous sample, physicians continue to report uncertainty about the diagnostic process for ME and CFS (Chew-Graham, Dowrick, Wearden, Richardson, & Peters, 2010); therefore, a heterogeneous sample may be more representative of the variability present among individuals given a diagnosis of ME and CFS, and the study's results may be more generalizable to the broader population of patients. Despite the large, heterogeneous sample, too few participants reported that their illness derived from "definitely psychological" or "mainly psychological" causes to allow for analysis of these categories. As recent reports have implicated a physical illness etiology (e.g., Institute of Medicine, 2015), fewer individuals may attribute their illness to a psychological cause. A final important limitation of the current study was its lack of experimental design. A prospective, experimental study that collects pre-illness data and systematically requests post-illness activity alterations would allow for a more robust examination of the cognitive behavioral model of CFS; however, if cost or time constraints preclude this type of experimental design in future research, the results of the current study suggest that investigators should document and utilize the most updated, stringent case definitions.

Despite the current study's limitations, its results have implications for the treatment and management of ME and CFS. This study, along with the Song and Jason (2005) study, was another attempt to replicate the Vercoulen et al. (1998) model, and both replication attempts were inconsistent with the original model. Findings suggest that individuals' activity level is unrelated to perceptions about illness etiology. These results are inconsistent with cognitive behavioral theories of CFS that presume that individuals' symptoms stem from deconditioning and maladaptive illness beliefs. The current study indicates that caution should be exercised when prescribing treatments, such as CBT or GET, that presume a relation among illness beliefs, activity, and impairment, particularly when working with individuals who fulfill more stringent case definitions for ME and CFS. A recent meta-

analysis of CBT treatments found a null effect (Smith et al., 2015), and investigators are now contesting the results of the largest GET intervention study to date (Marks, 2017), with some suggesting that GET interventions may be harmful to individuals with ME and CFS (e.g., Kindlon, 2017). In contrast to GET strategies, energy envelope and pacing interventions encourage individuals with ME and CFS to monitor their level of available energy to avoid over- and under-exertion (Jason et al., 2013). A review of energy envelope studies suggested that these interventions have resulted in modest gains in physical functioning (Jason et al., 2013); however, these treatments are not curative, and future research should continue to search for effective treatments for ME and CFS.

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Figure 1.

The Vercoulen et al. (1998) cognitive behavioral model of CFS. Darker boxes represent what this study refers to as the “behavioral pathway”

Figure 2. Moderated mediation analysis of predictors of impairment (controlling for sample source)

Figure 3. Moderating influence of case definition fulfillment on the relation between activity and impairment

Table 1

Sample characteristics

	DePaul	BioBank	Newcastle	Norway 1	Norway 2
# Participants	216	515	100	176	64
Recruitment Sources	<ul style="list-style-type: none"> • ME and CFS support groups • Online patient forums • Past research participants 	<ul style="list-style-type: none"> • Physician referrals • Solve ME/CFS Initiative website and social media account 	<ul style="list-style-type: none"> • Physician referral 	<ul style="list-style-type: none"> • Physician referral • Patient organizations • Oslo University Hospital website • Waitlist of a patient education program 	<ul style="list-style-type: none"> • Inpatient medical ward for severely ill individuals with ME and CFS • Multidisciplinary ME and CFS clinic
Participation Requirements	<ul style="list-style-type: none"> • 18 years or older • Current diagnosis of ME or CFS (self-reported) • Able to read/write in English 	<ul style="list-style-type: none"> • 18 years or older • Physician-confirmed diagnosis of ME or CFS(confirmed by specialists in ME and CFS) • Able to read/write in English 	<ul style="list-style-type: none"> • 18 years or older • Able to attend comprehensive medical/psychiatric exam at the Newcastle-upon-Tyne Royal Victoria Infirmary clinic • Able to read/write in English 	<ul style="list-style-type: none"> • 18 years or older • Physician-confirmed diagnosis of ME or CFS • Able to attend a CFS self-management program(study measures were completed prior to the start of this program) 	<ul style="list-style-type: none"> • Between 18 and 65 years old • Able to participate in comprehensive medical and psychiatric examinations

Table 2

Demographics by sample

	DePaul		BioBank		Newcastle		Norway 1		Norway 2	
	M(SD)		M(SD)		M(SD)		M(SD)		M(SD)	
Age	52(11.3)		54(12.5)		46(13.9)		44(11.9)		35(11.9)	
	% (n)		% (n)		% (n)		% (n)		% (n)	
Gender										
Female	84(182)		77(385)		81(81)		86(151)		81(52)	
Male	16(34)		23(113)		19(19)		14(24)		19(12)	
Race										
White	98(211)		98(484)		99(99)		99(175)		98(61)	
Asian/Pacific Islander	0(1)		0(1)		0(0)		1(1)		2(1)	
African-American	0(0)		0(2)		0(0)		0(0)		0(0)	
American Indian	0(0)		0(1)		0(0)		0(0)		0(0)	
Other	2(4)		2(7)		1(1)		0(0)		0(0)	
Hispanic/Latino Origin										
No	98(207)		97(501)		98(92)		100(176)		100(62)	
Yes	2(4)		3(14)		2(2)		0(0)		0(0)	
Work Status										
On disability	57(123)		46(225)		31(30)		90(159)		94(60)	
Retired	12(25)		14(71)		18(18)		2(4)		0(0)	
Unemployed	11(24)		15(75)		5(5)		1(1)		0(0)	
Working part-time	8(17)		–		22(22)		2(4)		3(2)	
Working full-time	6(12)		–		14(14)		2(3)		2(1)	
Working (unspecified)	–		21(104)		–		–		–	
Homemaker	4(9)		2(11)		1(1)		1(2)		0(0)	
Student	3(6)		2(9)		8(8)		2(3)		2(1)	
Education Level										
Less than high school	0(0)		1(6)		12(11)		8(14)		17(11)	
High school degree	25(54)		29(144)		39(36)		42(73)		45(29)	

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	DePaul	BioBank	Newcastle	Norway 1	Norway 2
	M(SD)	M(SD)	M(SD)	M(SD)	M(SD)
College degree	34(74)	70(346)	29(27)	40(70)	25(16)
Graduate degree	40(87)	–	20(19)	10(17)	13(8)

Table 3
Case definition criteria

	Oxford CFS Sharpe et al. (1991)	Canadian ME/CFS Carruthers et al. (2003)	ME Ramsay Jason et al. (2012)
Inclusion Criteria ¹	<ul style="list-style-type: none"> 6+ months of fatigue 	<ul style="list-style-type: none"> 6+ months of fatigue Substantial reduction in functioning (assessed via the SF-36, per Jason et al., 2011) At least 1 symptom from all of the following areas: <ul style="list-style-type: none"> Post-exertional malaise Sleep problems Pain At least 2 neurocognitive symptoms At least 1 symptom from 2 of the following areas: <ul style="list-style-type: none"> Autonomic Neuroendocrine Immune 	<ul style="list-style-type: none"> Sudden illness onset (<= 1 week) Post-exertional malaise At least 1 neurocognitive symptom At least 1 autonomic symptom
Exclusion Criteria	<ul style="list-style-type: none"> Medical or psychological conditions that could explain fatigue² 	<ul style="list-style-type: none"> Medical or psychological conditions that could explain fatigue² Morbid obesity² Lifelong fatigue³ 	<ul style="list-style-type: none"> Medical or psychological conditions that could explain fatigue² Morbid obesity²

Notes.

¹To meet criteria, all symptoms must be present at least half of the time and of at least moderate severity (i.e., ratings of 2 or greater on the following DePaul Symptom Questionnaire scales): Frequency: 0 = symptom not present; 1, a little of the time; 2, about half of the time; 3, most of the time; 4, all of the time Severity: 0, symptom not present; 1, mild; 2, moderate; 3, severe; 4, very severe

²To operationalize these conditions, guidelines from Reeves et al. (2003) were applied.

³To operationalize lifelong fatigue, guidelines from Sunnquist, Jason, Brown, Evans, and Berman (2015) were applied.

Table 4
Activity and impairment by case definition group

	Activity		Impairment	
	<i>M</i>	<i>(SD)</i>	<i>M</i>	<i>(SD)</i>
No Case Definition	29.23	<i>(19.85)</i>	48.80	<i>(27.99)</i>
Oxford CFS	25.34	<i>(18.49)</i>	43.31	<i>(23.56)</i>
Canadian ME/CFS	19.50	<i>(16.17)</i>	33.76	<i>(20.92)</i>
ME Ramsay	19.89	<i>(15.99)</i>	31.80	<i>(21.41)</i>