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A Reexamination of the Cognitive Behavioral Model of Chronic Fatigue Syndrome: Investigating the Cogency of the Model's Behavioral Pathway

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A Reexamination of the Cognitive Behavioral Model of Chronic Fatigue Syndrome: Investigating the Cogency of the Model's Behavioral Pathway

A Thesis Presented in Partial Fulfillment of the Requirements for the Degree of Master of Arts

By

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Biography

The author was born in Belleville, Illinois, on January 9, 1986. She received her Bachelor of Science degree from Indiana University in 2008 and is currently enrolled in the Clinical-Community Psychology doctoral program at DePaul University.

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Abstract

Cognitive behavioral theories of chronic fatigue syndrome (CFS) assert that cognitions and behaviors perpetuate the fatigue and impairment that individuals with CFS experience (Wessely, Butler, Chalder, & David, 1991). Vercoulen and colleagues (1998) utilized structural equation modeling to empirically develop a cognitive behavioral model of CFS. The resulting model indicated that attributing symptoms to a physical cause, focusing on symptoms, and feeling less control over symptoms were associated with increased fatigue. Additionally, individuals who attributed symptoms to a physical cause reported lower activity levels and more fatigue and impairment. However, in an attempt to replicate this model, Song and Jason (2005) demonstrated that the model displayed inadequate fit statistics for a well-characterized group of individuals with CFS; the model resulted in appropriate fit for individuals with chronic fatigue from psychiatric conditions. Despite uncertainty surrounding the model's validity, it continues to be cited to support the application of cognitive behavioral and graded exercise therapies to individuals with CFS (White et al., 2011). The current study utilized second-stage conditional process modeling (i.e., moderated mediation) to reexamine the behavioral pathway of the Vercoulen et al. (1998) model. This pathway is characterized by the association among causal attribution for symptoms, activity level, and fatigue and impairment. The use of a large sample allowed for a robust examination of the pathway, and moderators isolated potential factors that contributed to previous studies' discrepant results. Findings were generally inconsistent with the Vercoulen et al. (1998) model. Results

indicated that individuals did not reduce their activity level due to illness beliefs. Although activity level and impairment were significantly correlated, this correlation decreased as case definition stringency increased. Furthermore, a canonical correlation analysis demonstrated that activity level, impairment, and fatigue could be conceptualized as indicators of illness severity. Rather than implicating activity level as the cause of fatigue and impairment, the relation among these variables may be due to their shared association with the latent construct of illness severity. This study represents the second attempt to replicate the Vercoulen et al. (1998) model; neither the Song and Jason (2005) nor the current study resulted in findings consistent with the original model. As this model provides the theoretical foundation for cognitive behavioral and graded exercise treatments for ME and CFS, these failed replication attempts support patient-expressed concerns about the appropriateness and efficacy of these treatments.

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; Ramsay, 1988; Carruthers et al., 2011; Jason, Kot, et al., 2015), ME/CFS (Carruthers et al., 2003), CFS (Sharpe et al., 1991; Fukuda et al., 1994), 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; Jason, Sunnquist, Brown, Evans, & Newton, 2014; Johnston et al., 2014), and the same case definitions are applied inconsistently across research settings (McManimen, Jason, & Williams, 2015). Perhaps due to heterogeneity in the diagnostic process, no biological markers nor curative treatments have yet been discovered.

While 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).

To build upon this CBT literature, Surawy, Hackmann, Hawton, and Sharpe (1995) aggregated clinical observations of individuals with medically-unexplained chronic fatigue to develop a cognitive theory of CFS. This cognitive theory proposes that the illness develops through a diathesis-stress mechanism, while cognitions and behaviors perpetuate symptoms over time. This theory deviates from previous CBT literature in that it implicates personality characteristics, psychological factors, and life stressors as precipitants to the development of CFS. The etiological component of this theory suggests that when achievement-focused individuals (i.e., the diathesis) are confronted with a stressor that precludes them from performing at an expected level (e.g., severe illness or emotional distress), they may attempt to push through exhaustion and eventually experience perpetual fatigue. This theory further proposes that once individuals have entered into a state of chronic fatigue, those who attribute their fatigue to a physical disease process will reduce their activity level to avoid exacerbating symptoms. Thus, the cognitive theory of CFS implicates inactivity and emotional distress in maintaining individuals' symptoms. The authors further propose a cyclical pathway of activity and activity avoidance. They describe individuals' periodic attempts to recommence premorbid activities; however, individuals face symptom exacerbation from these activities due to an ostensible deconditioning process from previous inactivity. The authors suggest that this symptom exacerbation further confirms individuals' beliefs that activity should be avoided

(Surawy et al., 1995). While this article was the first to propose a theoretical framework to support the application of CBT to individuals with CFS, its conclusions were based solely on clinical observations of individuals with chronic fatigue. A valid interpretation of these observations would require a controlled, empirical research study of individuals who meet stringent case definitions for CFS or ME.

Development of the Cognitive Behavioral Model of CFS

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 two samples: 51 individuals with CFS and 50 individuals with Multiple Sclerosis (MS). MS was selected as a comparison illness due to its chronic nature and shared symptom of fatigue. An initial model for the CFS sample 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 for the CFS sample 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).

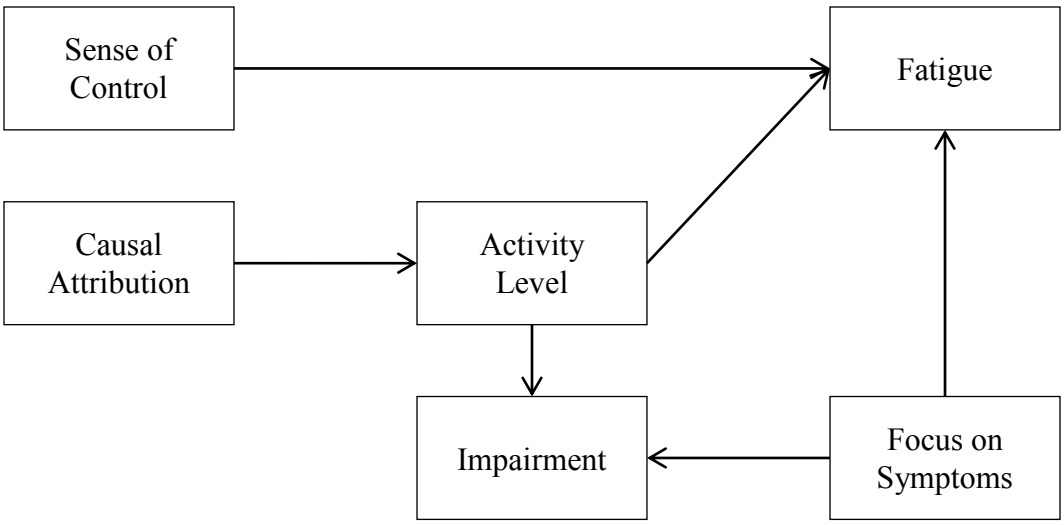


Figure 1. The Vercoulen et al. (1998) Cognitive Behavioral Model of CFS.

Specifically, individuals who attributed their illness to a physical cause had lower activity levels, and individuals with lower activity levels reported worse fatigue and impairment. Likewise, focusing on symptoms and feeling less control over symptoms were associated with more fatigue. When this model was applied to the sample of individuals with MS, fit statistics were inadequate. The final MS model indicated that disability status and sense of control over symptoms predicted activity level, and sense of control over symptoms was also associated with impairment via fatigue. The authors surmised that the final CFS model supported a cognitive behavioral theory of CFS, implicating cognitive (i.e., causal attribution, sense of control over symptoms, and focus on symptoms) and behavioral (i.e., activity level) factors in perpetuating fatigue and impairment. Though the results of the Vercoulen et al. (1998) study appear to coalesce with

the anecdotal observations reported in previous research, this study has several limitations that warrant further scrutiny.

Limitations of the Vercoulen et al. (1998) Study

Broad inclusion criteria. Vercoulen et al. (1998) utilized the Oxford CFS case definition (Sharpe et al., 1991) as inclusion criteria; this case definition simply 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. Thus, the Oxford criteria (Sharpe et al., 1991) likely select a heterogeneous group of individuals, and some of these individuals may have had 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.

Measurement selection. Low content validity of the Vercoulen et al. (1998) study's measures of impairment and activity level represent an additional design limitation. To operationalize the construct of impairment, the study utilized the two items from the Sickness Impact Profile questionnaire (Carter, Bobbitt, Bergner, Gilson, 1976) that comprise the Home Management subscale: *I have given up taking care of personal or household business affairs (e.g., paying bills, banking, working on budget)*; *I am doing less of the regular daily work around the house than I usually do*. While these items assess impairment in completing specific household tasks, they do not gauge the full range of impairment that individuals with chronic illness could experience. For example, some individuals who report reductions in household activities may also be completely bedbound, while others may be working full time and simply lack energy to complete household tasks. Likewise, individuals who report no reductions in household tasks could have a broad spectrum of physical abilities; some may be housebound, while others might avidly exercise. In other words, individuals with the same score on this measure of impairment could have vastly different physical capabilities. Moreover, household tasks represent just one potential area of impairment; individuals could also experience impairment in social, occupational, or cognitive functioning. Given these limitations, this measure appears to lack both sensitivity and specificity, as it does not represent a precise, nor comprehensive measure of impairment. A more valid measure of impairment might have resulted in different model pathways.

The study's measurement of activity level also lacked content validity. The Mobility subscale of the Sickness Impact Profile questionnaire (Carter et al., 1976) was used as one of two indicator variables for activity level. However, instead of assessing activity level, the two items that comprise this subscale appear closely related to the construct of impairment: *I stay in one room*; *I stop often when traveling because of health problems*. In fact, an earlier article by Vercoulen et al. (1996) proposed an assessment battery for individuals with CFS, and this Mobility subscale was recommended as a measure of impairment, not activity level. Measurement conflation of activity level and impairment may represent the true reason for their relation in the Vercoulen et al. (1998) model.

Sample size. In addition to these design limitations, the Vercoulen et al. (1998) study's sample size may have been too small for structural equation modeling (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 with CFS and 50 individuals with MS. While the article did not explicitly state whether error covariances were estimated, the final model consisted of at least 6 parameters, or approximately 8.5 cases per parameter. This ratio is lower than ideal (Kline, 2011); thus, the model may lack robustness.

Causal claims. 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).

Whether the study's exogenous variables temporally preceded its endogenous variables is not reported in the Vercoulen et al. (1998) study, though a previous study of the same samples (Vercoulen et al., 1996) indicated that all measures were collected over the same two-week time period. Daily data were collected for some of the measures; however, the Vercoulen et al. (1998) study did not specify whether data from specific days or composite scores were analyzed. If the measurement of variables implicated as "causal" (sense of control over symptoms, focus on symptoms, and causal attribution) did not occur prior to the measurement of the "effect" variables (i.e., activity level, fatigue, and impairment), then the temporal precedence requirement of causality was not met, and causal inferences cannot be made.

In addition to ambiguity surrounding the temporal order of variables analyzed in the Vercoulen et al. (1998) study, the study did not demonstrate covariance of cause and effect variables over time. Though significant associations were found (i.e., individuals who reported higher levels of activity

level also reported lower levels of fatigue), the cross-sectional nature of the study precluded the study from demonstrating that changes in exogenous variables led to changes in endogenous variables (i.e., increasing activity level leads to decreases in fatigue). In fact, a previous study of the same sample found that patient-reported fatigue, one of the outcome variables of the Vercoulen et al. (1998) model, remained relatively stable over the two-week period analyzed; on average, individuals' fatigue scores changed by 3% (Vercoulen et al., 1996). Because fatigue scores were relatively invariant over the data collection period, the Vercoulen et al. (1998) study could not have demonstrated that changes in activity level led to changes in fatigue; the study's model simply demonstrates a correlation between activity level and fatigue. This association could manifest from illness severity; individuals with a more severe illness would likely have lower activity levels and more fatigue.

Finally, the study did not control for other factors associated with its exogenous variables. As mentioned previously, activity level, fatigue, and impairment could be conceptualized as indirect measures of illness severity; this confound may have resulted in spurious correlations. As the Vercoulen et al. (1998) study design disallowed examination of controlled, temporal covariation of cause and effect variables, causal claims remain unsupported.

Replication Attempt of the Vercoulen et al. (1998) Model

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 lack generalizability.

Rationale

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, isolate factors that may explain divergent findings,

and remedy methodological limitations. 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 2).

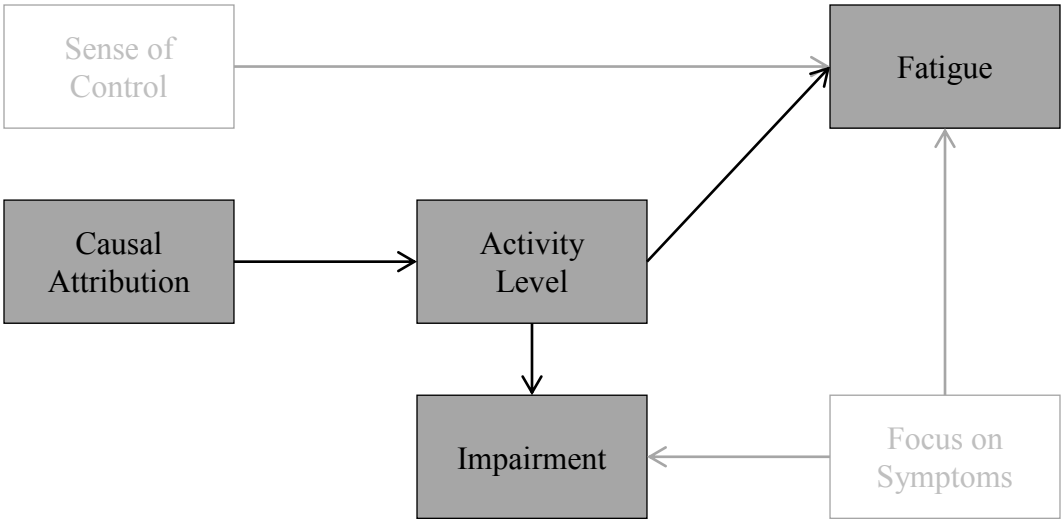


Figure 2. The "Behavioral Pathway" of the Vercoulen et al. (1998) model of CFS.

This pathway is used as justification for the prescription of Graded Exercise Therapy (GET) to individuals with CFS (Bavinton, Darbishire, & White, 2004). GET involves gradual, prearranged increases in activity, regardless of symptom severity, to combat the presumed deconditioning process delineated by the behavioral pathway (Bavinton, Darbishire, & White, 2004). Though the results of the Song and Jason (2005) study challenge the validity of the behavioral pathway, researchers and clinicians continue to explore GET as a treatment strategy for the illness (Chalder, Goldsmith, White, Sharpe, & Pickles, 2015;

White et al., 2011). However, other researchers assert that GET is ineffective and could amplify immunologic pathology in individuals with CFS (Twisk & Maes, 2008). Moreover, GET lacks constituent validity (Keys & Frank, 1987); in a recent survey of over 900 patients who had attempted GET, 64% reported that GET made their symptoms worse, while only 15% reported any improvement (ME Association, 2015). In an article summarizing the harms of GET and CBT treatment strategies, a patient was quoted as saying, "*Graded Exercise Therapy worsened me dramatically and I have no doubt had been a large factor in my being severely affected after 20 years.*" (Kindlon, 2011, p. 64) The current study will serve to further inform the debate regarding the appropriateness of GET for individuals with CFS.

Furthermore, this study seeks to isolate and examine potential reasons for the conflicting findings of the Vercoulen et al. (1998) and Song and Jason (2005) studies. Their discrepant results could have originated from three possible sources: a Type I error in the Vercoulen et al. (1998) study, a Type II error in the Song and Jason (2005) study, or the influence of moderators expressed through differences in study design and methodology. A Type I error occurs when a study identifies a significant effect when none truly exists (Glenberg & Andrzejewski, 2008). In structural equation modeling (SEM), the chance of a Type I error increases with each adjustment to the initially-proposed model (McCoach, Black, & O'Connell, 2007). The Vercoulen et al. (1998) study reported three adjustments to the initial model before the final model was derived; thus, it is possible that the final model pathways were specific to the sample data analyzed. An additional

replication attempt of this model will further assess the robustness of the behavioral pathway. In contrast to the possibility of a Type I error, the Song and Jason (2005) study could have been impacted by a Type II error. A Type II error occurs when a study fails to detect an effect due to lack of statistical power (Glenberg & Andrzejewski, 2008). Lack of power can result from low sample size, and both the Vercoulen et al. (1998) and Song and Jason (2005) studies reported sample size limitations. The current study will analyze a sample of 990 individuals with CFS, thus increasing statistical power to detect an effect.

As an alternate explanation for the studies' disparate findings, differences in study design implicate potential moderators that could have influenced the strength of the pathways identified in the Vercoulen et al. (1998) model. The current study will examine the influence of two potential moderators: case definition fulfillment and psychiatric diagnosis. Differences in inclusion criteria may partially explain the discrepant findings of the Vercoulen et al. (1998) and Song and Jason (2005) studies. The former applied the Oxford case definition for CFS (Sharpe et al., 1991) that simply requires six or more months of fatigue (i.e., chronic fatigue). As mentioned previously, over half of individuals who experience chronic fatigue have psychiatric or medical reasons (other than CFS) that explain their fatigue (Jason et al., 1999). As Song and Jason (2005) found that the Vercoulen et al. (1998) model displayed adequate fit only for individuals with chronic fatigue due to psychiatric reasons, the Vercoulen et al. (1998) study's broad inclusion criteria may have captured individuals with chronic fatigue due to psychiatric disorder.

Since the publication of the Vercoulen et al. (1998) study, researchers have developed several more stringent and specific case definitions for the illness, including the Canadian Clinical ME/CFS criteria (Carruthers et al., 2003) and the ME Ramsay criteria (Jason et al., 2012). The CFS Advisory Committee recommended the Canadian Clinical ME/CFS criteria as the standard for research studies (Chronic Fatigue Syndrome Advisory Committee, 2015). The ME Ramsay case definition was developed based on early clinical descriptions of the illness (Ramsay, 1988) and represents one of the most stringent case definitions for ME (Jason, Evans, et al., 2015). Individuals who meet the Oxford CFS criteria (Sharpe et al., 1991), used in the Vercoulen et al. (1998) study, may display different associations between activity and symptomatology than individuals who meet newer, more stringent case definitions. In addition to case definition fulfillment, history of psychiatric illness will be independently examined as a moderator. As Song and Jason (2005) analyzed individuals with fatigue due to a primary psychiatric disorder, assessing for a history of psychiatric disorder is not directly comparable to their methodology; however, investigating the impact of psychiatric history on model pathways may still generate information that contributes to explaining study discrepancies. An examination of the moderating influence of case definition fulfillment and psychiatric history will provide information on their role in the conflicting results of the Vercoulen et al. (1998) and Song and Jason (2005) studies.

To further explore the Vercoulen et al. (1998) model, the current investigation will incorporate novel research on symptomatology through

examining the role of post-exertional malaise in influencing variables in the behavioral pathway. Recent studies have identified post-exertional malaise as the pathognomonic symptom of CFS due to its accuracy in discriminating between patient and control groups (Institute of Medicine, 2015; Jason et al., 2014; Maes, Twisk & Johnson, 2012). Post-exertional malaise is described as an exacerbation of symptoms following physical or mental activity (Institute of Medicine, 2015). Its severity may explain activity reductions, fatigue, and impairment in a more parsimonious manner than causal attribution of symptoms. Specifically, patients with more severe post-exertional malaise may necessitate greater activity reductions and experience more fatigue and impairment.

In summary, the current study will assist in interpreting discrepant results from the two empirical studies of the cognitive behavioral model of CFS (Song & Jason, 2005; Vercoulen et al., 1998). An additional attempt to replicate the behavioral pathway of the Vercoulen et al. (1998) model will assess the pathway's robustness, and the study's large sample size will allow for more statistical power to detect significant relationships. To further isolate and identify factors that contributed to previous studies' conflicting results, case definition fulfillment and psychiatric history will be considered as moderators. This moderation analysis will evaluate whether case definition stringency and history of psychiatric diagnosis titrate the strength of the relations described in this behavioral pathway. Furthermore, the field's latest research will be reflected in the study's examination of the role of post-exertional malaise in impacting activity level, fatigue, and impairment. This evaluation of the behavioral pathway

of the Vercoulen et al. (1998) model will contribute to the field's ongoing discussion of the appropriateness and usefulness of CBT and GET for individuals with CFS. As individuals with CFS refute claims that these treatments lead to clinically significant improvements, findings from this study may further support their concerns and indicate that researchers and clinicians should shift their focus to developing new treatments.

Statement of Hypotheses

Hypothesis I. A moderated mediation analysis will examine the relation among causal attribution of illness, activity level, impairment, case definition fulfillment, and psychiatric diagnosis (see Figure 3). Hypothesized findings for each pathway follow.

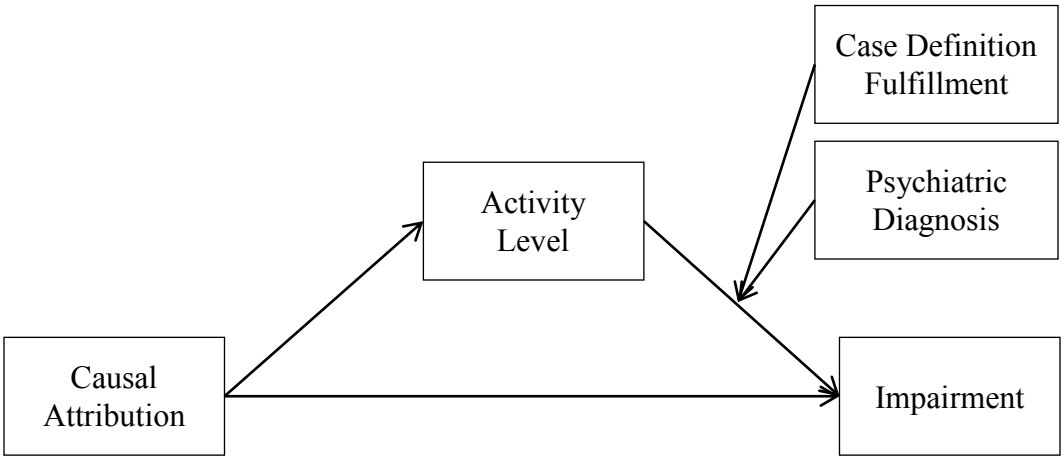


Figure 3. Hypothesis I: Moderated mediation model of the relation among causal attribution, activity level, and impairment.

Hypothesis Ia. Consistent with the Song and Jason (2005) study, casual attribution of illness will not be significantly associated to activity level or impairment.

Hypothesis Ib. Activity level and impairment will correlate with one another, such that individuals with lower levels of activity will report greater impairment.

Hypothesis Ic. Case definition fulfillment will moderate the relation between activity level and impairment. 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).

Hypothesis Id. History of psychiatric diagnosis will moderate the relation between activity level and impairment. Individuals without a history of major depressive disorder, an anxiety disorder, bipolar disorder, an eating disorder, a substance use disorder, or schizophrenia will demonstrate weaker associations between activity level and impairment than individuals with a history of psychiatric disorder.

Hypothesis II. A moderated mediation analysis will examine the relation among causal attribution of illness, activity level, fatigue, case definition fulfillment, and psychiatric diagnosis (see Figure 4). Hypothesized findings for each pathway follow.

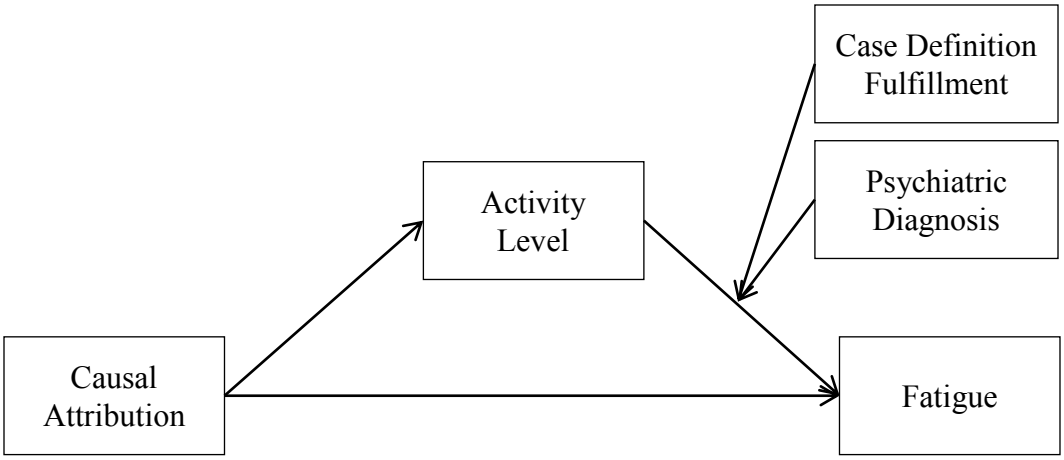


Figure 4. Hypothesis II: Moderated mediation model of the relation among causal attribution, activity level, and fatigue.

Hypothesis IIa. Consistent with the Song and Jason (2005) study, casual attribution of illness will not be significantly associated to activity level or fatigue.

Hypothesis IIb. Activity level and fatigue will significantly correlate with one another, such that individuals with lower levels of activity will report higher levels of fatigue.

Hypothesis IIc. Case definition fulfillment will moderate the relation between activity level and fatigue. 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 fatigue than individuals who meet the less stringent Oxford CFS criteria (Sharpe et al., 1991).

Hypothesis IId. History of psychiatric diagnosis will moderate the relation between activity level and fatigue. Individuals without a history of major

depressive disorder, an anxiety disorder, bipolar disorder, an eating disorder, a substance use disorder, or schizophrenia will demonstrate weaker associations between activity level and fatigue than individuals with a history of psychiatric disorder. Though psychiatric disorders that fully explain fatigue preclude a diagnosis of CFS, individuals can be diagnosed with CFS who have comorbid psychiatric disorders (that do not explain fatigue) or a history of fatiguing psychiatric disorders that did not coincide with CFS symptoms (Reeves et al., 2003).

Hypothesis III. A canonical correlation analysis will result in a significant correlation between post-exertional malaise and measures of illness severity (activity level, fatigue, and impairment), such that individuals who experience higher levels of post-exertional malaise will evidence lower activity levels, more severe fatigue, and greater impairment (see Figure 5).

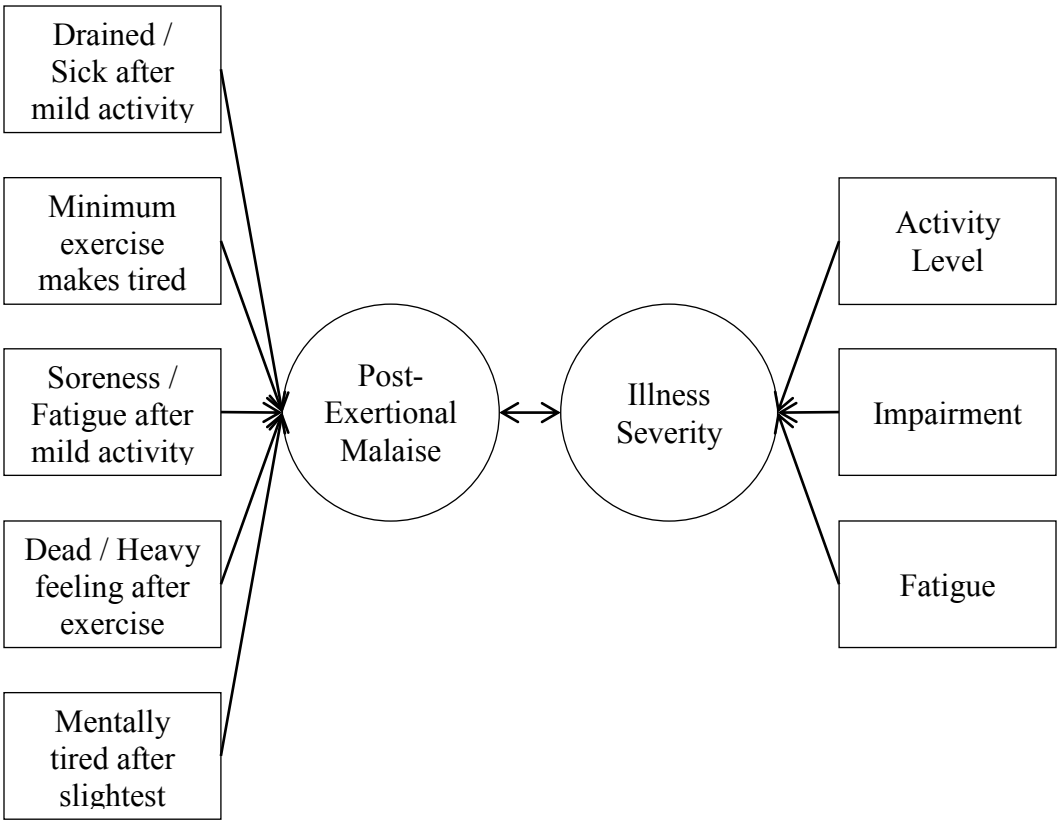


Figure 5. Hypothesis III: Canonical correlation of post-exertional malaise and illness severity variables.

Method

This study examined a sample of individuals with ME or CFS who were recruited from five settings. Participants completed self-report questionnaires that assessed their symptomatology, medical and psychiatric history, and impairment. 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.

Research Participants

DePaul sample. A total of 216 participants were enrolled in the DePaul sample. Most participants were female (84.2%) and identified as Caucasian (97.7%); one participant (0.5%) identified as Asian, and the remainder (1.9%) selected 'Other' when queried about race. The majority of the sample was on disability (57.2%), while 13.0% was working part-time or full-time. Regarding educational attainment, 40.2% of the sample had a graduate or professional degree; 34.6% had graduated from college; 18.2% had attended college for at least one year; and 7.0% had completed high school. The mean age of the sample was 52.0 years (SD = 11.3).

To be eligible for inclusion, participants needed to be 18 years or older and have a self-reported current diagnosis of myalgic encephalomyelitis (ME) or chronic fatigue syndrome (CFS). While 96.3% reported that they were diagnosed

by a medical doctor, participants were not asked to report the case definition that the physician used to diagnose them. Additionally, participants needed to be capable of reading and writing in English. Following approval from the DePaul University Institutional Review Board, participants were recruited through ME and CFS patient support groups and online patient forums; additionally, past DePaul research participants were contacted who had expressed interest in participating in future studies.

Through recruitment materials, participants were informed that their responses to study measures would be used to study ME and CFS case definitions and symptomatology. After providing consent, participants were given the option to complete study measures electronically, via hard copy, or over the phone. Approximately 94% of participants completed the electronic version of the questionnaires. Due to the unpredictable nature of illness symptoms, participants were not given a timeframe within which they must complete study measures; however, the first 100 participants to submit their questionnaires received $5.00 gift cards to Amazon.

Solve ME/CFS Initiative BioBank sample. Participants enrolled in the BioBank sample were required to be 18 years of age or older and have a diagnosis of ME or CFS from a licensed physician who specializes in the illness. Participants were recruited through physician referral, the Solve ME/CFS Initiative website, and the Solve ME/CFS Initiative social media accounts. The DePaul University research team submitted a research protocol to the organization to access the BioBank dataset; this protocol was reviewed and accepted. Upon

completion of study measures, participants' de-identified data was shared with the DePaul research team.

A total of 515 participants completed all study measures. The sample was 77% female and 23% male. The majority of participants were on disability (46%); 21% were working (the questionnaire for this sample did not have the option to specify part-time or full-time); and the remainder were unemployed (15%), retired (14%), students (2%), or homemakers (2%). Regarding educational attainment, 70% had a college degree or higher (this questionnaire did not have a "graduate degree" option), 29% had a high school degree or GED, and 1% had not completed high school. The mean age of this sample was 54.8 years (*SD* = 12.5).

Newcastle sample. Following referral due to a suspected diagnosis of CFS, participants who met eligibility criteria completed a written, informed consent process at the Newcastle-upon-Tyne Royal Victoria Infirmary clinic. Subsequently, they received a comprehensive medical examination by an experienced physician and completed study measures.

The Newcastle sample included 100 participants, of whom 99.0% were Caucasian and 1.0% were multiracial. The majority (81.0%) of participants were female. Of this sample, 30.6% of participants were on disability, while 36.7% of participants were working either part- or full-time; the remainder stated that they were students, homemakers, or retired. In reporting educational attainment, 11.9% had not completed high school; 14.0% held a high school degree; 24.7% had completed at least one year of college; 29.0% held a college degree; and 20.4%

held a graduate or professional degree. Participants' average age was 45.8 years (*SD* = 13.9).

Norway sample 1. Individuals who were diagnosed with CFS by a physician or medical specialist were invited to enroll in a randomized controlled trial of a CFS self-management program. Study brochures were distributed to healthcare professionals and patient organizations, and study announcements were posted on the Oslo University Hospital website. Participants who were on a waitlist for a patient education program were also invited to enroll. Recruitment occurred in four mid-sized towns in southern Norway, two suburbs of Oslo, and their surrounding communities. Individuals who expressed interest were given additional information over the telephone.

In addition to having a diagnosis of CFS, participants needed to be 18 years or older and physically able to attend the self-management program; they could not be pregnant. Participants completed a consent form that allowed the research team to contact their physician to confirm their CFS diagnosis. 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.

In total, 176 participants completed study measures. The majority were female (86.3%), and all but one participant was Caucasian (99.4%); the remaining participant selected 'Other' when asked about race. Most participants were on disability (83.5%); just 9.7% of participants were working. Regarding education, 9.8% of participants held a graduate or professional degree; 39.9% held a standard

college degree; 42.2% held high school degree; the remainder had not completed high school. Participants' mean age was 43.6 years (*SD* = 11.9).

Norway sample 2. Participants were recruited from two sources: an inpatient medical ward for severely ill patients and an outpatient, multidisciplinary clinic for ME and CFS. Participants were required to be between 18 and 65 years of age and capable of reading and writing in Norwegian. The project gained approval from the Privacy Ombudsman for research at Oslo University Hospital. Participants completed a written informed consent process. Experienced physicians conducted comprehensive medical history interviews and examinations to rule out other medical causes for the participants' symptoms, and a psychologist evaluated participants for psychological conditions that could explain their symptoms.

A total of 64 participants met eligibility requirements and completed study measures, and 81.3% of these participants were female. Most of the sample (95.2%) identified as Caucasian; 1.6% identified as Asian; and 3.2% selected 'Other' for their race. The majority of participants (76.6%) were on disability, while 18.8% stated that they held part- or full-time jobs. Regarding educational attainment, 12.5% reported a graduate or professional degree; 25.0% had a standard college degree; 45.3% had a high school degree; and 17.2% had not completed high school. Participants' average age was 35.3 years (*SD* = 11.9).

Combined sample. Table 1 summarizes the demographic characteristics of each individual sample and the combined sample. The DePaul 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 and 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 .

Table 1. 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)*
College degree	34 *(74)*	70 *(346)*	29 *(27)*	40 *(70)*	25 *(16)*
Graduate degree	40 *(87)*	-	20 *(19)*	10 *(17)*	13 *(8)*

Materials

DePaul Symptom Questionnaire (DSQ). The 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, fatigue, case definition fulfillment, post-exertional malaise, and history of psychiatric diagnosis.

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, 2014).

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 demonstrated strong test-retest reliability, $r = 0.70 – 0.93$, $p < 0.01$.

Participants also rated the level of fatigue they experienced the day prior on a continuous scale from 1 to 100, where 1 indicates *no fatigue* and 100 indicates *severe fatigue*. This item evidenced adequate test-retest reliability, $r = 0.71$, $p < 0.001$, indicating appropriate sensitivity to changes in daily fatigue over time.

To assess for case definition fulfillment and post-exertional malaise, 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 (*symptom 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. Additionally, five of these symptoms are used to assess post-exertional malaise: *physically drained or sick after mild activity, minimum exercise makes you physically tired, next day soreness or fatigue after mild activity, dead or heavy feeling after starting to exercise,* and *feeling mentally tired after the slightest effort*. For each of these symptoms, frequency and severity scores were multiplied by 25 and averaged to create one composite score per symptom. In an exploratory factor analysis that examined DSQ responses of individuals with CFS, these five symptoms loaded onto one factor, along with *fatigue*; this factor had a Cronbach's alpha of 0.95 (Jason, Sunnquist et al., 2015). Overall, DSQ symptoms have evidenced adequate test-retest reliability, $r = 0.40 – 0.96$, $p < 0.05$ (Jason et al., 2014), and strong internal consistency reliability (Brown & Jason, 2014).

Finally, participants were asked whether they had ever been diagnosed with one of the following psychological disorders: Major Depressive Disorder, Bipolar Disorder, Anxiety, Schizophrenia, Eating Disorder, or Substance Abuse.

Responses to these items have shown high test-retest agreement, $K = 0.76 – 0.92$, $p < 0.001$ (Jason, So, et al., 2014). Additionally, previous research demonstrated that individuals with CFS were more accurate in identifying lifetime mood or anxiety disorders than their physicians (Torres-Harding, Jason, Cane, Carrico, & Taylor).

Medical Outcomes Study 36-Item Short Form Health Questionnaire (SF-36). The SF-36 is a measure of physical and mental functioning given current health status. The questionnaire measures eight domains of functioning: physical functioning, role physical, bodily pain, general health, social functioning, vitality, role emotional, and mental health functioning. The current study utilized the physical functioning subscale to measure impairment. Items on the physical functioning subscale asked 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. 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).

Case Definitions

Oxford CFS case definition. To meet the Oxford CFS criteria (Sharpe et al., 1991), participants needed to report fatigue of at least moderate severity (2 or greater on the DSQ Likert scale) that has occurred at least half of the time (2 or greater on the Likert scale) over the past six months. Individuals with a medical condition that could explain fatigue or those with a current diagnosis of schizophrenia, bipolar disorder, substance use disorder, or eating disorder were precluded from meeting criteria.

Canadian Clinical ME/CFS case definition. The Canadian Clinical ME/CFS criteria (Carruthers et al., 2003) require a substantial reduction from premorbid functioning, six or more months of fatigue, and symptoms from at least six domains. To assess for substantial reduction in functioning, guidelines from previous research (Jason et al., 2011) are applied; a participant needed to meet two of the following three criteria: an SF-36 Role Physical score less than or equal to 50, an SF-36 Social Functioning score less than or equal to 62.5, or an SF-36 Vitality score less than or equal to 35. To meet the fatigue requirement, participants needed to report that they have experienced problems with fatigue or energy for six months or more. Additionally, participants must report symptoms of at least moderate severity (2 or greater on the DSQ Likert scale) that have occurred at least half of the time (2 or greater on the Likert scale) over the past six months from the following symptom domains: post-exertional malaise (at least one symptom), sleep dysfunction (at least one symptom), pain (at least one symptom), and neurocognitive dysfunction (at least two symptoms). Finally

participants needed to report at least one symptom of the same frequency and severity as above from two of the following three domains: autonomic dysfunction, neuroendocrine dysfunction, or immune dysfunction. Individuals with morbid obesity, lifelong fatigue, or medical or psychological conditions that could cause fatigue are precluded from meeting this case definition.

ME Ramsay case definition. Several physicians and researchers have published case definitions for ME based on the clinical descriptions of Melvin Ramsay (Ramsay, 1988; Dowsett, Ramsay, McCartney, & Bell, 1990; Goudsmit, Shepherd, Dancey, & Howes, 2009). More recently, Jason and colleagues (2012) published guidelines for operationalizing the work of these theorists; this operationalization requires a sudden illness onset, post-exertional malaise, neurological impairment, and autonomic dysfunction. Specifically, a participant must report that their illness began over the course of one week or less. Additionally, they must report one symptom of at least moderate severity (2 or greater on the DSQ Likert scale) that has occurred at least half of the time (2 or greater on the Likert scale) over the past six months from each of the following symptom domains: post-exertional malaise, neurological impairment, and autonomic dysfunction. Participants with morbid obesity or medical or psychiatric conditions that could explain fatigue are precluded from meeting criteria.

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, Sunnquist, Brown, Evans, & Newton, 2014; Jason, Evans, et al., 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).

Statistical Analyses

Assumptions. Prior to conducting the study's primary analyses, data were assessed to ensure that they met the analyses' assumptions: complete data, linearity, normality, and homoscedasticity (Hayes, 2013; Tabachnick & Fidell, 2013). Individuals without data for causal attribution of illness, at least three of the five post-exertional malaise variables or at least two of the four activity level variables were excluded, as it was deemed inappropriate to impute values when more than half of the indicator variables were missing. Subsequently, IBM SPSS Statistics version 23 was used to conduct Little's Missing Completely at Random (MCAR) test (Little, 1988) to determine the appropriateness of utilizing the multiple imputation method to replace missing values. To test for linearity, scatterplots of each pair of continuous variables were visually examined (Hayes, 2013). Though regression techniques are relatively robust to non-normality (Hayes, 2013), outliers were removed. Outliers were defined as data that exceeded 2.2 times the interquartile range (Hoaglin & Iglewicz, 1987). To assess for heteroscedasticity, scatterplots of regression-predicted values by residuals were

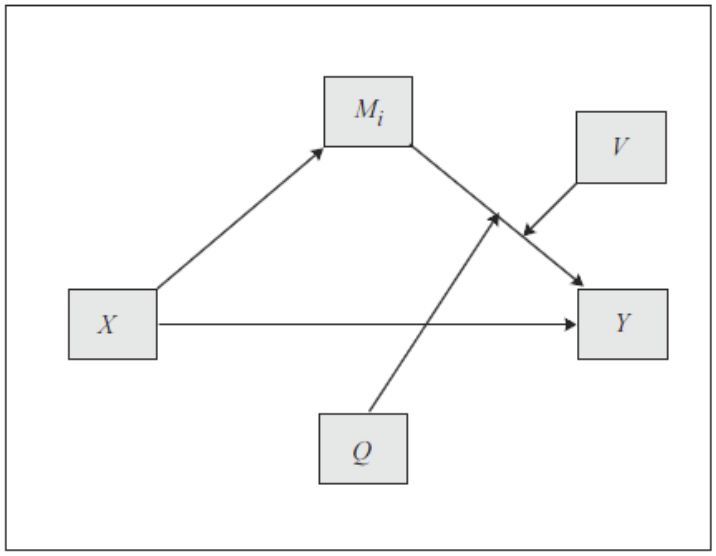
examined for each pair of continuous variables (Hayes, 2013): a regression of activity level on causal attribution, a regression of fatigue on activity level, and a regression of impairment on activity level.

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 (see Figure 6; Hayes, 2013). The PROCESS macro generates regression coefficients, standard errors, confidence intervals, and significance levels for each model pathway.

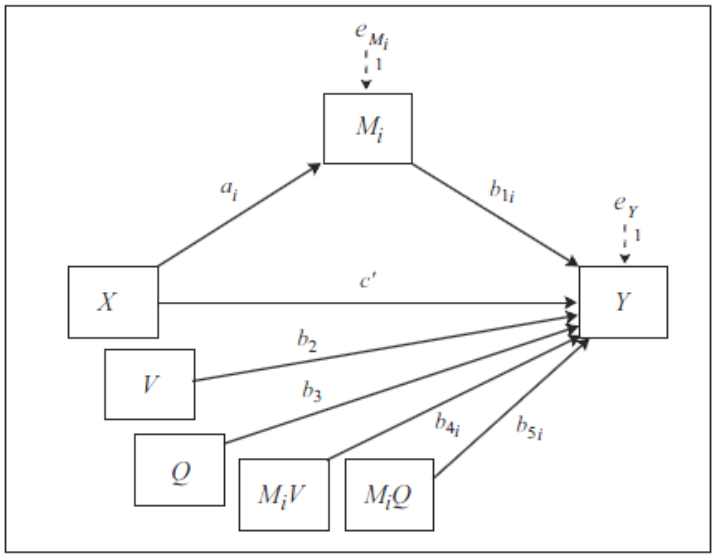
Model Templates for PROCESS for SPSS and SAS

Model 16

Conceptual Diagram



Statistical Diagram



Conditional indirect effect of X on Y through $M_i = a_i(b_{1i} + b_{4i}V + b_{5i}Q)$
Direct effect of X on $Y = c'$

Figure 6. Conceptual and statistical representations of second-stage conditional process modeling.

The first conditional process model examined activity level as a mediator of illness attribution's association with impairment; case definition fulfillment and psychiatric diagnosis were examined as moderators of the association between activity level and fatigue. The second conditional process model mimicked the first, but fatigue replaced impairment as the model's dependent variable. These analyses enabled the study to test each component of the Vercoulen et al. (1998) study's behavioral pathway while examining how case definition fulfillment and psychiatric diagnosis influenced the strength of the pathway from activity level to impairment and fatigue.

Canonical correlation. Canonical correlation allows for an examination of the relationship between two sets of variables (Tabachnick & Fidell, 2013). The five variables comprising post-exertional malaise were correlated with three variables that putatively indicated illness severity (activity level, fatigue, and impairment). IBM SPSS Statistics version 23 was utilized to assess the relationship between these two sets of variables and to examine the relationship of post-exertional malaise to activity level, fatigue, and impairment individually. This analysis allowed the study to examine the role of post-exertional malaise in influencing measures related to illness severity.

Results

Preliminary Analyses

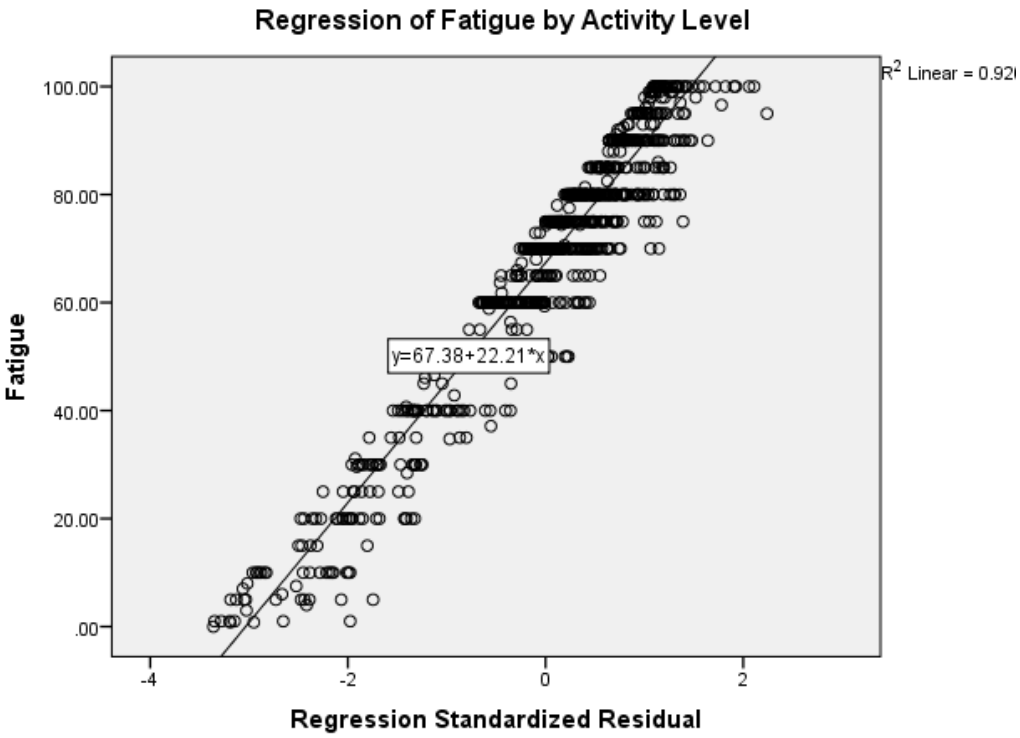
Outliers and Missing Data. Of the 1,071 participants, 14 had responses that were classified as outliers (13 reported 85.8 hours or more per week of household, family, social, and work activities; 1 reported frequency and severity

scores of 0 in response to the prompt, "*Minimum exercise makes me physically tired*"). As only 13 participants reported the cause of their illness to be "*Definitely psychological*" or "*Mainly psychological*," only participants who selected one of the remaining three levels could be analyzed: *Equally physical and psychological*; *Mainly physical*; *Definitely physical*. Twenty-seven participants did not report a causal attribution for their illness; six did not respond to at least three of the five post-exertional malaise items; and twenty-one did not respond to at least two of the four activity items. After excluding these participants with significant amounts of missing data, 990 individuals remained in the sample.

Little's Missing Completely at Random (MCAR) test was not significant for the variables included in the moderated mediation analyses [Moderated Mediation Analysis for Hypothesis I: $\chi^2(2) = 3.92$, $p = 0.14$; Moderated Mediation Analysis for Hypothesis II: $\chi^2(2) = 2.07$, $p = 0.36$], indicating that it would be appropriate to replace the remaining missing values using the multiple imputation method. However, Little's MCAR test was significant for the variables included in the canonical correlation analysis, $\chi^2(130) = 186.90$, $p = 0.001$. This significant result indicates that data from these variables were Missing at Random (MAR; missing due to participant differences unrelated to item with missing values) or Missing Not at Random (MNAR; missing due to participant differences related to the item with missing values). By definition, MAR and MNAR cannot be confidently differentiated without uncollected data. Multiple imputation is an appropriate method for MAR data, but not for MNAR data (Schafer, 1999). As no variable was missing data for more than 5% of cases, it is unlikely that multiple

imputation would significantly bias results (Schafer, 1999), so this method was used to replace missing values. Five sets of imputed data were calculated; analysis parameters presented below are the averaged parameters from the five imputed datasets (Schafer, 1999).

Analysis Assumptions. 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 (see Figure 7).



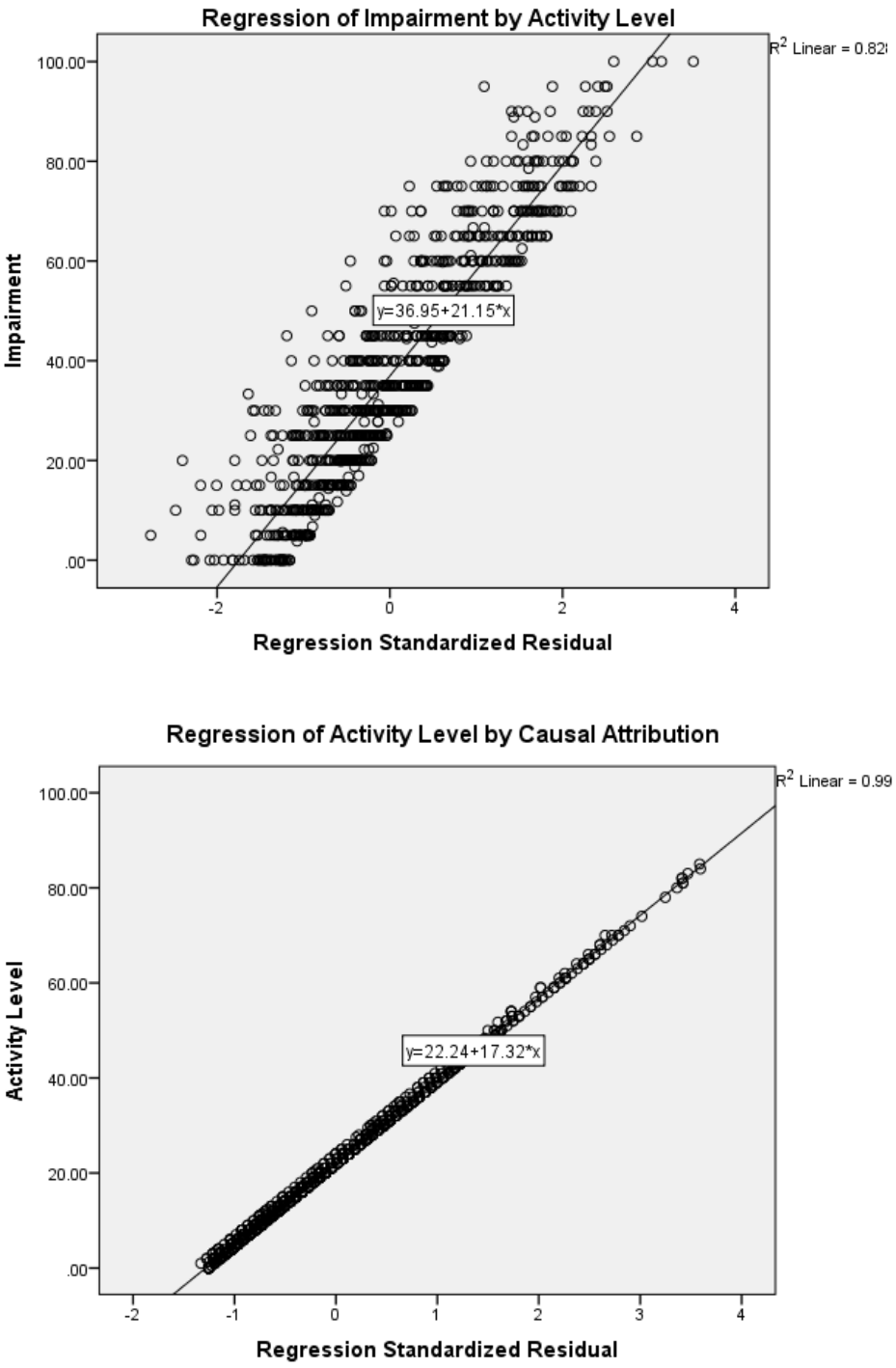


Figure 7. Regression-predicted values by residuals

Skewness and kurtosis values were all within an absolute value of two, indicating that data were relatively normal (see Table 2).

Table 2. Descriptive Statistics

Variable	M *(SD)*	Skewness	Kurtosis
Activity Level	22.19 *(17.31)*	1.06	0.72
Impairment	37.08 *(23.21)*	0.43	-0.58
Fatigue	67.55 *(23.12)*	-0.99	0.52
Post-exertional malaise			
Dead, heavy feeling after exercise	68.73 *(28.31)*	-0.87	0.01
Next-day soreness after activities	69.93 *(23.01)*	-0.67	0.10
Mentally tired after slightest effort	63.15 *(24.90)*	-0.43	-0.39
Minimum exercise makes tired	72.93 *(24.10)*	-0.86	0.25
Drained / Sick after mild activity	68.60 *(24.36)*	-0.67	-0.01

Variable	% *(n)*
Causal Attribution	
Definitely physical	68.28 *(676)*
Mainly physical	21.41 *(212)*
Equally physical or psychological	10.30 *(102)*
Case Definition Group	
Does not meet criteria	11.41 *(113)*
CFS	22.32 *(221)*
ME/CFS	44.85 *(444)*
ME	21.41 *(212)*
Psychiatric Diagnosis	
Yes	37.78 *(374)*
No	62.22 *(616)*

Moderated Mediation Analyses

Hypothesis I. Consistent with Hypothesis Ia, causal attribution did not significantly predict activity level [$R^2 = 0.002$, $F(1, 988) = 1.845$, $p = 0.175$]; thus, activity level did not mediate the relation between causal attribution and impairment. The second stage of the model was predictive of impairment [$R^2 = 0.232$, $F(6, 983) = 49.449$, $p < 0.001$]. Inconsistent with Hypothesis Ia, causal attribution predicted impairment ($\beta = 6.259$, $p < 0.001$), such that individuals who reported a physical illness etiology were more physically impaired than those who reported some psychological etiology. Consistent with Hypothesis Ib, activity

level was significantly related to impairment (β = 0.588, p < 0.001), and case definition fulfillment moderated the relation between activity level and impairment (β = -0.231, p = 0.048), such that individuals who met more stringent case definitions evidenced a weaker relation between activity level and impairment (Hypothesis Ic). Inconsistent with Hypothesis Id, psychiatric diagnosis did not moderate the relation between activity level and impairment (β = 0.086, p = 0.285). Coefficients and significant levels are displayed in Figure 8.

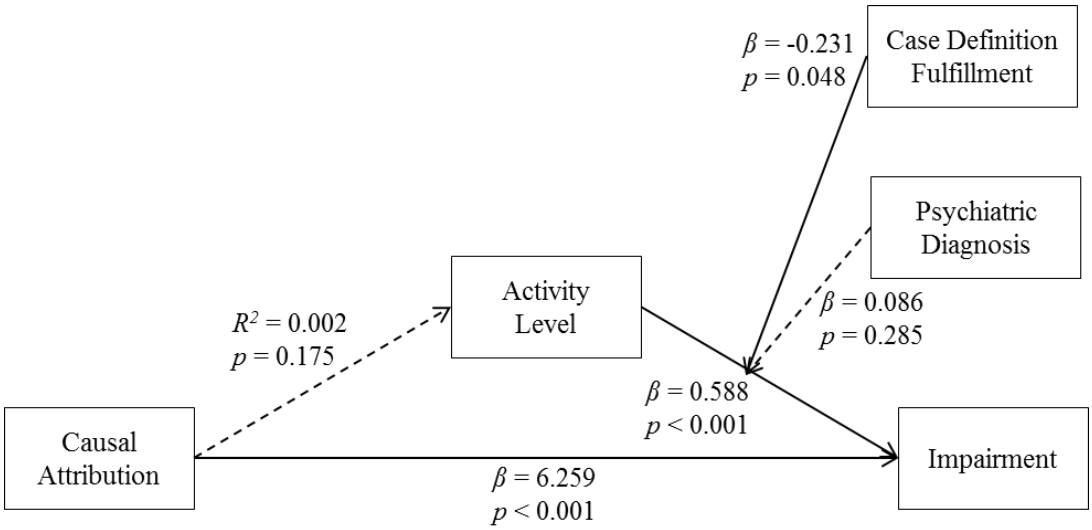


Figure 8. Moderated mediation analysis of predictors of impairment

Hypothesis II. Consistent with Hypothesis IIa, causal attribution was not predictive of activity level [R^2 = 0.002, F(1, 988) = 1.845, p = 0.175], demonstrating that activity level did not mediate the relation between causal attribution and fatigue. The second stage of the model significantly predicted fatigue [R^2 = 0.112, F(6, 983) = 20.627, p < 0.001]. As hypothesized (Hypothesis IIb), causal attribution was not significantly related to fatigue (β = -0.701, p =

0.506), while activity level was significantly associated with fatigue (β = -0.486, p < 0.001). Inconsistent with Hypotheses IIc and IId, neither case definition fulfillment (β = 0.059, p = 0.172) nor psychiatric diagnosis (β = 0.116, p = 0.174) moderated the relation between activity level and fatigue. Full results are displayed in Figure 9.

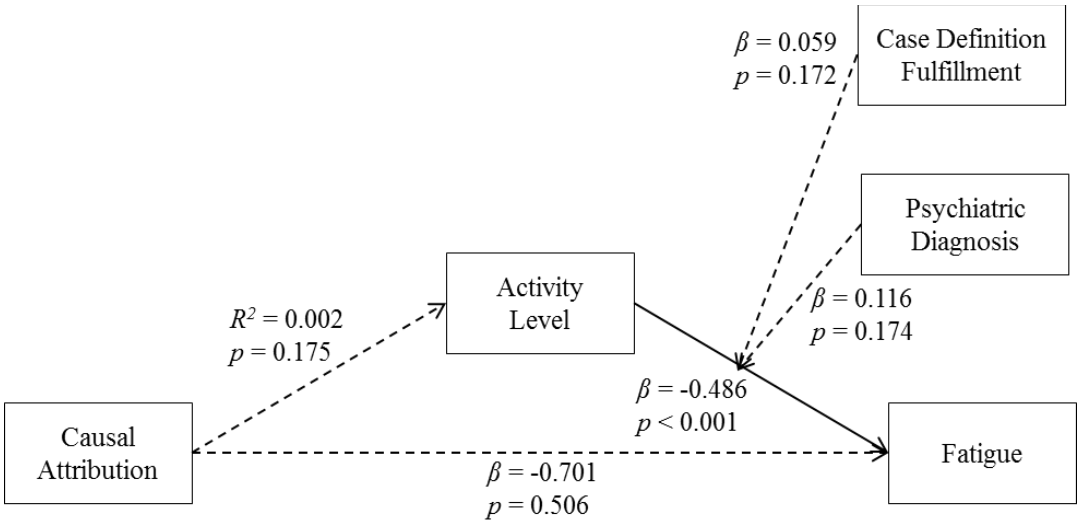


Figure 9. Moderated mediation analysis of predictors of fatigue

Canonical Correlation Analysis

Hypothesis III. The canonical correlation analysis assessed the relation between post-exertional malaise and illness severity items; it resulted in three functions with canonical correlations of 0.656, 0.144, and 0.060, respectively. The full model, including all three functions, was statistically significant [Wilks's λ = 0.555, F(15, 2711.27) = 42.918, p < 0.001]. Two of the three canonical functions were significant, indicating that these two sets of variables were significantly correlated; however, only the first function was further explored, as the second function did not explain a noteworthy amount of variance. Specifically, the first

function explained 43.1% of variance between the two sets of variables (post-exertional malaise and illness severity), and the second function explained just 2.1%.

Canonical loadings were consistent with Hypothesis III and are displayed in Figure 10. The post-exertional malaise canonical variable explained 66.6% of the variance among the five post-exertional malaise variables. The illness severity canonical variable explained 54.3% of the variance among the three illness severity variables.

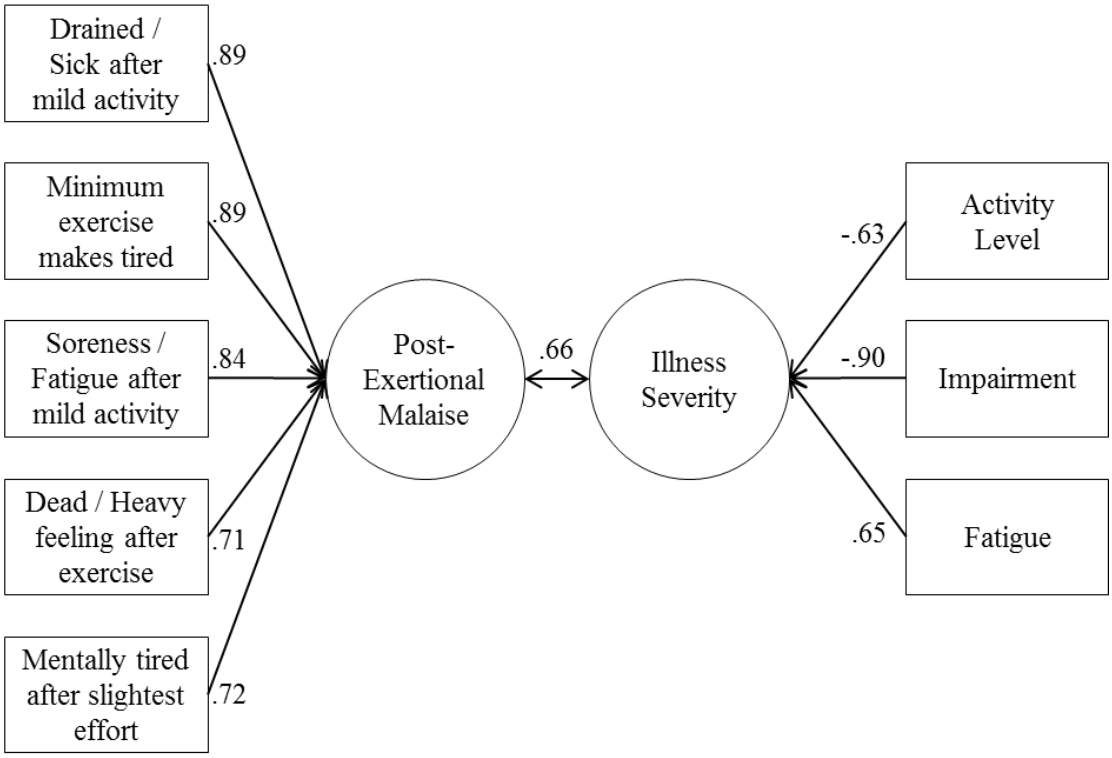


Figure 10. Canonical loadings of post-exertional malaise and illness severity items

Discussion

Results of the moderated mediation analyses were consistent with several of the study's hypotheses. Findings suggest that individuals with ME and CFS do not reduce their activity level due to perceptions about illness etiology. Activity level was associated with impairment and fatigue; 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, Evans, 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, p. 312). 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 countering 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.

Results of the canonical correlation analysis further elucidated the relation among activity level, impairment, and fatigue. The canonical correlation analysis examined these variables as a latent construct that represented illness severity, rather than conceptualizing activity level as the cause of impairment and fatigue. 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 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. Findings from the canonical correlation analysis indicated that activity level, impairment, and fatigue shared a significant amount of variance, suggesting that these variables may be associated with the more general construct of illness severity. Additionally, this analysis demonstrated that the construct of post-exertional malaise was strongly correlated with the construct of illness severity, such that individuals who experienced more frequent and severe post-exertional malaise over the past six months had also more recently experienced greater illness severity. This finding suggests a paradigm shift in the interpretation of activity level's relation to impairment and 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.

Two of the current study's hypotheses were unsupported. Contrary to prediction, causal attribution was associated with impairment; individuals who attributed their illness to physical causes had greater impairment than those who also 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. This interpretation is supported by the finding that causal attribution was not significantly related to fatigue, as fatigue can arise from both physical and psychological illnesses (e.g., depression with melancholic features).

As an additional unexpected finding, psychiatric diagnosis did not moderate activity level's relation to impairment or fatigue. This null finding may have been related to statistical or methodological factors. As the causal attribution variable may have been strongly associated with psychiatric diagnosis, the two variables may have shared a significant amount of variance, and the remaining variance of the psychiatric diagnosis variable may not have been as strongly associated with fatigue and impairment. Methodologically, the psychiatric

diagnosis variable assessed lifetime history of psychiatric diagnosis, as opposed to current or comorbid psychiatric diagnosis. The effect of this variable may have been stronger had only current psychiatric diagnoses been considered.

The current study improved upon previous literature in that it analyzed a large sample of 990 individuals with ME and CFS, examined moderators, 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. While these differences led to a heterogeneous sample, physicians continue to report uncertainty about the diagnostic process for ME and CFS (Bakken et al., 2014); 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; Smith et al., 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.

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; rather, activity level is an indicator of general illness severity, along with impairment and fatigue. These findings are inconsistent with cognitive behavioral theories of CFS that presume that individuals' symptoms stem from deconditioning and maladaptive illness beliefs. As these theories lack empirical support, and patients continue to express concerns about the efficacy of cognitive behavioral and graded exercise treatments, caution should be exercised in prescribing these treatments to patients. Furthermore, future research efforts may better serve individuals with ME and CFS by working toward developing alternative treatments.

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