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## Investigating Post-Exertional Malaise as a Core Symptom of Myalgic Encephalomyelitis and Chronic Fatigue Syndrome: A Meta-Analytic Approach

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Investigating Post-Exertional Malaise as a Core Symptom of Myalgic Encephalomyelitis and  
Chronic Fatigue Syndrome: A Meta-Analytic Approach

A Dissertation

Presented in

Partial Fulfillment of the

Requirement for the Degree of

Doctor of Philosophy

By

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In loving memory of my niece, Hazel Virginia Brown.

### **Vita**

The author was born in Wilmette, Illinois, July 5, 1987. She graduated from New Trier High School in 2005, received her Bachelor of Arts degree magna cum laude from DePaul University in 2009, and a Master of Arts degree in Psychology with distinction from DePaul in 2012. She is currently completing her pre-doctoral internship at the University of Michigan's Counseling and Psychological Services in Ann Arbor, Michigan and will begin a post-doctoral fellowship at Insight Behavioral Health-Eating Recovery Center in Chicago, Illinois upon the completion of her PhD in August 2017.

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## Abstract

Efforts to establish a reliable and valid case definition for myalgic encephalomyelitis and chronic fatigue syndrome (ME and CFS) have been complicated by an over-reliance on clinical consensus, and inconsistent application of established case definitions by researchers across study sites. This has resulted in the absence of an empirically-based case definition for ME and CFS, as well as failed replication studies on potential diagnostic tests and biomarkers. One step toward an empirically-driven case definition is determining which symptoms best discriminate between patients with ME and CFS versus controls. Post-exertional malaise (PEM) is considered a cardinal symptom of ME and CFS and is either required or included in many previously proposed case definitions. PEM refers to the symptom exacerbation and impairment/sickness that follows physical exertion or cognitive effort. PEM is typically assessed subjectively, with a patient describing his or her experience to a physician or on a self-report measure. To date, there have been no meta-analyses of the findings from studies that investigate PEM differences between patients and controls. A meta-analysis of odds ratios (association between patient status and PEM status) and a number of potential moderators (i.e., study level characteristics) of effect size were conducted for a total of 31 studies. PEM was found to be 10.4 times more likely to be associated with an ME and CFS diagnosis than with control status. Significant moderators of effect size included patient recruitment strategy and control selection. These findings strongly suggest that PEM should be considered a cardinal symptom of ME and CFS, and the implications of the moderator analyses are discussed.

## **Introduction**

### **Overview of Myalgic Encephalomyelitis and Chronic Fatigue Syndrome**

Myalgic encephalomyelitis (ME) and chronic fatigue syndrome (CFS) are debilitating illnesses (Nacul, Lacerda, Campion et al., 2011) characterized by profound fatigue, neurocognitive dysfunction, unrefreshing sleep, and a worsening of the symptom complex following mental or physical activity; secondary symptoms include pain and immune, autonomic, and neuroendocrine dysfunction (Carruthers et al., 2003). The illness has been referred to as chronic fatigue syndrome (CFS) (Fukuda et al., 1994), myalgic encephalomyelitis or encephalopathy (ME) (Ramsay, 1988), ME/CFS (Carruthers et al., 2003), and most recently as systemic exertion intolerance disease (SEID) (Institute of Medicine, 2015). For the purposes of the present paper, the term “ME and CFS” will be utilized.

About one million adults in the United States are believed to have ME and CFS, and the illness has been found to disproportionately affect women (Reyes et al., 2003) and ethnic minorities (Steele et al., 1998; Jason, Richman et al., 1999). ME and CFS also affect children and adolescents (Crawley, Emond & Sterne, 2011), although research on pediatric populations is limited. Onset of the illness can be sudden or gradual (De Becker, McGregor & Meirleir, 2002), and the etiology of the illness remains controversial (Afari & Buchwald, 2003; Erlwein et al., 2010). Because the cause of the condition remains unknown, individuals with ME and CFS are often met with disbelief and are stigmatized by medical professionals, employers, friends, and family (Dickson, Knussen, & Flowers, 2007). Early psychogenic explanations for the illness suggested that patients were malingerers, and that the symptoms experienced were a result of the desire to remain sick (Abbey, 1993) and/or were the result of deconditioning due to a learned fear of activity (Clark & White, 2005). In contrast, following the first well-publicized outbreak in

the US, other researchers suggested the condition was most likely linked to a virus (Buchwald et al., 1992).

A number of potential risk factors for ME and CFS onset have been identified. The variables with the most empirical support are female gender (Clark, Goodwin, Stansfeld, Hotopf & White, 2011; Harvey, Wadsworth, Wessely & Hotopf, 2008; Pheby & Saffron, 2009; Viner & Hotopf, 2004) and ethnic minority status (Jason, Richman et al., 1999). The findings regarding socioeconomic status are mixed (Huibers et al., 2004; Viner & Hotopf), with prevalence studies based on samples referred by physicians suggesting that ME and CFS are more likely to affect middle and upper class individuals (Lloyd, Hickie, Boughton, Spencer & Wakefield, 1990; Reyes et al., 1997), and studies based on community-based samples finding that lower educational and occupational status are associated with greater intensity of fatigue and other ME and CFS symptoms (Jason, Richman et al., 1999; Reyes et al., 2003).

Although atypical immune manifestations (Fletcher et al., 2010; Klimas & Koneru, 2007; Maher, Klimas, & Fletcher, 2005) and neurocognitive (Hou et al., 2014; Michiels & Cluydts, 2001), central nervous system (Gur & Oktayoglu, 2008; Nakatomi et al., 2014; Natelson, Cohen, Brassloff, & Lee, 1993) and autonomic dysfunction (Hurwitz et al., 2010; Newton et al., 2007) have been documented in ME and CFS samples, there is no universally accepted biomarker or objective diagnostic test for the illness. Failed replications are common within the field due to the heterogeneous, non-comparable patient samples used across studies, a potential consequence of varying inclusion criteria and continued controversy over the actual case definition for the illness (Jason et al., 2012). Multiple research and clinical case definitions have been proposed, with a recent count by Brurberg, Fonhous, Larun, Flottorp and Malterud (2014) placing the number at 20 definitions, with no consensus to date on a singular definition. Further issues arise

when research groups that intend to utilize the same case definition vary drastically in their operationalization of the definitions (Christley, Duffy & Martin, 2012). The issue of heterogeneous patient samples has plagued the research community since the Centers for Disease Control and Prevention's (CDC) publication of the first diagnostic criteria for CFS (Holmes et al., 1988).

Thus, there continues to be a lack of clarity about ME and CFS on the part of researchers, and the subsequent lack of clinical knowledge imparted to medical providers. The illness is underrepresented in American medical schools (Jason, Paavola, Porter & Morello, 2010), with ME and CFS-related content largely absent from curricula, and the majority of American medical programs lacking faculty with research or clinical expertise in ME and CFS (Peterson et al., 2013). Not surprisingly, physicians surveyed about the illness tend to rate themselves as lacking basic knowledge, and as feeling unprepared to treat patients presenting with ME and CFS symptoms (Bowen, Pheby, Charlett & McNulty, 2005; Brimmer, Fridinger, Lin & Reeves, 2010). Although a number of potential treatments have been investigated, the issues with criterion variance as outlined above have led to treatment studies with a number of limitations (Kindlon, 2011).

### **ME and CFS Case Definitions**

The heterogeneous patient samples used in ME and CFS research may be a product of the vague and poorly operationalized diagnostic criteria that have been established (Jason, King et al., 1999). Since the illness became formally recognized as CFS in the late 1980s in the US following reports of cluster outbreaks in Nevada (Buchwald et al., 1992) and New York (Bell, Bell, & Cheney, 1994), consensus for a singular case definition has yet to be reached by researchers, practitioners and patient advocates. Thus, the diagnosis of ME and CFS is an

exclusionary process that relies heavily on self-reported symptom profiles (Afari & Buchwald, 2003). Therefore, selecting the cardinal or core symptoms of the illness and developing a standardized process for assessing these symptoms is vital (King & Jason, 2004). Many attempts have been made to clarify and define a case of ME and CFS since the late 1980s.

The Holmes et al. CFS criteria (1988) require a patient to experience persistent, unexplained fatigue at least 50% of the time with a definite onset, accompanied by eight out of 11 definitional symptoms. These criteria have been criticized as vague and poorly operationalized, which has led to inconsistent application by clinicians and researchers (Fukuda et al., 1994). Further, by placing the definitional symptom threshold so high, the Holmes criteria may inadvertently select for individuals with primary psychiatric explanations for their fatigue (Katon & Russo, 1992).

In the early 1990s, a group of British researchers published what is referred to as the Oxford criteria (Sharpe et al., 1991). The primary focus of this definition is the symptom of fatigue, with little specificity about other minor symptoms. Severe and disabling fatigue that has been present for at least six months, 50% of the time, is the sole criterion, although the authors suggest that common co-occurring symptoms include muscle pain, mood disturbance and sleep disturbance. Although these criteria are quite broad, the Oxford definition has been one of the applied case definitions in the study of ME and CFS (Dinos et al., 2009). However, an NIH-appointed panel recently recommended the Oxford definition be retired due to its lack of specificity (Green, Cowan, Elk, O'Neil, & Rasmussen, 2015).

In response to the criticisms of the Holmes et al. (1988) case definition, the CDC convened an international working group to improve upon these diagnostic criteria, which resulted in the development of the Fukuda et al. (1994) criteria. The improved criteria have also

been criticized as vague and clinically unhelpful (De Becker, McGregor, & De Meirleir, 2002; Jason, King et al., 1999), lacking specific guidelines or operationalization. Further, the Fukuda et al. criteria are polythetic, meaning that individuals who meet the criteria will not necessarily have common features. To meet criteria, an individual must have at least six months of unexplained persistent fatigue of new or definite onset, experienced concurrently with just four out of eight definitional symptoms (i.e. unrefreshing sleep, multijoint pain, muscle pain, headaches, post-exertional malaise, lymph node pain, impairment in memory and concentration, sore throat). Further, this symptom complex must cause “substantial reductions in functioning.” The Fukuda criteria, with minor updates made by Reeves et al. (2003), remain the most universally utilized criteria to date for research and clinical purposes.

In an attempt to operationalize the fatigue, symptom complex, and substantial reductions required by Fukuda et al. (1994)/Reeves et al. (2003), the CDC developed the Empiric criteria (Reeves et al., 2005), which specifies the use of validated self-report measures and cut-off scores to aid in diagnosis. The first community-based epidemiological study that utilized these criteria raised the CDC’s estimated prevalence rate of CFS from 0.24% (Reyes et al., 2003) to 2.54% of the population (Reeves et al., 2007), which was also significantly higher than previous outside estimates of 0.42% (Jason, Richman et al., 1999). This led many to question the validity of the criteria, and Jason, Najar, Porter, and Reh (2009) found that the Empiric criteria incorrectly identified 38% of a sample with primary major depressive disorder as having CFS due to the lack of specificity of this case definition.

In 2003, an international group working independently of the CDC developed new criteria in which the condition was explicitly labeled ME/CFS (Carruthers et al., 2003). In contrast to the polythetic CDC CFS case definitions, this new ME/CFS criteria, referred to as the

Clinical Canadian Criteria (CCC), require two of the symptoms thought to be core to the illness to be present for a diagnosis: post-exertional malaise and neurocognitive impairment. To meet the CCC, a person must experience post-exertional malaise, at least two neurocognitive symptoms, at least one symptom indicating sleep dysfunction, at least one symptom indicating significant bodily pain, and at least one symptom from two of the following three categories: autonomic, neuroendocrine and immune manifestations. Additionally, this symptom complex must result in “substantial reduction” of an individual’s functioning. As these criteria require specific symptoms, they may select for a more homogenous group of individuals than the polythetic approach of the Holmes et al. (1988) and Fukuda et al. (1994) case definitions. Jason, Brown et al. (2012) compared those meeting the CCC case definition to those not meeting the CCC but meeting the Fukuda et al. (1994) criteria only. Findings indicated that the ME/CFS case definition identified individuals with more severe symptoms and greater functional disability than those meeting only the Fukuda criteria. However, the CCC still lack operationalization with no guidelines regarding frequency or severity thresholds for required symptoms (Jason, Evans, Porter et al., 2010). Therefore, although the CCC may identify a more homogenous sample with regards to what symptoms are occurring, the intensity of these symptoms could range significantly.

A more recently proposed set of criteria (Carruthers et al., 2011) were described by the authors as an update to the ME/CFS Clinical Canadian Criteria (CCC) (Carruthers et al., 2003). The ME International Consensus criteria (ME-ICC) require an individual to experience post-exertional malaise, at least one symptom out of three of four distinct neurological domains, at least one symptom out of three of five distinct immune domains, and at least one energy production symptom. Additionally, an individual’s functioning must be reduced by 50%

compared to their pre-illness activity level. Brown, Jason, Evans and Flores (2013) found that these criteria identified a more impaired and homogenous group than the Fukuda criteria (1994), although rates of psychiatric comorbidity were also higher in the ME-ICC group. This aligned with Katon and Russo's (1992) conclusion that with increased symptom requirements, psychiatric comorbidity becomes more likely.

Finally, in early 2015, the Institute of Medicine released a report recommending a new case definition, and also a new illness label: systemic exertion intolerance disease (SEID). This label is notable for its use of the term 'disease,' its removal of the term fatigue, as well its focus on post-exertional illness which has long been considered a cardinal symptom of the illness (Carruthers et al., 2003). To meet SEID criteria, a patient must evidence substantial impairment in functioning, unrefreshing sleep, post-exertional malaise, and either cognitive impairment or orthostatic intolerance. These criteria are similar to the Clinical Canadian Criteria (Carruthers et al., 2003) with regards to requiring core symptoms, but are also similar to the Fukuda et al. criteria (1994) as the symptom requirement has once again been set to four. The SEID criteria are also the first to specify orthostatic intolerance rather than autonomic dysfunction more broadly. Jason, Sunnquist et al. (2015) found that the SEID criteria select a group of patients quite comparable to those selected by the Fukuda criteria (1994), and that a greater percentage of patients meet SEID than the Clinical Canadian Criteria (Carruthers et al., 2003). However, the SEID criteria do not specify any exclusionary illnesses and its use may lead to a significantly higher prevalence rate and inappropriate inclusion of individuals with primary MDD (Jason, Sunnquist, Kot & Brown, 2015).

Notably, before the illness was referred to as CFS in the US, an anonymous 1956 editorial in the British journal the *Lancet* referred to the illness as "benign myalgic



encephalomyelitis.” Ramsay (a British physician who oversaw an outbreak in London hospitals in the 1950s) later published his own criteria, specifically using the term ME (1988). His work has generated many other ME-based case definitions: the London criteria (Tyrrell et al., 1994), the Nightingale definition (Hyde, 2007), and the Goudsmit et al. criteria (2009). In contrast to the definitions described above, Ramsay did not consider fatigue to be the hallmark symptom of ME, but rather “muscle fatigability after minimal exertion” and he believed strongly in central nervous system involvement (1988). Many of the ME theorists influenced by Ramsay believe ME to be distinctive from CFS, and consider ME to be a more severe neurological illness, characterized by a sudden onset (Goudsmit et al., 2009). Thus, the relationships between ME, CFS, ME/CFS and SEID remain ambiguous and controversial, with some researchers treating these illnesses as one condition under an umbrella term of ME/CFS (Carruthers et al., 2003; Carruthers et al., 2011; IOM, 2015), and others suggesting that these are distinct entities that must be studied separately (Goudsmit et al., Hyde).

While similar themes emerge across the case definitions for CFS, ME, ME/CFS and SEID outlined above, they diverge substantially on which symptoms should be required for a diagnosis. Clarifying the “core” symptoms for a diagnosis of ME and CFS has become a focus for the field, as has the notion that case definitions should be arrived at empirically rather than be based upon expert, clinical consensus. It has been suggested that consistent inclusion of homogenous patient groups into studies, as well as identification of phenotypical subtypes of patients, could assist in the pursuit of biomarkers for ME and CFS (Nacul, Lacerda, Pheby et al., 2011), which would ultimately allow for a more circumscribed investigation into potential treatments.

### **Core Symptoms of ME and CFS**

One common approach to establishing “core symptoms” of ME and CFS has been to examine which symptoms best distinguish between individuals with ME and CFS and control groups (e.g., healthy groups, groups with other illnesses). A number of statistical approaches have been utilized in the literature to address the question of what should be considered “core” to this illness. Hawk, Jason and Torres-Harding (2006) employed stepwise discriminant function analysis to examine which of the eight Fukuda et al. (1994) symptoms could best distinguish individuals with ME and CFS from those with major depressive disorder. The authors found that when entering severity ratings for the eight Fukuda symptoms into the discriminant function analysis, post-exertional malaise, unrefreshing sleep and impaired memory/concentration were the best predictors of group membership, correctly classifying 91.1% of cases. Using Receiver Operating Characteristic curve analysis (ROC), Jason, Jessen and colleagues (2009) found that items loading to a post-exertional malaise factor on the ME/CFS Fatigue Types Questionnaire had good sensitivity (90%) and specificity (93%) in distinguishing between patients and controls.

Factor analysis has also been utilized to inform our understanding of “core” ME and CFS domains. Brown and Jason (2014) employed an exploratory factor analysis with a well-defined patient sample on a comprehensive list of 54 ME and CFS-related symptoms, and a three-factor solution was found to fit the data. Two of these factors were easily interpretable, and provided support for both post-exertional malaise and neurocognitive impairment as core domains of the illness. A third factor encompassed items relating to symptom domains that have been considered secondary such as neuroendocrine, autonomic and immune. These findings of a post-exertional malaise factor were in line with other factor analytic studies that found post-exertional factors in other symptom inventories (Arroll & Senior, 2009; Friedberg, Dechene, McKenzie, &

Fontanetta, 2000; Jason, Corradi & Torres-Harding, 2007; Jason et al., 2015; Nisenbaum, Reyes, Unger & Reeves, 2004).

Recently, more advanced statistical methods that utilize computer learning techniques have been implemented to determine which symptoms best distinguish patients with ME and CFS from other groups using large datasets. Using a technique called data mining, Jason, Skendrovic, et al. (2011) found that the inability to concentrate, post-exertional malaise and unrefreshing sleep were the best symptom discriminators between patients with ME and CFS and controls. A more recent study that employed data mining with a larger sample and empirically established severity thresholds, found that fatigue, post-exertional malaise, neurocognitive dysfunction, and unrefreshing sleep differentiated ME and CFS patients from controls with good accuracy (Jason, Kot, et al., 2015). When the authors utilized that four-symptom criteria to categorize patients, they found that this identified group was significantly more functionally impaired than patients who did not meet these criteria. Interestingly, this empirically derived case definition has some similarities to the recent, consensus-based SEID criteria that called for post-exertional malaise, unrefreshing sleep, and either cognitive dysfunction or orthostatic intolerance to be present for a diagnosis (IOM, 2015). Given the results of these previous studies and the move toward considering post-exertional malaise a “core” symptom of this illness in the most recently proposed SEID case definition, the present review and subsequent meta-analysis will focus solely on this symptom.

### **Post-Exertional Malaise**

Post-exertional malaise (PEM), also referred to as post-exertional neuroimmune exhaustion (Carruthers et al., 2011), is included in most case definitions for ME and CFS, although the description of this symptom varies across criteria. The Fukuda et al. criteria (1994)

simply refer to it as “postexertional malaise lasting more than 24 hours,” whereas the Clinical Canadian Criteria (Carruthers et al., 2003) provide much greater specificity, “an inappropriate loss of physical and mental stamina, rapid muscular and cognitive fatigability... and a tendency for other associated symptoms to worsen.” The newest criteria for the illness, SEID (IOM, 2015) describe PEM as “prolonged exacerbation of a patient’s baseline symptoms after physical/cognitive/orthostatic stress; [it] may be delayed relative to the trigger.” PEM is considered cardinal or required for diagnosis under many case definitions (Carruthers et al., 2003; Carruthers et al., 2011; Hyde, 2007; Ramsay, David, Wessely, Pelosi & Dowsett, 1988) but is not required for diagnosis using the Fukuda et al. (1994) or Empiric criteria (Reeves et al., 2005). A recent article that examined 53 unique ME and CFS patient samples all meeting the Fukuda criteria, found that between 24.7-100% of these patient samples had PEM, with a mean of 85% (McManimen et al., 2015).

However described or defined, PEM is often referred to as the most debilitating aspect of the ME and CFS symptom complex by patients (FDA, 2013), leading to profound reductions in functioning (Davenport, Stevens, Baroni, Van Ness & Snell, 2011). Further, PEM is often cited as a primary reason that treatment protocols based upon vigorous, incremental exercise may be inappropriate for individuals with this illness (Nijs, Paul & Wallman, 2008). Those researchers and clinicians who endorse a more psychogenic explanation for the illness consider PEM the result of deconditioning or a learned fear of activity, and encourage patients to treat their illness with exercise or cognitive behavioral therapy to learn strategies for reevaluating certain illness cognitions and adopting recovery focused cognitions (Surawy, Hackmann, Hawton & Sharpe, 1995; White et al., 2011). However, the majority of patients prefer pacing strategies (Shepherd, 2001), whereby they learn to assess and stay within their “energy envelope” (Jason, Benton,

Torres-Harding & Muldowney, 2009) to avoid PEM, rather than pushing themselves beyond their envelope as recommended by many exercise-based therapies. Learning to stay within one's energy envelope has been associated with improved physical functioning and less PEM for some patients (Brown, Evans, Jones & Jason, 2013).

### **Subjective Reporting of Post-Exertional Malaise**

Given the varied case definitional descriptions of PEM, assessing and operationalizing PEM in both clinical and research settings has been a challenge for the field. A number of self-report measures have been developed and validated to assess for PEM in patients, including the ME/CFS Fatigue Types Questionnaire (Jason, Jessen et al., 2009), the Symptom Inventory (Wagner et al., 2005), the CFS Screening Questionnaire (Jason, Ropacki et al., 1997), the Medical Questionnaire (Komaroff & Buchwald, 1991), and the DePaul Symptom Questionnaire (Jason, Evans, et al., 2010). These questionnaires utilize varying symptom descriptions and question stems to elicit a patient's experience of PEM. For example, the DePaul Symptom Questionnaire asks respondents to rate five PEM-related items on frequency and severity Likert-scales (e.g., "Dead, heavy feeling after starting to exercise"; "Next day soreness or fatigue after non-strenuous, everyday activities"; "Mentally tired after the slightest effort," etc.), whereas the Symptom Inventory simply asks respondents about "unusual fatigue after exertion."

In a recent study, Jason, Evans, So, Scott and Brown (2015) applied an item that is commonly used to define PEM according to the Fukuda criteria (taken from the CFS Screening Questionnaire), "Do you feel generally worse than usual or fatigued for 24 hours or more after you have exercised?" to a clinically evaluated sample of patients with ME and CFS.

Approximately 25% of the patients responded "no" to this question. However, when this symptom was probed differently (e.g., by a physician or by the item: "Do you experience high

levels of fatigue or weakness following normal daily activity?") all of the patients appeared to have PEM. Similarly, Jason, King and colleagues (1999) found that within a clinically evaluated ME and CFS sample, the percentage of the sample endorsing PEM ranged from 40-93%, dependent upon how the symptom was operationalized. The results from these studies demonstrate the critical role symptom operationalization plays in ME and CFS diagnosis. Although self-reported PEM has been found to be a sensitive and specific discriminator between ME and CFS patients and healthy controls, as well as between ME and CFS patients and depressed individuals (Hawk, Jason & Torres-Harding, 2006), the varied approach to PEM assessment across studies makes it difficult to interpret the true occurrence of self-reported PEM in patients.

It has been suggested that PEM is a core symptom of ME and CFS, and capable of discriminating between patients and controls. It is required for formal diagnosis under many case definitions. However, to date there have been no meta-analyses of PEM findings to examine the true strength of the PEM phenomenon in ME and CFS samples. Thus, studies that assess PEM in ME and CFS samples (as contrasted to controls) are appropriate for meta-analysis. The present study will extract and pool odds ratios from studies that report on occurrence of self-reported PEM in patients and controls. The resulting mean effect size will provide a better estimate of the true differences between patients with ME and CFS and controls on PEM, which could provide evidence for or against the claim that PEM distinguishes between patients and controls well and should be considered a required, cardinal or core symptom of ME and CFS.

### **Study-Level Moderators**

Given the substantial variability observed across studies of ME and CFS on a number of methodological design decisions, there are many potential study-level factors that may impact

the outcome of a study beyond group membership (ME and CFS or control). That is, certain aspects of a study's design may result in a larger or smaller observed difference between patients and controls on PEM outcomes.

**Recruitment method.** ME and CFS patient samples are drawn from a number of sources, and this may result in substantial variability between studies. Patients may be identified for study participation from primary care, from tertiary (or specialized care) settings, through random community-based methods, or through convenience methods. Patients identified through tertiary care settings have been found to be more severely ill than patients from community-based samples (Jason, Plioplys, Torres-Harding & Corradi, 2003). Further, patients identified using randomized community approaches tend to be less severely ill and are more likely to be receiving a diagnosis for the first time compared to patients recruited from primary or tertiary care (Jason, Porter et al., 2009). Community-based recruitment also results in more ethnically and socioeconomically diverse samples, because these recruitment methods are not biased to only select for individuals with access to healthcare (Jason, Taylor, Kennedy, et al., 2000). Finally, convenience methods such as online recruitment or recruiting through support groups will likely result in patient samples that are similar to tertiary care samples as these are likely individuals that identify with this illness and are actively involved in ME and CFS communities (Jason, Sunnquist, et al., 2015). Thus, the method of patient recruitment utilized in the studies to be included in the present meta-analysis may be an important moderator of the observed differences between ME and CFS and controls on subjective PEM experience. It is hypothesized that studies that recruit from tertiary care settings or utilize convenience methods may select for patients with more severe symptomatology, whereas studies that recruit using randomized, community-based methods may have milder symptomatology. Thus, the effect of the PEM

phenomenon may be significantly greater in studies that compare controls to patients recruited from tertiary care or through convenience sampling than in studies that utilize community-based methods.

**Diagnosis.** Once a patient is recruited and brought into a study, the method of ME and CFS diagnostic confirmation may also vary across studies. Many studies employ thorough physical and psychiatric evaluations to diagnosis ME and CFS, while other studies rely upon self-reported ME and CFS or documentation from an outside medical provider to confirm diagnosis. Clinically evaluated patient samples are more homogenous with regards to symptomatology compared to non-clinically evaluated patient samples (Johnston, Brenu, Staines & Marshall-Gradisnik, 2013). Further, accepting self-reported diagnoses with no documentation may introduce significant bias into a study, and it has been suggested that prevalence studies based upon self-reported ME or CFS should be interpreted cautiously (Johnston et al., 2013). It is hypothesized that studies that employ thorough evaluations may result in more profound differences on PEM outcomes between patients and controls, as these studies may avoid erroneous inclusion of non-patients or patients with other conditions (as might occur with self-reported ME and CFS). Documentation from outside physicians may also not be sufficient as they may not have the clinical expertise that specialists have, as has been demonstrated by many studies of physicians (Anderson, Jason, Hlavaty, Porter & Cudia, 2011; Bayliss et al., 2014).

**Case definition.** The case definition adhered to for diagnosis would also be a desirable moderator to examine, given the breadth of findings from case definitional comparison studies, but the vast majority of studies employ the Fukuda et al. criteria (1994) and this may make subgroup analyses difficult.



**Symptom measurement.** Many different approaches to assessing symptomatology are represented in the literature. Some studies utilize a validated and accepted self-report tool to assess symptomatology such as the CDC Symptom Inventory (Wagner et al., 2005), the DePaul Symptom Questionnaire (Jason, Evans et al., 2010) or the CFS Questionnaire (Komaroff et al., 1996), while other studies utilize non-validated tools to assess symptoms (e.g., a set of questions developed for a study that are not used by other researchers). Studies may also rely upon interviewing alone. Definitions of “presence” or “occurrence” of a symptom also vary across studies (Jason, King, Taylor & Kennedy, 2000). While the major case definitions (Fukuda et al., 1994; Carruthers et al., 2003) state that the symptom complex must be present for at least six months, it is unclear if a symptom has to occur at a certain severity and frequency to be considered present. Jason, Evans et al. (2010) attempted to operationalize the Clinical Canadian Criteria (Carruthers et al., 2003) by recommending that symptoms must be rated as occurring at least “half the time” and being of at least “moderate” severity to count as truly “occurring.” However, many investigators do not offer this level of specificity and simply rely upon endorsement of a symptom at any intensity to count as present. For studies that provide additional information about symptom assessment, additional moderators of effect size can be investigated. For example, how PEM was assessed (e.g., through a validated tool, physician assessment or a non-validated tool) will be treated as a moderator, as well as how “occurrence” of PEM was defined (e.g., utilizing intensity thresholds versus occurrence). It is hypothesized that studies that utilize a validated questionnaire to assess PEM and apply some sort of intensity thresholding may find a greater effect than studies that do not.

**Control selection.** Many types of controls are represented in the literature as comparison samples, including physically and mentally “healthy” samples, or sedentary but otherwise

healthy samples. Another common approach is to utilize other illness groups as controls, such as samples with depressive disorders or other samples that may experience some shared symptoms such as severe fatigue (e.g. lupus, multiple sclerosis, cancer). It is hypothesized that studies that utilize healthy controls will find a greater effect than studies that utilize other illness groups.

Considerable effort has focused on establishing a reliable and valid case definition for ME and CFS and on investigating potential diagnostic tests for the illness. However, these efforts have been complicated by an over-reliance on clinical consensus for establishing case definitions, and inconsistent application of case definitions by researchers across study sites. This has resulted in the absence of an empirically-based case definition for ME and CFS, as well as failed replication studies on potential diagnostic tests and biomarkers. One step of empirically-driven case definition development is establishing which symptoms might be able to discriminate well between patients with ME and CFS and controls (healthy controls or other illness groups). As reviewed above, one symptom thought to be “core” or “cardinal” to this illness is post-exertional malaise (PEM). However, to date, there have been no meta-analyses of the findings from studies that investigate PEM differences between patients and controls. Thus, a meta-analytic approach to synthesizing the data on PEM and an investigation of potential moderators of effect size in the literature are both logical next steps in case definition development. It is hypothesized that the presence of PEM is associated with an increased odds of having ME and CFS as measured by a 95% confidence interval around the mean odds ratio that does not contain the null value,  $\log \text{odds ratio} = 0$ .

## **Method**

### **Overview of Meta-Analysis**

Meta-analysis is a quantitative technique for summarizing results of studies that attempt to measure the same phenomenon (Card, 2011). The primary unit of interest in meta-analysis is the effect size, or the strength or practical importance of a study's finding beyond its statistical significance. Meta-analysis also allows for measurement of effect-size heterogeneity in the literature, and if significant heterogeneity is detected, allows for an investigation of what observable, study-level characteristics might be driving this heterogeneity. Meta-analysis is a systematic and transparent process which is becoming increasingly common in the social, physical and medical sciences. It consists of the following steps: establishing study inclusion and exclusion criteria; conducting a thorough and systematic review of the literature for appropriate studies; coding the subsequent sample of studies on key characteristics utilizing a standardized coding protocol; computing effect sizes for individual studies; calculating the overall mean effect size and confidence interval for the phenomenon of interest; investigating the presence of and contributors to heterogeneity of effect size in the sample of studies utilizing subgroup analysis; and finally, considering and addressing the potential impact of publication bias on the findings. The guidance and recommendations of Card (2011) primarily shaped this writer's understanding of the stages of a rigorous meta-analysis.

### **Inclusion Criteria**

Studies were included that met the following criteria: (a) they reported on the presence or occurrence of PEM in both patients with ME and CFS and controls, (b) they reported sufficient information for computing effect size, (c) they were published between January 1988 and December 2016, (d) they investigated an adult sample (18 years or older), (e) they presented data from independent samples, and (f) they were available in English.

### **Literature Search**

Eligible studies were identified through searches of two major databases, PsycINFO and PubMed. The most recently published meta-analysis in the ME and CFS field (Cockshell & Mathias, 2010) relied upon the following search terms: “chronic fatigue syndrome”; “chronic fatigue and immune dysfunction syndrome”; “chronic fatigue disorder”; “chronic fatigue-fibromyalgia syndrome”; “chronic infectious mononucleosis-like syndrome”; “myalgic encephalomyelitis”; “myalgic encephalopathy”; “post viral fatigue syndrome”; and “royal free disease.” These terms and an additional term, “myalgic encephalomyelitis/chronic fatigue syndrome” were included. To avoid potential publication bias, the ProQuest Dissertation and Theses Database was also searched.

### **Coding Procedure**

The author identified articles for inclusion and further coding by reviewing the title and abstract. If necessary, the full article was scanned to determine eligibility. Relevant study information was recorded using a standardized coding protocol developed by the author (see Appendix A). This coding protocol was developed with the proposed effect size and moderator analyses in mind, as well as other potentially relevant information.

### **Analytic Strategy**

**Computing effect size.** Effect sizes were computed as odds ratios (*OR*) from outcomes from the two independent groups (patients and controls). An *OR* describes the strength of association between two binary variables (Bland, 2000). For the current study, the two binary variables were “presence of ME and CFS” (yes/no) and “presence of PEM” (yes/no). In order to account for the sample size of a study the *OR* was transformed to the log scale, and then weighted by the inverse variance as proposed by Lipsey and Wilson (2001) before being

averaged. This sample size weighting is done because larger studies are thought to more precisely estimate the population effect size than smaller studies.

**Statistical model.** A random effects model was used due to the assumed significant variability between the studies. This is a more conservative approach than utilizing a fixed effects model, as a random effects model accounts for random error as well as study-level variability (e.g., research design, sample characteristics, etc.) (Hunter & Schmidt, 2000). Given what is known about the heterogeneity of study design within the ME and CFS literature as discussed in the introduction, this approach is most appropriate. Further, this random effects approach allows for a more valid generalization of the present findings to studies that aren't included in the analysis (Hedges & Vevea, 1998). The statistical packages “metafor” version 1.9-9 (Viechtbauer, 2016) and “meta” version 4.8-1 (Schwarzer, 2017) for *R* were used for all analyses.

**Heterogeneity analyses.** Variability in effect size across studies was statistically tested by investigating the Cochran  $Q$  statistic (Cochran, 1954). The null hypothesis for the  $Q$  statistic states that variance in effect size is due to random error alone, and is not due to true differences between studies. If the  $Q$  is statistically significant, this suggests that the variance of effect size is significantly greater than 0, and thus the null hypothesis is rejected because at least some of this variability might be explained by known study-level characteristics. Moderator analyses may then be considered appropriate in order to investigate the potential factors contributing to the effect size variability. However, it has been suggested that the  $Q$  statistic may not do well at detecting true heterogeneity due to power issues and that a failure to reject the null should not be taken as evidence of effect size homogeneity (Higgins, Thompson, Deeks & Altman, 2003). An alternative statistic,  $I^2$ , developed by Higgins and Thompson (2002), measures the inconsistency

of results across studies. This statistic provides the percentage of variation across studies included in the meta-analysis that is due to true heterogeneity rather than random error (ranging from 0-100%). Both the  $Q$  and  $I^2$  statistics were investigated and considered before moving forward with moderator analyses.

**Moderator analyses.** Investigating moderators using sub-group analysis in a meta-analysis can be thought of as analogous to ANOVA in an individual study; groups defined by their level of some independent variable  $X$  (e.g., patient or control) are compared on the outcome  $Y$  (e.g. fatigue level). In sub-group analysis within a meta-analysis, groups are defined by their level of some observable *study* characteristic (e.g. patient recruitment method, type of control sample, etc.), and compared on the outcome of mean effect size. Initially, a meta-regression with a mixed-effects model and maximum likelihood estimation was utilized to see which potential moderators significantly contributed to effect size variability (van Houwelingen, Arends & Stijnen, 2002). Those moderators found to be significant were further investigated by comparing the resulting sub-groups for significant differences within a fixed-effects model by computing the  $Q$ -between statistic based on analysis of variance (Borenstein, Hedges, Higgins & Rothstein, 2009). A Bonferroni correction was utilized based on the number of planned comparisons; subgroup contrasts had to be significant at  $p < .001$ . The within-group Cochran's  $Q$  statistic was also computed for each subgroup of studies just as it was computed for the total set of studies.

**Investigation of publication bias.** Publication bias is said to occur when peer-reviewed, published articles in the literature (typically the basis for systematic reviews and meta-analyses) are not truly representative of the group of studies that have actually been conducted on a given phenomenon (Rothstein, Sutton & Borenstein, 2005). The “file-drawer effect” refers to the tendency for studies with significant and positive results to be published more often than studies

that fail to reject the null hypothesis or studies that result in findings in the opposite direction of what was hypothesized, and thus these non-significant or negative findings are “placed in the file-drawer” rather than being submitted for publication or disseminated (Rosenthal, 1979). Thus, systematic reviews and meta-analyses may be biased due to the fact that studies that are readily available for analysis likely show a stronger overall effect of a given phenomenon than if all conducted studies were included. One strategy to combat publication bias before beginning the analysis, as mentioned above, is the inclusion of unpublished (but accessible) dissertations and theses. Once the sample of studies to be included was established, and the meta-analysis was conducted, a number of statistical approaches were used to investigate the potential impact of publication bias on the results. The following approaches, as described by Card (2011), were used.

***Funnel plot.*** A funnel plot allows for a graphical representation of potential publication bias, and is a simple scatterplot. The effect sizes of all studies were plotted (on the x-axis) relative to a measure of study size (on the y-axis; standard error was utilized for the present study), and the resulting scatterplot was evaluated for symmetry and a triangular shape.

***Rank correlation test.*** As developed by Begg and Mazumdar (1994), a more objective assessment of funnel plot symmetry involves the computation of an adjusted rank correlation between effect size and standard error for all included studies. For each study, the variance of the effect size from the mean effect size and the standardized effect size are both computed and used to estimate Kendall’s rank correlation. If power is adequate, and the correlation is significant, this is indicative of funnel plot asymmetry and potential publication bias.

***Egger’s linear regression.*** Another evaluation of funnel plot symmetry, as developed by Sterne and Egger (2005), involves regressing the standardized effect sizes onto the standard

errors. In the resulting regression equation:  $z_i = B_0 + B_1 + e_1$ ; the slope ( $B_1$ ) is the mean effect size and the intercept ( $B_0$ ) is the measure of bias. Thus, a nonzero intercept value is indicative of funnel plot asymmetry or potential publication bias.

**Failsafe  $N$ .** Failsafe  $N$  refers to the number of excluded studies with an average effect size of zero that would have to be included in the meta-analysis to lower the observed mean effect size to a non-significant level. Rosenthal (1979) introduced this concept, and it can be thought of as the number of studies that found (on average) no effect that would have to have been “filed away” in order to make the present meta-analysis meaningless. The larger the number, the more robust to publication bias the findings can be thought to be.

## Results

### Search Outcome

The search of PubMed resulted in 6,208 publications, 26 of which met inclusion criteria. The search of PsycInfo resulted in 788 additional, unique publications, only three of which met inclusion criteria. The search of ProQuest Dissertations & Theses Global resulted in 157 manuscripts. Of these, only two met inclusion criteria. In the case of duplicate samples, only the first study found that utilized the sample was included. Table 1 includes a description of all included studies ( $N=31$ ) on key study characteristics. The complete list of APA citations is included as Appendix B.



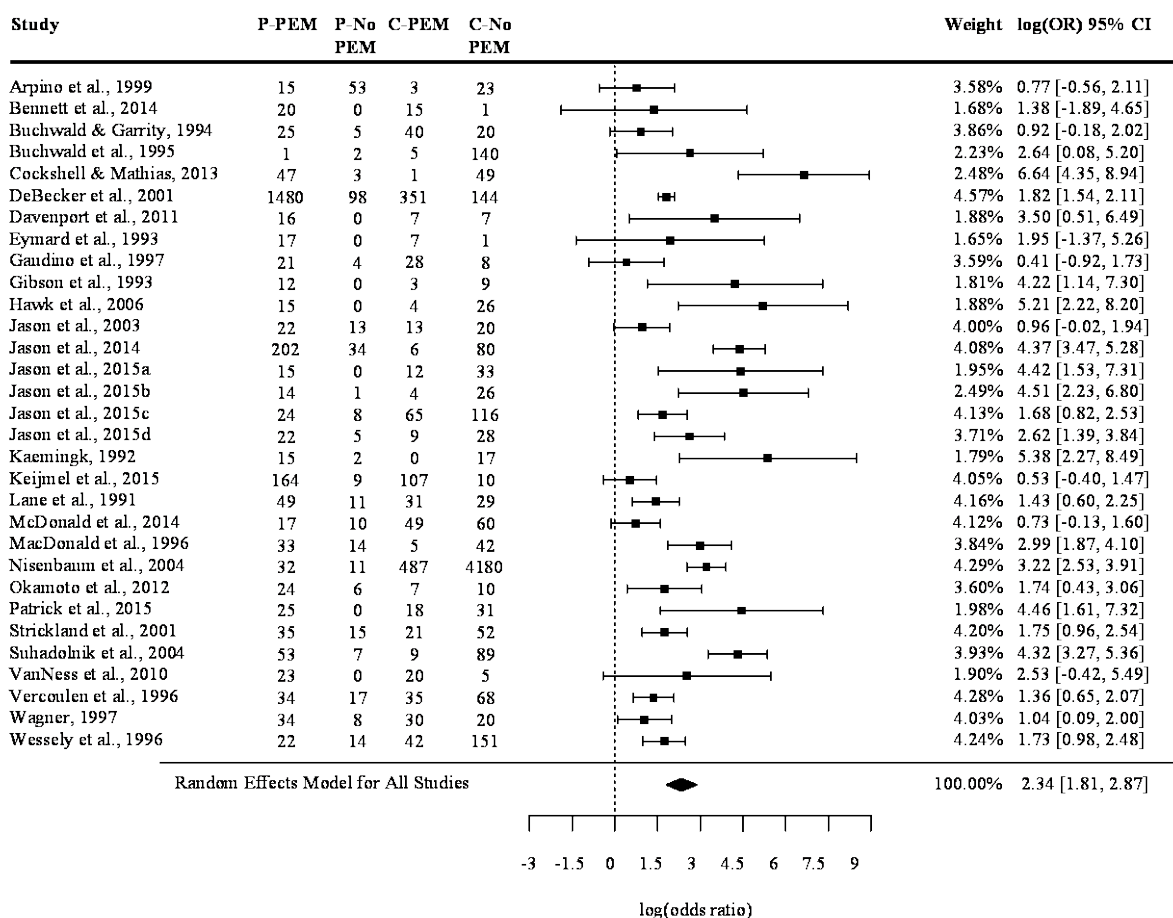
**Table 1.** Summary of Studies ( $N = 31$ )

Study	Patient Recruitment	Diagnosis	Case Def.	PEM Assessment	Controls
Arpino et al., 1993	Primary Care	MD- Study	Fukuda & Holmes	Interview; Occur.	CF
Bennett et al., 2014	Unknown	MD- Study	Fukuda	Interview; Occur.	MDD
Buchwald & Garrity, 1994	Tertiary Care	MD- Study	Holmes	NV Quest.; Occur.	FM & MCS
Buchwald et al., 1995	Primary Care	MD- Study	Fukuda	NV Quest.; Occur.	CF & HC
Cockshell & Mathias, 2013	Primary & Tertiary Care	MD- Study	Fukuda	CDC-SI; Occur.	HC
De Becker et al., 2001	Tertiary Care	MD- Study	Fukuda	GSC; Sev.	CF
Davenport et al., 2011	Convenience	Self-report	Fukuda	NV Quest.; Occur.	HC
Eymard et al., 1993	Tertiary Care	MD- Study	Holmes	Interview; Occur.	CF
Gaudino et al., 1997	Tertiary Care	MD- Study	Fukuda	NV Quest.; Freq.	Lyme
Gibson et al., 1993	Tertiary Care	MD- Outside	Oxford	Interview; Occur.	HC
Hawk et al., 2006	Convenience	MD- Outside	Fukuda	NV Quest.; Occur.	MDD & HC
Jason et al., 2003	Random- CB	MD- Study	Fukuda & London	NV Quest.; Occur.	CF
Jason et al., 2014	Convenience	MD- Outside	Fukuda	DSQ; Freq. & Sev.	HC
Jason et al., 2015a	Convenience	MD- Study	Fukuda	Interview; Occur.	MS, Lupus & HC
Jason et al., 2015b	Convenience	MD- Outside	Fukuda	NV Quest.; Occur.	MDD & HC
Jason et al., 2015c	Random- CB	MD- Study	Fukuda	Interview; Occur.	CF & HC
Jason et al., 2015d	Convenience	MD- Outside	Fukuda	CDC SI; Freq./Sev.	MDD
Kaemingk, 1992*	Tertiary Care	MD- Outside	Unknown	NV Quest.; Sev.	HC
Keijmel et al., 2015	Tertiary Care	MD-Outside	Fukuda	NV Quest.; Occur.	Q-Fever
Lane et al., 1991	Tertiary Care	MD- Study	Holmes	Interview; Occur.	CF
McDonald et al., 2014	Tertiary Care	Self-report	Unknown	NV Quest.; Occur.	POTS
MacDonald et al., 1996	Tertiary Care	MD- Study	Holmes	Interview; Freq.	HC
Nisenbaum et al., 2004	Random- CB	MD- Study	Fukuda	NV Quest.; Occur.	CF & HC
Okamoto et al., 2012	Tertiary Care	MD- Study	Fukuda	Unknown	POTS
Patrick et al., 2015	Convenience	MD- Study	Canadian	NV Quest.; Occur.	Lyme, Lupus & HC
Strickland et al., 2001	Tertiary Care	MD- Outside	Fukuda	NV Quest.; Occur.	CF
Suhadolnik et al., 2004	Tertiary Care	MD- Study	Fukuda & Holmes	NV Quest.; Occur.	HC & MDD
VanNess et al., 2010	Tertiary Care	MD- Outside	Fukuda	NV Quest.; Occur.	HC
Vercoulen et al., 1996	Tertiary Care	MD- Study	Unknown	NV Quest., Freq.	HC & MS
Wagner, 1997*	Other	MD- Review	Fukuda	NV Quest., Occur.	CF
Wessely et al., 1996	Primary Care	MD- Study	Fukuda	NV Quest., Occur.	HC

\*Dissertation; *Random-CB*= Randomized community-based sampling; *Occur.*= Reported occurrence of PEM only w/o thresholding; *NV Quest.*= Non-validated questionnaire used to assess PEM; *CDC-SI*= Centers for Disease Control Symptom Inventory used to assess PEM; *GSC*= Goldstein Symptom Checklist used to assess PEM; *Sev.*= Utilized some threshold of severity to assess PEM; *Freq.*= Utilized some threshold of frequency to assess PEM; *DSQ*= DePaul Symptom Questionnaire used to assess PEM; *CF*= chronic fatigue or idiopathic chronic fatigue; *MDD*= major depressive disorder; *FM*= fibromyalgia; *MCS*= multiple chemical sensitivities; *HC*= healthy controls; *MS*= multiple sclerosis; *POTS*= postural orthostatic tachycardia syndrome

## **Effect Size**

The weighted mean effect size (log odds ratio) with a 95% confidence interval for all studies was found to be 2.34 [1.81-2.87]. Thus, the odds of the presence of PEM being associated with an ME and CFS diagnosis is roughly 10.4 times more likely than the presence of PEM being associated with a non-ME and CFS diagnosis. The Forest Plot is a visual representation of the effect size and 95% confidence interval of all studies included in the meta-analysis, with studies listed on the vertical axis, and effect sizes on the horizontal axis of the figure (Card, 2011). The weighted mean effect size of all studies is indicated with a black diamond, as well as a dotted line indicating the null result (e.g., a log odds ratio value of 0). The Forest Plot is included as Figure 1.



**Figure 1.** Forest Plot, Random Effects Model

Legend: *P-PEM*, individuals w/ ME and CFS w/ post-exertional malaise; *P-No PEM*, individuals w/ ME and CFS w/o post-exertional malaise; *C-PEM*, controls w/ post-exertional malaise; *C-No PEM*, controls w/o post-exertional malaise; *log(OR)*, log odds ratio

### Tests of Study Heterogeneity

The Cochran  $Q$  statistic (Cochran, 1954) was significant,  $X^2(30) = 145.48, p < .001$ . The  $I^2$  (Higgins & Thompson, 2002) was 85.8%, suggesting that a considerable percentage of the variability in effect estimates is due to true heterogeneity. Together both results suggest that the included studies had significant effect size heterogeneity that is likely not accounted for by random error alone and thus moderator analyses were appropriate to investigate.

## Moderator Findings

A summary of subgroup mean effect size comparisons are included as Table 2. All subgroups of studies including more than one study had a significant within group  $Q$  statistic aside from one subgroup (dissertation). This suggests that significant effect size variability exists even within subgroups of studies that share certain moderators. The moderators with non-significant findings within the meta-regression included: publication status, method of diagnosis, case definition, mode of PEM assessment, and thresholding. That is, these were not found to be significant moderators of overall effect size variability and thus were not further investigated.

Patient recruitment strategy and control type were found to be significant moderators within the meta-regression. Regarding patient recruitment strategy, in studies that utilized a convenience method for recruiting individuals with ME and CFS the effect was found to be significantly greater than in studies that recruited individuals with ME and CFS through tertiary care and primary care settings. Regarding control type, in studies that utilized healthy controls or a combination of healthy controls and individuals with major depressive disorder, the effect was found to be significantly greater than in studies that utilized chronically fatigued individuals, individuals with POTS, or the “other” category which was composed of studies that utilized combinations of other illness groups such as multiple sclerosis, lupus or Lyme disease.

**Table 2.** Sub-Group Comparisons

<b>Moderators</b>	<b>log(odds ratio)</b>	<b># of studies</b>	<b><math>Q_{\text{within group}}</math></b>
<b>Publication Status</b>			
Published	2.33	29	137.32**
Dissertation	2.65	2	6.82
<b>Recruitment Approach<sup>1</sup></b>			
Tertiary Care	1.85 <sub>a</sub>	15	55.8**
Convenience	3.93 <sub>ab</sub>	7	6.59**
Primary Care	1.57 <sub>b</sub>	3	2.22**
Randomized Community-Based	2	3	15.94**
Other	2	3	19.54*

<b>Diagnosis</b>			
MD- Study	2.22	18	77.89**
MD- Outside	2.89	10	52.76**
Self-Report	0.95	2	3.03*
Other	1.04	1	0
<b>Case Definition</b>			
Fukuda	2.48	19	90.01**
Holmes	1.76	4	7.47**
Unknown	1.23	3	8.21**
Other	2.68	3	8.29**
Fukuda & Holmes	2.59	2	16.79*
<b>PEM Mode of Assessment</b>			
Non-Validated Questionnaire	2.14	18	85.56**
Interview	1.96	8	13.01**
Validated Questionnaire	3.61	4	43.49**
Other	1.74	1	0
<b>PEM Thresholding</b>			
No	2.33	23	99.97**
Yes	2.48	7	45.03**
Other	1.74	1	0
<b>Control<sup>1</sup></b>			
Healthy Controls (HC)	3.7 <sub>abc</sub>	8	32.23**
Chronic Fatigue (CF)	1.5 <sub>ad</sub>	7	6.97**
Other	1.13 <sub>be</sub>	6	13.47**
CF & HC	2.51	3	7.52**
MDD & HC	4.43 <sub>def</sub>	3	.31**
MDD (major depressive disorder)	2.46	2	.48**
POTS	1.04 <sub>cf</sub>	2	1.58**

*POTS* = postural orthostatic tachycardia syndrome

<sup>1</sup>Significant moderator category based upon meta-regression

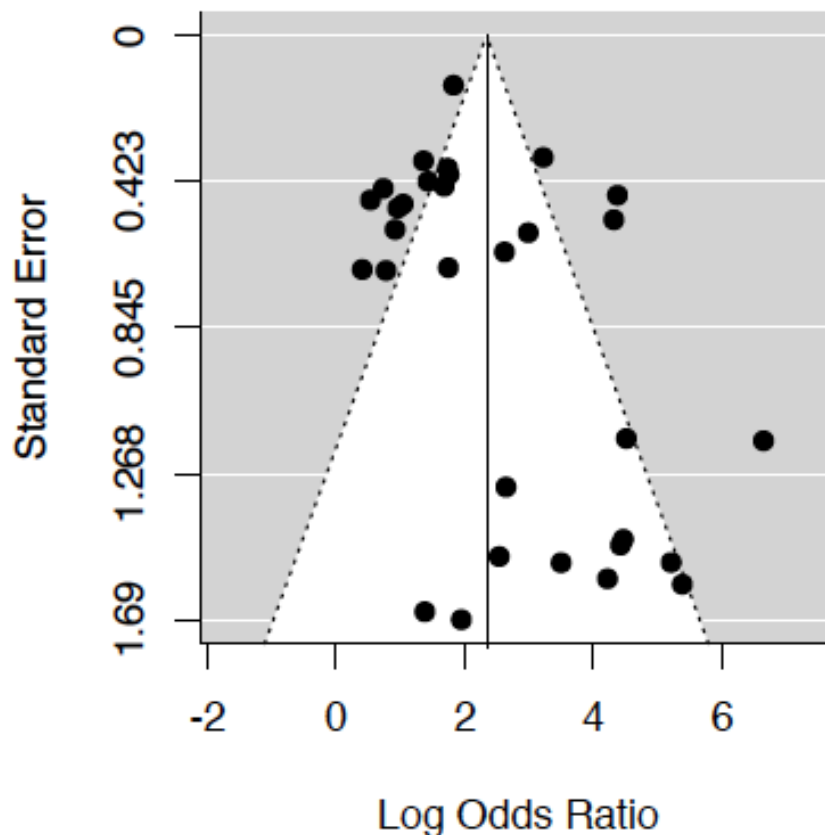
\* $p < .05$ , \*\* $p < .001$  on  $Q_{\text{within group}}$

Subscripts within a column for a given moderator reveal a significant contrast on  $Q_{\text{between group}}$  at  $p < .001$

## Publication Bias Findings

The Funnel Plot is included as Figure 2. Although this is a subjective visual assessment, studies with small sample sizes appear to be more variable on effect size (representing the “base” of the triangle), and as sample sizes increase the variability in effect size decreases (representing the “point” of the triangle). The shape suggests that publication bias may not be an issue.

Additionally, the Fail-Safe  $N$  was found to be 4,811 ( $p < .001$ ) utilizing the Rosenthal Approach. Thus, 4,811 studies with an average effect size of zero would have to be included in the meta-analysis to lower the observed mean effect size to a non-significant level, suggesting that the present results are quite robust to potential publication bias. Begg-Mazumdar's rank correlation test, an objective assessment of funnel plot asymmetry (Kendall's  $\tau = 0.19, p = .14$ ) suggests publication bias is not an issue but power may be too low to detect significance. Egger's linear regression approach found the intercept value (estimate of potential bias) to be  $1.07, p = .02$  which suggests possible publication bias. However, Higgins and Green (2011) suggest that when utilizing odds-ratios, both Begg-Mazumdar's and Egger's approaches may be problematic due to the natural correlation of odds-ratios to their standard errors. Taking this into account, and the high Fail-Safe  $N$  value, the present results seem to be robust to publication bias.



**Figure 2.** Funnel Plot

## Discussion

The major finding of the present meta-analysis is that the presence of subjectively reported post-exertional malaise is 10.4 times more likely to be associated with an ME and CFS diagnosis than with control status. This finding can reasonably be considered robust to publication bias, and strongly suggests that self-reported PEM discriminates well between ME and CFS and controls and has meta-analytic support as a cardinal symptom of the disease. The hypothesis that PEM and ME and CFS would be significantly associated is supported. Thus, case definitions that require PEM for a diagnosis may be most appropriate for use (e.g., Carruthers et al., 2003) and should be relied upon rather than the most commonly utilized polythetic Fukuda et al. (1994) criteria.

### Implications of Moderator Analyses

The total sample of studies ( $N=31$ ) and all of the study subgroups defined by study-level characteristics evidenced significant within-group variability on effect size. Thus, the hypothesis that studies on ME and CFS and PEM are heterogeneous on effect size was supported. The overall estimate of effect size was significantly impacted by two study-level moderators: patient recruitment strategy and control selection. The hypothesis that studies that utilized a healthy control group would find a stronger effect was supported by the results. It should be noted that neither of the moderators changed the overall pattern of the effect (PEM is strongly associated with ME and CFS regardless), but significantly changed the strength of the effect. That is, studies that utilized healthy individuals or a combination of healthy individuals and individuals with major depressive disorder (MDD) as comparison groups found significantly higher odds of ME and CFS being associated with PEM (40.4 times more likely when utilizing healthy individuals and 81.5 times more likely when utilizing the combination) than the studies that

utilized other disease groups or chronically fatigued groups as comparisons. Surprisingly, the group of studies that utilized an MDD-only control group were not significantly different from the other disease study subgroups, but this is likely due to low power as just two studies were included in the MDD-only group. These findings suggest that PEM may discriminate ME and CFS from healthy or depressed individuals more strongly than it discriminates ME and CFS from other illness groups. This fits with previous literature suggesting that ME and CFS and MDD are distinct entities (Barnden, Crouch, Kwiatek, Burnet & Del Fante, 2015; Christley, Duffy, Everall & Martin, 2013).

When considering the impact of patient recruitment strategy, the effect was much stronger in the studies that utilized convenience methods (50.9 times more likely that PEM and ME and CFS are associated) than studies recruiting patients from primary or tertiary care settings. Thus, the hypothesis that studies that recruit from tertiary care settings or utilize convenience methods may select for patients with more severe symptomatology was only partially supported. The hypothesis that studies that recruit using randomized, community-based methods would have milder symptomatology was not supported. It is somewhat counterintuitive that the convenience sampling and tertiary care sampling subgroups were significantly different given that these strategies tend to capture similar patient groups (Jason, Sunnquist, et al., 2015). The strength of the phenomenon in the convenience sampling subgroup compared to the other subgroups may suggest that individuals with ME and CFS that are recruited from support groups or online are some of the most profoundly ill.

Many of the moderators that were hypothesized to be of import were not significant contributors to effect size variability (diagnostic approach, method of PEM assessment, and case definition) and thus subgroup comparison hypotheses could not be investigated. Further, the



intersections of many of the proposed moderators may have provided more rich information (e.g., subgroups defined by their patient recruitment strategy *and* case definition used) but the resulting subgroups would have been too small for comparison. Future meta-analytic studies of ME and CFS should investigate subgroups defined by a number of study-level characteristics if power allows.

### **Limitations**

This study has a number of limitations. Most importantly, the number of studies that met inclusion criteria is relatively low (while still being appropriate for meta-analysis). The primary reasons studies were excluded was lack of reporting on PEM. Many studies focused exclusively on the symptom of fatigue, missing the unique element of post-exertional sickness and symptom exacerbation that PEM describes. Other studies reported just one composite somatic symptom severity score that didn't allow for the teasing out of unique symptom occurrence. Ideally, it might have been possible to reach out to lead authors about the latter issue to collect this data, but this was outside the scope of the present investigation.

Regarding publication bias, while an attempt was made to include dissertations and theses, many of the abstracts that seemed promising were inaccessible and thus could not be included in the present study. After assessing for publication bias, a decision was made not to contact leaders in the field for unpublished data from the timeframe of interest due to the large result of the Fail-Safe  $N$  analysis. However, this could also be considered a limitation.

The use of just one coder for the meta-analysis was both a limitation and a strength. This may mean that more bias was introduced than if multiple coders were used (Buscemi, Hartling, Vandermeer, Tjosvold & Klassen, 2006), but also allowed for more consistency in applying the inclusion criteria and in the subsequent coding process. That is, the introduction of bias may

have been more systematic than if multiple coders had been utilized. Additionally, while those studies that were included provided data on independent samples, it is not possible to be fully confident that individuals with ME and CFS were not represented in more than one study.

### **Future Directions**

This meta-analysis was only focused on subjective presence of PEM. While method of PEM assessment (thresholding for frequency and severity versus occurrence alone) was considered as a moderator, it would also be important to meta-analyze PEM severity outcomes in patients versus controls. However, this may be difficult until more researchers begin reporting on the intensity of specific symptom domains rather than just reporting composite somatic symptom scores. Future meta-analyses of PEM should also focus on studies that investigate objective performance on exercise testing, and how well this testing may distinguish between patients and controls. Cognitive functioning has already been investigated meta-analytically (Cockshell & Mathias, 2010), but other core symptoms of ME and CFS (sleep dysfunction, autonomic dysfunction, pain, etc.) could be investigated in a similar way.

### **Conclusion**

As the field continues to move toward an empirical approach to ME and CFS case definition, it is key to utilize the tool of meta-analysis to quantitatively synthesize results. While treatment trials have traditionally been the basis for meta-analyses in the ME and CFS field, more attention should be paid to the role of meta-analysis in empirical case definition development. Meta-analysis allows for a unique type of systematic communication between researchers and permits broader claims to be made about an understanding of phenomena. This study highlights the importance of considering not only the mean effect size of a sample of studies that purport to study the same outcome, but also how that effect is moderated by the

study design choices of researchers. Through increased collaboration, multi-site studies, and more consistent adherence to best practices [such as considering the minimum data elements for ME and CFS research reports recommended by Jason et al. (2012)], the field can move closer to more comparable and replicable investigations. The present study lends strong support for PEM as a core symptom of ME and CFS that is capable of distinguishing between individuals with and without this disease and should be required under a research case definition.

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**Appendix A.**  
**Coding Protocol**

Descriptive Information about the Article

Full APA 6<sup>th</sup> edition citation:

If unpublished, title:

Is this an unpublished thesis or dissertation? (Yes/No)

If so, list institution:

Is this an unpublished study that was obtained from a researcher? (Yes/No)

Full list of authors (if didn't provide APA 6<sup>th</sup> citation above):

Statistical Information

Total sample size of both patients and controls:

ME/CFS patient sample size:

Control sample size:

If included in MA 1:

Number of patients with PEM:

Number of controls with PEM:

Patient Recruitment Method- complete for all studies

Were patients recruited from a primary care setting? (Yes/No)

Were patients recruited from tertiary or specialty care settings? (Yes/No)

Were patients recruited using randomized, community-based methods? (Yes/No)

Were patients recruited via convenience methods (e.g., from internet forums, through advocacy groups, public postings)? (Yes/No)

Were patients recruited based upon having a viral illness? (Yes/No)

Additional notes about patient recruitment:

Method of Diagnostic Confirmation- complete for all studies

Were patients assessed and diagnosed with ME or CFS by a physician for the present study?

(Yes/No)

Were patients diagnosed with ME or CFS based upon self-reported symptoms? (Yes/No)

Did patients provide diagnostic confirmation from an outside physician? (Yes/No)

Did patients self-report their diagnosis only (no assessment of symptoms or physician assessment)? (Yes/No)

Additional notes about diagnostic confirmation method:

Control Selection- complete for all studies

Were controls described as healthy?

If yes, was healthy defined as the absence of ME/CFS? (Yes/No)

As the absence of other physical illness? (Yes/No)

As the absence of mental illness? (Yes/No)

Was healthy undefined? (Yes/No)

Were controls described as demographically matched to patients? (Yes/No)

If yes, on what demographic variables were they matched to patients on:

Age

Gender

Ethnicity

Work status

Socioeconomic status

Other (list):

Were controls assessed by a physician for the present study? (Yes/No)

Were controls described as sedentary? (Yes/No)

If yes, was sedentary defined by a certain level of activity? (Yes/No)

If so, what was the cut-off for sedentary?

Was sedentary was defined in another way? (Yes/No)

Please list:

Was sedentary undefined? (Yes/No)

Were controls from another illness group? (Yes/No)

If yes, what illness group?

Were controls family members of the patient sample? (Yes/No)

Were controls friends of the patient sample? (Yes/No)

Additional notes about control selection:

Case Definitions- complete for all studies

Did the study use an ME, CFS, or ME/CFS case definition to identify cases? (Yes/No)

If yes, which case definition? Select all that apply:

Holmes CFS (1988)

Oxford CFS (1991)

Fukuda CFS (1994)

Clinical Canadian Criteria ME/CFS (2003)

CDC Empiric Criteria for CFS (2005)

ME International Consensus Criteria (2012)

Institute of Medicine's Systemic Exertion Intolerance Disease (2015)

Other (list):

Additional notes about case definition:

Demographic information for patients- complete for all studies

Age range/Mean/SD:

*Gender*

% (n) female/% (n) male/% (n) other:

*Ethnicity:*

% (n) Caucasian

% (n) African-American

% (n) Hispanic

% (n) Asian/Pacific Islander

% (n) American Indian/Alaskan Native

% (n) Other

*Marital Status:*

% (n) Married

% (n) Single

% (n) Divorced

% (n) Widowed

% (n) Other

*Work Status*

% (n) Working full- or part-time

% (n) Student

% (n) On disability

% (n) Retired

% (n) Unemployed

% (n) Homemaker



% (n) Other

Illness duration in years:

Onset type (sudden vs gradual):

If provided, how were sudden and gradual defined?

Demographic information for controls- complete for all studies

Age range/Mean/SD:

*Gender*

% (n) female/% (n) male/% (n) other:

*Ethnicity:*

% (n) Caucasian

% (n) African-American

% (n) Hispanic

% (n) Asian/Pacific Islander

% (n) American Indian/Alaskan Native

% (n) Other

*Marital Status:*

% (n) Married

% (n) Single

% (n) Divorced

% (n) Widowed

% (n) other

*Work Status*

% (n) Working full- or part-time

% (n) Student

% (n) On disability

% (n) Retired

% (n) Unemployed

% (n) Homemaker

% (n) other

Assessment of PEM occurrence- Complete for MA #1 only

Was PEM assessed using a validated self-report measure? (Yes/No)

If yes, what was the measure called?

CDC Symptom Inventory

DePaul Symptom Questionnaire

The CFS Questionnaire

The Medical Questionnaire

Other (describe):

Was PEM assessed through physician interview? (Yes/No)

Was PEM assessed using a non-validated, self-report measure? (Yes/No)

If yes, describe:

Was PEM assessed using some measure of frequency? (Yes/No)

If yes, describe:

Was PEM assessed using some measure of severity? (Yes/No)

If yes, describe:

Was occurrence of PEM defined by meeting certain criteria or a defined threshold for frequency?  
(Yes/No)

If yes, describe:

Was occurrence of PEM defined by meeting certain criteria or a defined threshold for severity?

(Yes/No)

If yes, describe:

Was PEM defined simply as present or absent, with no mention of frequency or severity?

(Yes/No)

**Appendix B.**

**List of Studies Included in the Meta-Analysis**

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