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The implications of using a broad versus narrow set of criteria in research

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Abstract

The Fukuda *et al.* criteria is the most widely used clinical case definition for diagnosing patients with chronic fatigue syndrome (CFS). Despite the frequency with which the Fukuda criteria are applied, the list of symptoms outlined in this case definition were not well enough specified to be easily applied to research settings. In 2005, Reeves *et al.* laid out a set of standards for operationalizing the Fukuda definition, specifying scales and cutoff scores for measuring the symptom criteria. This operationalization, often known as the empirical criteria, has been shown to identify an unexpectedly large number of patients, seemingly widening the net of inclusion for CFS diagnostic criteria. However, in a recent study in 2016 by Unger and colleagues it has been suggested that the 2005 Reeves *et al.* 2005 operationalization of the Fukuda criteria does not over-identify the number of patients with CFS as had been previously reported. This article reviews prior studies which provide context for these findings and offers a possible explanation for the discrepancies. Clearly, determining what case definition to use and how to operationalize it remains an important activity for scientists in this field, as it will influence work in multiple domains, including etiology, pathophysiology, epidemiology and treatment.

The implications of using a broad versus narrow set of criteria in research

Although the Fukuda criteria [1] are widely as a research case definition for diagnosing patients with chronic fatigue syndrome (CFS), the symptoms and other characteristics outlined in Fukuda were not well enough specified to be easily and reliably applied across a variety of settings. In an effort to resolve this problem, Reeves and colleagues in 2005 [2] laid out a set of standards for operationalizing the Fukuda case definition, specifying scales and cut off scores for assessing the symptom criteria. This operationalization, often known as the "empirical criteria," had been shown to identify an unexpectedly large number of patients [2], seemingly widening the net of inclusion for the Fukuda case definition. However, recently, Unger and colleagues [3] have published an article revisiting the 2005 Reeves *et al.* operationalization as well as examining the issue of increased prevalence rates from the 2007 study by Reeves and colleagues [4]. We review these new findings, putting them in context and trying to highlight some of the reasons for the dramatic shifts in CFS prevalence rates across various studies.

Most notably, the Center for Disease Control (CDC) estimates of CFS prevalence rates have increased dramatically over the years. In 2003, Reyes *et al.* published a prevalence study using the traditional approach to diagnosing CFS via Fukuda and found a prevalence rate of .24% in Wichita, Kansas [5].[1] This rate was somewhat comparable to a previous population prevalence study in Chicago, which found a rate of .42% [6], again using the traditional approach to the Fukuda criteria. However, in a subsequent CDC population based study in Georgia, using the 2005 Reeves *et al.* empirical criteria, Reeves and colleagues concluded that the CFS prevalence rate had risen to 2.54% [4], which represents a 10-fold increase compared to the earlier CDC estimates. One explanation for the 10-fold increase is that cases of CFS did indeed increase over time, though this seems unlikely. When Jason and colleagues [7] conducted a follow-up to their original community-based prevalence study [6] using the same traditional approach to diagnosing with the Fukuda criteria, they found that 10 years later CFS prevalence rates had remained relatively stable [7]. In light of this, other explanations for the increase in CDC prevalence rates need to be explored.

CDC prevalence studies

It is, therefore, important to revisit the earlier studies conducted by the CDC to better understand the differences in methodological design that could have led to these the prevalence rate discrepancies. The first CDC prevalence study using the Fukuda criteria was conducted by Reyes and colleagues [5] from 1997 to 2000 in Wichita, Kansas, and involved 56,146 adults who participated in a structured interview via telephone. Those who reported experiencing CFS-like symptoms, including fatigue and at least 4 of the required Fukuda symptoms (n = 299) were brought into a clinic for a comprehensive assessment. Of those assessed in person at the clinic, 141 participants were found to have medical/psychiatric exclusions which explained their fatigue with other diagnoses, and 43 were diagnosed with CFS. This final total of 43 patients with CFS out of the 56,146 participants screened resulted in the reported prevalence rate of .24%.

In 2002 and 2003, Reeves and colleagues evaluated 227 participants from the original Wichita sample who had agreed to participate in a clinical follow-up study [2]. During the original Wichita study, participants had been followed at regular intervals for four years. A total of 70 individuals from the original sample were diagnosed with CFS at

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least once during this 4-year period. Fifty-eight of these 70 agreed to be medically and psychiatrically evaluated and were included in the Reeves *et al.*'s 2005 study [2] follow-up sample of 227. The remainder of the 227 consisted of 55 matched controls; a group of 59 individuals who reported fatigue, but did not meet a sufficient number of criteria to be diagnosed with CFS; and 55 individuals with melancholic depression and some level of fatigue. This follow-up study used two different approaches to classifying participants, both of which were based on the Fukuda criteria. The first approach followed the same interview question protocol used for classifying participants in the 2003 Reyes *et al.* study and was labeled the "surveillance criteria." This approach, which we refer to as the "traditional approach," used an interview protocol asking about specific symptoms associated with the Fukuda case definition. The second method used a series of questionnaires and cutoff criteria aimed at reliably operationalizing the Fukuda case definition. The authors called this approach the "clinically empirical definition," which we will refer to as the empirical criteria. However, they found little agreement between these two classification systems. The traditional method, or "surveillance criteria" only classified 16 individuals as having CFS, whereas 43 were diagnosed with CFS using the empirical criteria [2]. Clearly, the empirical criteria identified considerably more individuals with CFS than the traditional approach.

The next community-based CDC prevalence study was conducted in Georgia from 2005-2006 and published by Reeves *et al.* in 2007 [4]. Again, this study used the empirical criteria. In the Georgia study, about half as many individuals were initially interviewed (N = 19,381), compared to the original Reyes *et al.* Wichita study (N = 56,146) [5]. After the initial telephone interviews, Reeves *et al.* [4] identified a total of 292 participants with CFS-like symptoms (versus 299 in the Wichita study). In addition to those with CFS-like symptoms, a randomly selected set individuals from other illness categories were also invited for clinical evaluation: 1) chronically unwell (*i.e.*, ill for 6 months or more with or without fatigue but not classified as having CFS-like symptoms; n = 268) 2) prolonged unwell (*i.e.*, unwell for less than 6 months; n = 60); and 3) well (n = 163).

Of the 292 participants with CFS-like symptoms, 141 were excluded for medical/psychiatric reasons (equal to the 141 in the Wichita study), and 84 individuals were diagnosed with CFS (versus 43 in the Wichita study). In fact, the Georgia study found about twice the number of individuals with CFS as did the Wichita study and did so with a sample less than half the size. When the Reeves group examined the wider set of clinic participants who had not initially self-reported CFS-like symptoms, they identified several more CFS cases [4]. The chronically unwell group yielded 26 CFS cases; the prolonged unwell group yielded 2 cases, and the well group yielded 1 case, for a final total of 113 individuals identified as having CFS. To summarize, using a considerably smaller sample, the Georgia study [3] identified many more patients with CFS when using the empirical criteria, which equates to a 10-fold in prevalence estimates between the .24% rate from the 2003 Reyes *et al.* study [5] and the 2.54% rate from Reeves and colleagues 2007 study [4].

Most recently, Unger *et al.* [3] used follow-up data collected between 2007 and 2009 from the same Georgia study sample to comprehensively evaluate 751 individuals in a clinic. Of the 751, a subgroup of 499 were eligible for inclusion in a comparison of two diagnostic methods (249 had been excluded due to medical/exclusionary conditions, and 3 were excluded due to incomplete data). Both diagnostic methods were based on the Fukuda case definition. The first method used the same traditional approach as used in the 2003 study by Reyes and colleagues [5]. This approach used an interview protocol that directly questioned participants about symptoms and then made diagnostic determinations based on their self-report symptoms. The second approach used the set of standardized questionnaires and related cut points established by Reeves and colleagues [2]. While Reeves *et al.* [2] used the label "clinically empirical criteria," Unger *et al.* [3] referred to this as the "Georgia method," (we will continue to use "empirical criteria" when discussing this approach). Unger and colleagues found that 71 of their 499 eligible participants (14%) met CFS criteria using the empirical criteria, whereas 59 (12%) met diagnostic criteria using the traditional approach [3]. The 12 additional individuals identified as having CFS using the empirical criteria represents only a small increase in the number of diagnoses compared to the traditional method [3].

Based on these findings, Unger and colleagues have suggested that "The two methods demonstrated substantial concordance" [3], suggesting that there are no substantial differences between the traditional approach to evaluating the Fukuda criteria versus the empirical criteria. If this is the case, it would be important to understand why CDC estimates of CFS prevalence rates have fluctuated so dramatically between the 2003 Reyes *et al.* study [5] and the 2007 Reeves *et al.* study [4] that reported prevalence rates that are 10-fold higher.

Explaining variation in prevalence estimates

Unger and colleagues identified a number of issues that attempt to explain the large increase in prevalence estimates for CFS marked by these two previous studies. We focus on several of the major issues laid out in the Unger *et al.* article [3] as well as some additional issues in an attempt to differentiate Reyes *et al.*'s 2003 Wichita study [5] and the Georgia studies [3,4]. More minor issues in the Unger study are covered elsewhere[2].

Study inclusion

The first issue is related to the method by which participants were selected for both prevalence studies [4,5]. The Georgia study by Reeves *et al.* in 2007 [4] expanded the screening criteria required for enrollment in the clinical valuation phase from only requiring fatigue to enrolling a larger subset of all those who had reported one or more of the four major core symptoms of the syndrome: fatigue, cognitive impairment, unrefreshing sleep, and pain. However, this alone cannot explain the 10-fold increase in prevalence rates. In fact, Reeves and colleagues [4], in the original Georgia study noted that only "11.5% of subjects with CFS would not have been detected in previous studies that queried participants only for fatigue."

Operationalization

A second issue relates to the instruments and cutoffs utilized in the empirical criteria. The 2007 Reeves *et al.* study [4] used empirical criteria that involved standardized instruments and cut offs compared to the traditional method, possibly accounting for some of the discrepancies. It could be possible that the 10-fold increase in CFS prevalence could be partly accounted for by differences in the two methods of diagnosing patients. It is, therefore, important to examine the standardized instruments used in the 2005 Reeves *et al.* empirical criteria [2] in order to better understand what might have led to the increased estimation of prevalence rates.

Reeves *et al.* [2] recommended the use of the Medical Outcome Survey Short-Form-36 (SF-36; [8]), Multidimensional Fatigue Inventory (MFI;[9]) and the CDC Symptom Inventory (SI; [10]) to

implement the empirical criteria. Reeves *et al.* [2] used the SF-36, along with norms-based cutoff scores, in order to operationalize disability. To meet the empirical criteria for substantial reduction, individuals only needed to score in the lower 25th percentile on one of four specific SF-36 subscales. One of the four SF-36 subscales assessed includes the role emotional scale, which measures issues such as problems with work or other daily activities that stem from emotional issues. Ware and Sherbourne [8] found that the mean score for the role emotional subscale for a group with clinical depression was 38.9. Almost all those with clinical depression would meet the CFS empirical criteria for substantial reduction (*i.e.*, at or below the lower 25th percentile on this scale, defined as a score of less than or equal to 66.7).

In addition to assessing substantial reduction via the SF-36 disability measure, the empirical criteria also measured other key CFS symptoms using the CDC Symptom Inventory, which gathers information about symptom occurrences within the past month rather than the past six months as had been required by the Fukuda case definition. Most importantly, this instrument was scored in a way that did not require several key symptoms for CFS, which include post-exertional malaise, unrefreshing sleep, and cognitive impairment. In the CDC Symptom Inventory, each symptom is given the same value. For example, a participant reporting severe and frequent headaches would be assigned the same value as a participant reporting severe and frequent post-exertional malaise. In fact, using the Fukuda criteria, an individual might not have any of the symptoms repeatedly shown to be core and critical symptoms of CFS, yet could still be diagnosed with the illness. However, this critique would apply to both the traditional and empiric method for diagnosing patients with CFS.

Finally, the 2005 Reeves *et al.* empirical criteria [2] used the Multidimensional Fatigue Inventory (MFI; [9]) to measure fatigue. Jason and colleagues [11] have since shown that 74% of a group identified as having major depression would meet the 2005 Reeves *et al.* empirical criteria for fatigue using the MFI. For example, an individual with depression could meet CFS criteria by answering true to the following MFI items: "I get little done" or "I do very little in a day," while also answering negatively to "I feel very active" or "I think I do a lot in a day." It is, therefore, relatively common for individuals with depression to meet the empirical criteria for both disability and fatigue.

Possible inclusion of patients with solely psychiatric conditions

One possible reason for the prevalence discrepancies involves the means by which these instruments assess for psychiatric problems. Specifically, it is possible that individuals with a purely affective illness, such as Major Depressive Disorder (MDD), might have been included in the increased estimates. The CDC CFS prevalence rate of 2.54% [4] is remarkably comparable to the prevalence rate of MDD [12]. For major depressive episode, the one-month prevalence is 2.2%, and lifetime prevalence is 5.8%. A person with primary MDD could be misdiagnosed with CFS, as people with MDD often experience chronic fatigue and several of the other minor symptoms, such as unrefreshing sleep, joint pain, muscle pain, and impairment in concentration. To address this, in the past, our research group performed an investigation that found it possible to discriminate with 100% accuracy between CFS and individuals with MDD, using instruments that differentiate these conditions [13].

Because it is possible that those with a purely affective disorder might be inappropriately diagnosed with CFS, our research team conducted a study to clarify this situation. Jason and colleagues [11] found that 38% of a group with a primary affective disorder (*i.e.*, MDD) would have been misdiagnosed with CFS using the 2005 Reeves *et al.* empirical operationalization of the CFS case definition. In another study [14] , when using all three of Reeves *et al.*'s empirical criteria for 1) fatigue, 2) symptoms and 3) disability, the sensitivity was at an unacceptably low level of .65. In other words, only 65% of true CFS cases were identified, suggesting that the empirical criteria were not able accurately to identify individuals who have this illness.

An accurate case definition must reliably exclude psychiatric confounds. Studies conducted by researchers not affiliated with the CDC are worth noting in this regard in comparison to the varying prevalence estimates published by the CDC. British studies [e.g., 15] have found a CFS prevalence rate of 2.6% (similar to [4]), but if psychological disorders were excluded from the British study, the CFS prevalence rate drops to only .5% in this sample. Other work [16] has compared those diagnosed with CFS in the Britain study [15] to a CFS sample from a hospital unit. Euba and colleagues [16] found that 59% of the community sample reported thinking their illness might be due to psychological or psychosocial causes, whereas only 7% of the hospital sample expressed this view.

Additionally, in a recent Institute of Medicine (IOM) report on CFS [17], the authors reviewed a study by Heim and colleagues [18] involving the role of childhood trauma in ME/CFS. Heim *et al.* [18] used the 2005 Reeves *et al.* empirical criteria [2], prompting the IOM panel to suggest that the use of these criteria resulted in a biased sample with overrepresentation of individuals with depression and posttraumatic stress disorder (PTSD). The panel also proposed that the high proportion of patients with serious psychiatric problems likely explained the study finding of an association between CFS and adverse childhood experiences [17].

It is possible that Unger and colleagues [3] were successful in eliminating psychiatric confounds, as they incorporated a number of methods to screen out these exclusionary conditions. Indeed, only one of the CFS cases they identified was diagnosed with moderate to severe depression. If this most recent iteration of the empirical criteria was successful in screening out those with exclusionary illnesses, then this might help explain why the two diagnostic methods (*i.e.*, the traditional approach and the empirical approach) in the Unger *et al.* [3] study resulted in the identification of a fairly similar number of CFS cases. However, many, if not most, ongoing CFS studies do not include structured clinical interviews aimed at identifying exclusionary psychiatric problems and ruling out the other potential causal factors.

Identification of core features of the illness

Another important issue is whether individuals with CFS are being correctly identified in these epidemiological studies. It is also possible that the Unger *et al.*'s study [3] did not include individuals who have the core symptoms or characteristics of CFS. In the Unger *et al.* study [3], only 10-11% of the CFS group reported a sudden onset, whereas in most tertiary clinics sudden onset is predominate [19]. Additionally, of the individuals who were classified as having CFS using the 2005 Reeves *et al.* empirical criteria [2], only 52% met the physical functioning disability criteria. In addition, only 77.8% were identified as having post-exertional malaise of 6 months or longer and 25.93% as having memory or concentration problems lasting for six months or longer (although rates are somewhat higher when including those who met either the traditional or empiric criteria). These levels of key symptoms are unusually low, indicating the inclusion of a high proportion of CFS cases that are missing key symptomology.

In fact, both the Fukuda case definition and the Reeves *et al.* empirical operationalization do not require several cardinal symptoms including post-exertional malaise, memory and concentration problems, and unrefreshing sleep. A recent review of 53 studies that used the Fukuda criteria for diagnosing CFS found that these three critical symptoms were detected among the groups identified as having CFS at variable rates: post-exertional malaise ranged from 25-100%, neurocognitive deficits from 16-100%, and unrefreshing sleep from 16-100% [20]. It is possible that those patients with CFS identified by the Fukuda criteria do not consistently report these core symptoms. For example, consider two hypothetical patients who meet the Fukuda criteria: Patient 1 has a sore throat, tender lymph nodes, joint, and muscle pain but not unrefreshing sleep, memory and concentration problems, and post-exertional malaise. Patient 2 has unrefreshing sleep, memory and concentration problems, and post-exertional malaise. The fact that both patients would be diagnosed with CFS using the Fukuda case definition shows the potential variability among this group of identified patients, who may experience only partially overlapping, or entirely non-overlapping core symptoms. Any attempt at creating an accurate research case definition would need to include the cardinal symptoms of the illness.

This problem of identifying patients who have classic CFS characteristics also occurred in the CDC community-based epidemiology study in Wichita, Kansas [5,21], 58 individuals who identified as having CFS during the first wave from 1997 through 2000, were brought back for a two day inpatient study that occurred from 2002 to 2003. Only 16 of these 58 (28% of the original group diagnosed with CFS) had a current consistent diagnosis of CFS at the follow-up. Recovery is not a likely explanation for this, as evidence suggests that the proportion of patients who recover is smaller [22]. It could be that the use of Fukuda, a fairly broad case definition, resulted in the identification of cases that differed substantially from what is typically seen in tertiary settings.

The role of lifestyle factors

Perhaps the most important factor worth consideration in understanding changes in the prevalence rates is whether there are understandable lifestyle explanations for the fatigue and other symptoms experienced by some of the patients in the 2007 Reeves *et al.* sample [4] and 2016 Unger *et al.* sample [3]. In today's society, many individuals are exhausted from working multiple jobs while meeting challenging family responsibilities, and as may experience cognitive and fatigue problems a result. Many of these individuals report high levels of symptoms, and if the evaluators are not extremely careful, some could be inappropriately classified as having CFS using the empirical criteria. Therefore a variety of factors, in addition to psychiatric issues, can result in CFS-like symptoms. These include but may not be limited to: medication side effects, poor sleep hygiene, weight, poor diet, deconditioning, and inactivity. It would be important for any research case definition to assess for and exclude these causes of fatigue. For instance, the empirical criteria does not seem to have a mechanism for excluding those whose fatigue and symptoms were due to ongoing excessive exertion.

Additionally, there is likely to be a good amount of variability in how this case definition is used. In particular, the potential for variation in the methods used to assess substantial reduction has not yet been adequately explored. Operationalizing key concepts outlined in the Fukuda criteria is important. For example, it would be useful to find a reproducible way to specify fatigue as outlined in Fukuda [1]: "chronic fatigue that is of new or definite onset (*i.e.,* not lifelong). The fatigue is not the result of ongoing exertion. The fatigue is not substantially alleviated by rest." To this end, others have outlined a way to define "lifelong,"[3] which is indeed a challenging task [23].

Let's examine how Unger and colleagues [3] operationalized "not substantially alleviated by rest." First the person would need to answer "no" to fatigue was made a lot better by rest to fulfill this requirement. But if they responded "yes" to fatigue was made a lot better by rest, they could be included if their fatigue was relieved by rest "some of the time," "a little of the time," "or hardly ever." They would be not included if they said that their fatigue was relieved by rest "all of the time" or "most of the time." The problem with this approach stems from the fact that much of the time, rest does relieve fatigue symptoms for many patients with CFS. However, for these patients, rest is not fully curative and does not increase the stamina and endurance necessary to carry on life tasks. Therefore, while it is important to operationalize this part of the Fukuda case definition, it is critical to do so in a way that distinguishes between those who's rest fully eliminates the symptom complex and those form whom this does not occur (e.g., patients with CFS). It is equally important to determine if CFS induced fatigue is result of ongoing exertion. The failure of the Unger *et al.* article [3] and the empiric criteria to address this key issue of ongoing exertion causing the fatigue is problematic. In other words, unless questions have been carefully crafted and validated, a person could meet the CFS diagnosis whose fatigue is mainly due to excessive exertion, and with lifestyle issues such as being over-committed.

The IOM case definition

A new case criteria for CFS was recently proposed by the IOM [17], and it does specify the 4 cardinal symptoms of CFS for inclusion in their new clinical criteria: 1) substantial reduction or impairment in the ability to engage in pre-illness levels of occupational, educational, social or personal activities; 2) post-exertional malaise; 3) unrefreshing sleep; and 4) at least one of the two following symptoms: cognitive impairment or orthostatic intolerance. While this approach does recognize the importance of the key symptoms, in practice it is vulnerable to other problems.

First, the IOM case definition [17] is different from the previous Fukuda *et al.* [1] and Carruthers *et al.* [24] case definitions in classifying psychiatric and medical issues as co-morbidities instead of exclusionary conditions. Using a community based sample that had not been screened for exclusionary illnesses, Jason and colleagues [25] estimated the IOM prevalence rate would be 2.8 times greater than past estimates using the traditional approach to the Fukuda criteria. This major discrepancy was the result of the new IOM clinical criteria including 47% of those with Melancholic Depression and 48% of those with a medical reason for their fatigue. In other words, the expansion of the CFS case definiton that has occurred with the 2005 Reeves *et al.* empirical criteria may likely continue with the deletion of the exclusionary criteria in the IOM recommendation.

These issues suggest that the clinical IOM criteria [17] are not to be used as a research case definition for CFS. While many researchers will continue to use the Fukuda case definition as a research criteria, some may now begin using the IOM clinical criteria for research purposes. Some researchers may feel that it is acceptable to use a variety of research criteria as long as definitions and methods are adequately explained in publication. However, this reduces the possibility of comparisons across studies or research labs, as each research group is likely to apply these different criteria in a variety of approaches to

diagnosing CFS. Alternatively, and toward the end of reducing the impact of this limitation, the research community might select one research criteria, either an empirically based one (though not the 2005 Reeves *et al.* criteria [2]), the Myalgic Encephalomyalitis-International Consensus Criteria (ME-ICC), the Canadian Consensus Criteria (CCC), the Ramsay Criteria, or the IOM clinical criteria with more extensive and concretely specified exclusions.

Conclusion

In this article, we have outlined the issues that should be considered and addressed in order to develop the kind of case criteria that could be reliably used across studies to accurately identify a homogeneous group of individuals with CFS. We believe it is critically important that research related to CFS is capable of reliably identifying a group of individuals with the illness, without including cases that confound CFS with other issues such as psychiatric disorders, medical conditions, and lifestyle issues. The discrepancies in prevalence estimates across the different studies outlined above may be related to the extent to which each study included or excluded these confounding issues in their assessment of CFS cases. If there are ambiguities with case definitions and improper operationalization of criteria, research aimed at accurately identifying individuals with CFS will continue to produce fundamentally different samples, resulting in difficulties replicating findings across different labs, estimating the prevalence of the illness, consistently identifying biomarkers, and determining which treatments help patients. In addition to a focus on reproducible operationalization of key elements, there is a need to develop a consensus about what research case definition to use.

Foot notes

[1]These rates were considerably higher than a prior CDC study, which found considerably lower rates from 0.004% to 0.0087% [26] but as this study used a different CFS case definition, we will limit our focus on those studies using the Fukuda *et al.* [1]criteria.

[2]Below are several more minor issues that are discrepancies from the original Reeves *et al.* [4] paper and the recent paper by Unger *et al.* Reeves *et al.* completed 5,623 interviews representing 3 groups of individuals who were unwell without fatigue, unwell with fatigue and well. However, on page 3 of Unger *et al.* [3] it is stated that 5,630 were interviewed. The number 5,630 came from an article by Decker *et al.* [27], and the numbers do not match what was reported in the Reeves *et al.* article. We are informed that in the Unger *et al.* study, 783 had a baseline medical examination, but in the Reeves *et al.* paper, the number is 781 (280 with exclusionary illnesses and 501 without). Finally, we are informed in the Unger *et al.* study that of those eligible for the 2007-2009 study, 681 participants were included who had been seen in the clinic without permanent exclusions [4] study indicates that there were only 501 individuals seen in the clinic without exclusionary illnesses).

[3]Initially, participants' responses to the question, "Have you always had persistent or recurring fatigue/energy problems, even back to your earliest memories as a child?" (Question 67 in the DSQ) were noted. Of the participants who answered "Yes" to this question, responses to two additional questions related to lifelong fatigue were considered. The question "How long ago did your fatigue/energy problem begin?" indicated whether participants remembered a time prior to their illness, and the question "Over what period of time did your fatigue/energy related illness develop?" indicated whether their illness had a new or definite onset (Questions 69 and 77 in the DSQ). Based on responses to these two questions, participants with suspected lifelong fatigue were re-contacted and asked five additional questions about the onset of their illness: (1) Around what age did your fatigue/energy-related illness begin? (2) When did you first begin to experience symptoms? (3) Even if you have always dealt with fatigue/energy problems, was there a point of "onset" of your illness, or a time when your symptoms became significantly worse? (4) In the case that you do not remember a time without fatigue/energy problems, have friends or family ever told you that there was a time when you did not have fatigue/energy problems? (5) Are there other relevant details we should know about the timing or onset of your fatigue/energy-related illness? Responses to these open-ended questions provided the information needed to determine which participants truly had lifelong fatigue.

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