CFS: A Review of Epidemiology and Natural History Studies

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The authors appreciate the financial assistance provided by the National Institute of Allergy and Infectious Diseases (grant number AI055735).
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ABSTRACT

Almost all studies with samples of patients who have chronic fatigue syndrome (CFS) have relied on referrals from physicians or health facilities. Under-served minorities, who not only tend to manifest higher levels of chronic illness, but are also less likely to seek and receive adequate medical care, have not been represented in these studies (1). This may have contributed to an under-estimation of CFS among minority groups (2). Few studies have derived their samples from socioeconomically and ethnically diverse community-based populations. A technical report issued by the Agency for Healthcare Research and Quality (3) concluded that estimating rates of recovery/improvement or relapse from CFS are not possible because there are so few natural history studies and those that are available have involved selected referral populations. This paper provides a review of epidemiologic studies of CFS followed by a discussion of diagnostic issues and risk factors for the illness. Findings from Jason et al.’s (4) epidemiologic study in a multi-ethnic, economically diverse urban area are highlighted as this research group is now examining the natural course of CFS over the past 10 years with this community-based sample. The current study will add to current epidemiologic and risk factors research by assessing the course, progression, and risk factors of CFS among a demographically diverse sample of participants who are unbiased by illness, help-seeking behaviors, or differential access to the health care system.
CFS: A Review of Epidemiology and Natural History Studies

The first widely publicized study of chronic fatigue syndrome (CFS) epidemiology was initiated by the Centers for Disease Control and Prevention (CDC) in the late 1980’s (5). Investigators requested that physicians in four cities identify patients who had a group of specified fatigue-related symptoms. Prevalence rates of CFS were found to range from 4.0 to 8.7 individuals per 100,000 cases (6). The majority of CFS cases were Caucasian females who were well-educated and potentially high-income earners. This epidemiological study conducted by the CDC, as well as others (7), derived its sample from physician referrals in hospital and community-based clinics. These and other similar studies may under-represent low-income individuals and minorities who have been shown to manifest higher levels of chronic illness, but are less likely to receive adequate care, and thus less likely to be counted in prevalence rates derived from treatment sources (8). It is also probable that these studies underestimated the prevalence of CFS in the general population because they did not account for low-income individuals who lack access to the health care system or patients with unexplained fatigue who tend to drop out of the medical care system (2). Further, early epidemiological studies utilized an older case definition for CFS than is currently in use, and more recent reports of CFS prevalence may differ as a result.

In 1993, Jason and colleagues interviewed a random community-based sample of adults in Chicago (9). Those individuals who self-reported having CFS or many of the symptoms of CFS were examined by a physician and interviewed by a psychiatrist in order to determine whether they met CFS case criteria. The research team diagnosed 0.2% of the sample with current CFS, a number higher than expected, given rates from past epidemiological studies. This rate of 200 individuals per 100,000 was considerably higher than the rate originally reported by the CDC. The sample size for this study, however, was relatively small (N = 1,031).

Chicago Community-Based Study

Epidemiology: In a larger study conducted from 1995 to 1998, Jason and colleagues (10) screened a random sample of 18,675 individuals for CFS symptomatology. Approximately .42% (420 per 100,000) of the sample was determined to have CFS, with rates being higher among Latino and African American respondents compared to White respondents (10). The results of this epidemiological study suggested that this illness may affect approximately 800,000 people in the United States. Women, Latinos, middle-aged individuals, and persons of middle to lower socioeconomic status were found to be at higher risk for this illness. The findings directly
contradicted the perception that middle to upper-class Caucasian women were most at risk for this illness. Moreover, about 90% of people identified as having CFS in this sample had not been previously diagnosed by a physician prior to participation in the study. This finding highlights the limitations of prior CFS epidemiological studies based solely on samples recruited from hospitals or primary care providers. Below we provide some of the findings that have emerged from this sample.

**Treatment and Comorbid Illness:** Jason et al. (11) found that among the individuals diagnosed with CFS, 21 of the 32 individuals (65.6%) were under current treatment (traditional medical care, alternative, or psychiatric) for a medical or psychiatric diagnosis at the time of participation. Participants were receiving treatment for an average of 2.1 diagnoses per individual. Diagnoses treated most frequently among the 21 individuals included high blood pressure (28.6%), depression (28.6%), fatigue/CFS (19.0%), arthritis (14.3%), and insomnia (14.3%). Four of the 21 individuals receiving current treatment identified utilizing one or more alternative medicine treatments, including consulting a Chinese herbalist, undergoing acupuncture, and self-treating with herbal medicines and teas. Jason, Taylor, and Kennedy (12) found that among those diagnosed with CFS, 40.6% met criteria for multiple chemical sensitivities and 15.6% met criteria for fibromyalgia.

**Diagnostic Distinctions:** Our research team has used data from the large 1995 epidemiological study to explore several diagnostic issues. For example, Jason and Taylor (13) employed a cluster analysis to define a typology of chronic fatigue symptomatology. Findings indicated that the majority of individuals with moderate to severe symptoms could be accurately classified into two important subgroups. These two clusters, which contained almost all participants with CFS, were characterized by markedly high severity of post-exertional fatigue and severe cognitive problems. Results from this investigation highlight the relative importance of these symptoms as diagnostic markers for CFS.

This data set was also used by Taylor, Jason, and Schoeny (14), who examined the diagnostic validity of conditions that have been labeled functional somatic syndromes. Results of confirmatory factor analysis supported diagnostic distinctions between five syndromes (fibromyalgia, CFS, somatic depression, somatic anxiety, and irritable bowel syndrome). The discrete diagnostic categories of fibromyalgia and CFS were then tested using logistic regression analysis, in which the outcome involved independent diagnosis of these conditions based upon physician evaluation. The diagnostic validity of the latent constructs of fibromyalgia and CFS emerging from this five-factor model were cross-validated using findings from an independent physician evaluation.
These data have also been used in other efforts to evaluate CFS case definitions (15). For example, Jason, Torres-Harding, Taylor, and Carrico (16) compared individuals with CFS defined by the Holmes et al. (17) criteria, by the Fukuda et al. (18) criteria, and to those individuals with psychiatrically explained chronic fatigue. The Holmes et al. CFS criteria in comparison to the Fukuda et al. criteria selected a group of participants with more symptomatology and functional impairment, but no significant differences in psychiatric co-morbidity. Another study compared those classified by a clinical Canadian CFS case definition (19) to those defined by the Fukuda et al. CFS criteria to those with psychiatrically explained chronic fatigue. The Canadian criteria, in contrast to the Fukuda et al. criteria, selected cases with less psychiatric co-morbidity and more physical functional impairment and fatigue/weakness (20).

Onset: Further, we have investigated several other CFS issues with our data by comparing CFS and other fatigued groups (21). Jason, Taylor, and Carrico (22) found that the distribution of the month of illness onset for people with CFS and idiopathic chronic fatigue (ICF; at least 6 months duration of fatigue, but with insufficient symptoms or fatigue to meet the case definition of CFS) was nonrandom, with greater numbers of participants than expected reporting an onset of CFS and ICF during January.

Impairment and Fatigue Groups: In terms of level of impairment, previous studies have found that those in any of the fatigue groups (CFS, ICF, medically or psychiatrically explained chronic fatigue) were more likely to be unemployed or receiving disability income (10) and had significantly more multiple chemical sensitivities and fibromyalgia than controls (12). Our research group has found differences in symptom severity among different fatigue groups. For example, Jason, King, Taylor, and Kennedy (23) found that those with CFS had significantly more severe muscle pain, impaired memory/concentration, headaches, and unrefreshing sleep than those with psychiatrically explained chronic fatigue. Jason and Taylor (13) compared individuals with CFS, ICF, medically explained chronic fatigue, and psychiatrically explained chronic fatigue, and found that the medically explained chronic fatigue group had the most severe post-exertional malaise.

Psychological Factors: Psychological functioning and coping have also been explored with this data set. Jason, Witter, and Torres-Harding (24) explored psychological factors, such as coping styles, optimism, and perceived social support with the participants. Among the chronic fatigue groups, those with CFS had the highest levels of optimism and satisfaction with social supports, whereas those with ICF had the lowest scores. Among those with CFS, behavioral disengagement was related to decreased mental composite scores while maintaining activities and
optimism was related to more positive mental composite scores. Those in the medically explained chronic fatigue group used the highest levels of venting and focusing on symptoms.

Other Epidemiological Studies

Health Care Samples: Buchwald and associates (25) found rates from 75 to 267 per 100,000 in a sample of individuals enrolled in a health maintenance organization (HMO). Because these respondents all had access to an HMO, individuals lacking access to the health care system were under-represented. In Great Britain, Wessely and associates (26) determined that 2.6% or 2,600 per 100,000 of a primary health care setting sample had CFS. However, this study did not utilize complete medical examination as a means of ruling out exclusionary conditions in order to diagnose CFS.

Community-Based Samples: The CDC conducted a community-based survey in San Francisco (27). Using telephone interviewing between June 1 and December 1, 1994, these investigators surveyed 8,004 households, providing data on 16,970 adult and minor residents. Of the 14,627 adults in the screened population, 6.3% reported they had been fatigued for one month or longer, and 4.3% reported chronic fatigue lasting six months or longer. Of this group, 51.5% with chronic fatigue reported a medical or psychiatric diagnosis that could plausibly explain their fatigue. Thirty-three adults (.2% of the study population) were classified as having CFS-like illness, and 259 (1.8%) as having ICF (individuals not meeting the severity criteria of CFS-like). The authors estimated that the prevalence of CFS-like illness is between .076 and .233% (76 and 233 per 100,000). Unfortunately, medical and psychiatric evaluations were not included in this study.

Reyes and associates (28) reported on another CDC population-based prevalence study of fatigue-related disorders. Nearly 25% of the population of Sedgwick County (Wichita), Kansas was surveyed. Of the households called, a person in 54.4% of the households agreed to be interviewed. Within a random sample of greater than 90,319 persons (derived from 33,997 households) including 56,154 adults aged 18-69, they further interviewed 4,215 adults who reported one or more months of fatigue and 4,149 adults who reported none.

A CDC article by Reyes et al. (29) calculated CFS prevalence to be 235 per 100,000, in contrast to the Jason et al. (10) Chicago sample which calculated CFS prevalence to be 420 per 100,000. There are several possible reasons why the rate of prevalence was higher in the Chicago sample. The CDC sample in Wichita consisted of 85.7% Caucasian participants whereas only 53% of the Chicago sample
identified themselves as such. The CDC found that rates of CFS were higher among their nonwhite sample. It is plausible that higher prevalence rates in the Chicago sample might be due to ethnic differences between the two samples.

Based on data from the Wichita study (29), Solomon, Nisenbaum, Reyes, Papanicolaou, and Reeves (30) examined those with CFS, those with ICF and those with chronic fatigue explained by medical or psychiatric conditions. Findings showed that these chronically fatigued groups spent less time working and fewer total hours on meaningful activities compared to a no fatigue comparison group. Those with medical or psychiatric reasons for chronic fatigue spent less time on chores than those with CFS or ICF. In general, however, those with CFS were as severely impaired as people whose fatigue is associated with known chronic disabling conditions. Unfortunately, in this study involving CFS and different fatigue conditions (30), most of the subjects were not clinically or medically evaluated, and so some individuals might have had a medical or psychiatric exclusionary illness that was overlooked, and some may have misreported the presence of a medical or psychiatric illness.

**Follow-Up Studies:** In recent years, other investigators have been describing characteristics of the Wichita study noted above. For example, Nisenbaum, Jones, Unger, Reyes, and Reeves (31) reported that among 40 individuals with CFS who were followed for two consecutive years, only 10% sustained total remission and 22.5% sustained partial remission. From a practical standpoint, subjects remained severely fatigued throughout the follow-up. Higher fatigue scores were negatively associated with the experience of remission. While most subjects reported using a combination of traditional medicine, self-help strategies, and complementary and alternative medicine therapies, remission was not associated with any particular treatment. Further, Jones, Nisenbaum, and Reeves (32) found that subjects with CFS were more likely than controls to use a variety of drugs.

**Sociodemographic Factors:** Bierl et al. (33) reported on a national study that involved 2,728 households. Unfortunately, there were no medical or psychiatric examinations provided for those with CFS-like symptoms. Of interest was that lower income and education were associated with higher levels of chronic fatigue. In another study, Herrell (34) examined CFS-like illness in American Indian tribes and in Mexican American populations of Fresno County, California. Resulting prevalence rates of .2 to .4% clearly demonstrate that this illness is found among different ethnic groups. Unfortunately, medical examinations did not occur with these surveys, so it is unclear whether similar rates would have been found for CFS.
In the San Francisco CDC study (27), relative to Caucasians, CFS-like illness was significantly elevated among African Americans and Native Americans, and CFS-like illness was more prevalent among people with annual household incomes below $40,000. Additionally, CFS-like illness was elevated among clerical workers and those engaged in health care occupations. These findings suggest that unexplained chronic fatigue does not primarily affect Caucasian, affluent professionals.

In a non-US based community prevalence study, Njoku, Jason, and Torres-Harding (35) found a 0.68% CFS adult prevalence rate in Nigeria. The slightly higher CFS rates in this developing country might be due to the fact that poverty and malnourishment, which occur more frequently in developing countries, increase a person’s risk of having health problems.

**Influence of Diagnostic Criteria in Epidemiological Studies:** The CDC has recently released findings from another community-based epidemiologic study that was carried out in Georgia (36). While the prior CFS prevalence rate was estimated to be 0.24% in Wichita, Kansas (29), the new CDC estimated prevalence rates were reported to be considerably higher at 2.54%, which is remarkably similar to the 2.6% primary care rate in Great Britain (26). The CDC now estimates that there are about 4 million people with this illness in the United States.

In the CDC study (36), the authors screened for persons who reported fatigue, problems with memory/concentration, unrefreshing sleep or pain rather than simply focusing on the single symptom of fatigue, and the authors indicated that these criteria increased the identified cases by 13%. In addition, the authors used what they referred to as a standardized, empirical case definition to identify cases, and this process identified three times the number of CFS cases compared to the more traditional Fukuda et al. (18) criteria that has been used to identify cases in other epidemiological studies. Jason, Najar, Porter, and Reh (37) investigated this new CFS empirical case definition with 27 participants with a diagnosis of CFS and 37 participants with a diagnosis of a major depressive disorder. Findings indicated that 38% of those with a diagnosis of a major depressive disorder were misclassified as having CFS using the new CDC empirical case definition. This new empirical case definition might result in the erroneous inclusion of people with primary psychiatric conditions in CFS samples, which would have detrimental consequences for the interpretation of epidemiologic findings for people with CFS.

**Risk Factors**

In 2001, The Agency for Healthcare Research and Quality of the US Department of Health and Human Services issued an Evidence Report on CFS (3). The authors
concluded that estimating rates of recovery/improvement or relapse from severe fatigue is not possible because there are so few natural history studies available. Most studies of the natural history of CFS have been confounded by a variety of factors including the use of care-seeking or medically referred non-random samples, small sample sizes, lack of a medical examination, and the study of CFS-like illness instead of CFS (38, 39). Clearly, there is a need for longitudinal cohort studies with representative samples that identify risk factors for both recovery/improvement and relapse.

Based on the literature, several of the most theoretically important risk factors are discussed below.

**Gender:** CFS is more prevalent among women than men (10). There is some evidence that there are gender-related differences in the impact of CFS. Among a sample of individuals with CFS, women were found to have a higher frequency of fibromyalgia, tender/enlarged lymph nodes, and lower scores on the physical functioning subscale of the Medical Outcomes Study Short-Form-36, when compared to men (40). In the Chicago community-based sample, gender predicted fatigue severity, with women exhibiting higher fatigue scores than men (41). Also, within this sample, women had significantly poorer physical functioning, more bodily pain, poorer emotional role functioning, significantly more severe muscle pain, and significantly greater impairment of work activities (42).

**Age:** In previous studies, over half of the subjects aged 65 years or older have experienced tiredness during the previous month (43), and there is a steady increase of fatigue from middle to old age (44). In terms of prognosis, an influential review article by Joyce, Hotopf, and Wessely (45) concluded that older age was a risk factor for poor prognosis among individuals with CFS. Clark and associates (46) found that being over 38 years old predicted persistent illness in chronic fatigue patients. Kroenke, Wood, Mangelsdorf, Meier, and Powell (47) found that only a minority of patients with CFS improved, and that older age was a risk factor for poorer prognosis. Tiersky et al. (48) also found prognosis for CFS to be poor, with age being a significant predictor of outcome.

Age also appears to influence disability and symptom severity among patients with CFS. Schmaling, Fiedelak, Katon, Bader, and Buchwald (49) furthermore found that older age predicted a decline in physical functioning among individuals with unexplained chronic fatigue. Finally, in the Chicago community-based sample, Jason et al. (42) found that those patients with CFS who were older had higher frequencies of symptoms and were more severely disabled. Conceivably, those who are older are either less physically fit or have had more opportunities to experience other...
physical illnesses or stressors that can cause fatigue.

**Ethnicity:** Almost everything we know about CFS is based upon Caucasian samples from clinic and hospital based settings (50). However, rates of minorities with CFS are higher than expected based on community-based studies. For example, Steele et al. (27) found that relative to Caucasians, CFS-like illnesses were significantly elevated among African Americans and Native Americans; and Herrell (34) found high rates of CFS-like illnesses in American Indian tribes and in Mexican American populations (unfortunately, both studies did not involve medical examinations so rates of CFS were not assessed). In the Wichita community-based CDC study, rates of CFS were actually higher among the African Americans than Caucasians (51). In the Chicago community-based study, the prevalence of CFS was higher for Latinos and African Americans than for Caucasians (10).

In terms of ethnicity and symptom severity, findings from the Chicago community-based study revealed that, when compared to Caucasians, minorities had more severe sore throat pain, more severe fatigue following exercise, more severe headaches, more severe unrefreshing sleep, and poorer general health (42). In addition, Latinas who were older reported the highest relative severity of fatigue (52). Coping mechanisms among minorities with chronic fatigue also appear to be different than among Caucasians. For example, Njoku (53) found that use of denial was a significant predictor of fatigue severity among African Americans and physical disability among Latinos. Ethnic diversity provides important contextual information about CFS that few investigations have yet pursued comprehensively.

**Socioeconomic Status:** While CFS has frequently been referred to as the “Yuppie Disease” because it was thought to primarily affect middle to upper class women, it should be noted that these findings were obtained from tertiary care clinics (50). In Great Britain, Wessely et al. (26) found higher rates of CFS for individuals of lower socioeconomic status than for those of higher socioeconomic status. Bierl et al. (33) reported on a national US study that involved 2,728 households and found that lower income and education were associated with higher levels of chronic fatigue.

Increased impairment has been reported among patients of lower socioeconomic status. In the Chicago community-based study, Jason et al. (4) furthermore found that individuals with lower educational and occupational status reported higher levels of fatigue than those with higher educational and occupational status. Those from the lowest socioeconomic status group had significantly higher disability ratings than those from the highest socioeconomic status group. Higher prevalence rates and higher fatigue levels among low income groups might be due to psychosocial and environmental risk factors.
Individuals of varying socioeconomic backgrounds have been found to differ with respect to a number of issues, including: health care practices (e.g., nutrition, regular exercise, routine medical examinations), behavioral risk factors (e.g., condom use, use of alcohol, drugs, and tobacco), access to adequate health care (e.g., health insurance benefits and adequacy of care provided), level of psychosocial stress (e.g., racism, discrimination, and unemployment), amount of negative environmental exposures (e.g., air pollution, lead, and other toxins), and level of hazard with respect to occupation (54, 55, 56). These factors have been cited to explain observations of other medical conditions affecting low-income groups at differentially higher rates, such as HIV, hypertension, and heart disease (57, 58, 59).

Fatigue Severity: Fatigue severity is strongly implicated in a poor prognosis for CFS. This is understandable given that fatigue severity is associated with more severe somatic symptoms and functional limitations (60). In Joyce, Hotopf, and Wessely’s (45) review article of prognostic studies, fatigue severity was one of the most consistent and important predictors of a more severe illness and poorer outcome. As an example of these studies, Lawrie et al. (61) re-surveyed a sample of individuals with CFS. This investigation found that pre-morbid fatigue scores were a significant predictor for developing chronic fatigue. Pheley, Melby, Schenck, Mandel, and Peterson (62) found that while recovery from CFS was rare, those patients who had less severe illness and fatigue at the initial clinic visit were more likely to have a positive prognosis. In the Chicago community-based study, Taylor, Jason, and Curie (63) discovered that higher baseline fatigue scores predicted higher fatigue severity at a follow-up assessment. Those who are more fatigued experience a greater number of somatic symptoms and an increase in functional limitations. These factors might likely make it more difficult to recover from CFS.

Stressful Life Events: Stressful life events have also been implicated as a risk factor for CFS. Buchwald et al. (64) found that a greater number of stressful life events predicted a worse functional and fatigue symptom profile at six months. Salit (65) found that stressful events were common in the year preceding fatigue onset. Similarly, Theorell and associates (66) found that individuals with CFS were nearly twice as likely to report the occurrence of negative life events during the three months preceding onset. Lim et al. (67) found those who recovered from CFS over one year reported lower levels of life stress than those who did not recover. Jason et al. (11) indicated that half of the individuals with CFS in their community based sample were able to identify a stressful event occurring at the time of onset. Individuals who were experiencing unusually severe stress at the time of onset reported lower levels of vitality and lower emotional role functioning. Stresses reported by these individuals included family problems, death of a loved one, marital separation, financial difficulty, and medical problems.
**Biological Factors:** Hickie et al. (68) followed up with people who had cases of mononucleosis (glandular fever), Q fever, and Ross River virus, respectively, who later met the criteria for CFS. The syndrome was predicted largely by the severity of the acute illness rather than by demographic, psychological, or microbiological factors. Vollmer-Conna et al. (69) found that individuals with high levels of IFN-gamma (a pro-inflammatory cytokine) and low levels of IL10 (an anti-inflammatory cytokine) were significantly more likely to experience severe acute illness following infection. In addition, Glass et al. (70) found that healthy individuals with certain biological patterns (i.e., lower cortisol, more heart rate variability, and attenuated natural killer cell response to stress) developed somatic symptoms when asked to stop exercising for a week.

Individuals with diminished GABA functioning might also be more likely to develop kindling (71). These might be some of the predisposing neuroendocrine and immunologic irregularities of individuals who are at increased risk for developing CFS. Kindling might appear after prolonged stimulation of the limbic-hypothalamic-pituitary-adrenal axis, either by high-intensity stimulation (e.g., brain trauma) or by chronically repeated low-intensity stimulation (e.g., an infectious illness) (72).

**Other Factors:** A host of other variables have been implicated, and the list is too long to present in this article (73). For example, Harvey et al., (74) found frequent exercise early in life was related to later self-report of CFS. Schmaling et al. (49) found increases in body mass index among patients, but this did not predict changes in clinical status. Different fatigue diagnostic labels have also been related to prognosis (75). Finally, psychiatric comorbidity appears to be correlated with, and in some studies predictive of, CFS (45).

**DISCUSSION**

Despite growing knowledge about long-term predictors of outcome in this area, many follow-up studies are not prospective in that they either rely on retrospective self-report at a single point in time or they consist of longitudinal data that are analyzed in a cross-sectional manner without taking into account the influence of baseline findings. Moreover, many CFS follow-up studies employ medical care samples instead of random community samples of socioeconomically and ethnically diverse populations (76). Our current natural history investigation aims to provide information about the course of CFS in a randomly selected, ethnically and socioeconomically diverse, urban community population.

In prior studies, our group in Chicago has found associations identified between CFS and life stressors, female gender, older age, minority status, lower socioeconomic
status, higher fatigue severity life stressors, and biological factors. For example, Jason et al. (11) found that half of the individuals with CFS identified a stressful event occurring at the time of onset. Jason et al. (42) found that women with CFS had significantly poorer physical functioning, more bodily pain, poorer emotional role functioning, significantly more severe muscle pain, and significantly more impairment of work activities than men with CFS. Additionally Jason et al. (42) found those older patients had higher frequencies of symptoms and were more severely disabled. Minorities experience significantly more severe symptomatology including sore throats, post-exertional malaise, headaches, and unrefreshing sleep than Caucasians, and reported poorer general health status (42). Jason et al. (10) also found that socioeconomic status was a significantly related to functional status. Finally, Taylor et al. (63) found that baseline fatigue scores predicted higher fatigue severity at a follow-up assessment.

Increasingly, studies in the CFS literature suggest that a variety of risk factors are associated with maintenance over time. Some individuals might be at a higher risk of maintaining CFS. In our current work with a ten year follow-up study of our original community based sample, we will prospectively examine the roles of gender, age, minority status, socioeconomic status, fatigue severity, life stressors and biological factors as predictors of prognosis for individuals who were diagnosed with CFS. The data generated will be unique due to its diversity, identification of cases from the community rather than the health care system, and the use of a medical exam to confirm CFS diagnosis. We will also try to better understand the natural history of these conditions.
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