The Face of CFS in the U.S.

What does the face of chronic fatigue syndrome look like? Is it male or female, adult or child, Caucasian, African American or Latino? Is it the face of someone who has been ill for 15 months or 15 years? Is it someone who became ill suddenly or gradually? Read on for what we know so far.

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The epidemiology of chronic fatigue syndrome (CFS) has stimulated significant interest and controversy within the scientific community since the mid-1980s. Because reliable epidemiological data can be invaluable in advancing understanding of the etiology, diagnostic validity, basic prevalence and the long-term course and prognosis of many poorly understood conditions, including CFS, epidemiology is a critical focus in unraveling the complexities of this illness.

Although this research focus on CFS is relatively recent, chronic fatigue syndrome is not a new phenomenon. Severe fatigue illnesses of unknown origin have been reported for more than 150 years in countries across the world.[1] The diagnosis of these illnesses has varied considerably, depending on the predominant symptoms, country of origin and other factors. Across the world, these fatigue illnesses have been labeled epidemic neuromyasthenia, myalgic encephalomyelitis (ME), atypical poliomyelitis, post-polio syndrome, chronic encephalomyelitis and various other names, with no universally accepted diagnostic criteria to determine if the same illness was responsible for some, or many, reported cases.

The emergence of chronic Epstein-Barr virus syndrome and two cluster outbreaks during the 1980s—184 cases in Lake Tahoe, Nevada, and 214 cases in upstate New York—renewed interest in fatigue illnesses in the United States. These outbreaks eventually led to the involvement of the Centers for Disease Control and Prevention (CDC), which named the illness *chronic fatigue syndrome* (CFS) and created a U.S. case definition for diagnosis in 1988.[2] That case definition was refined in 1994 by an international consensus group, and it is this definition, commonly called the Fukuda definition, that forms the basis for most current research in the U.S.[3]

However, there are other case definitions, including the Ramsey definition, the first true case definition, which was developed in England in 1981; the London criteria of 1992; the Australian case definition; and the 2004 Canadian consensus definition.[4,5] Unfortunately, the criteria differ, clouding the diagnostic, epidemiological and etiological picture worldwide and making many research comparisons difficult.

There is a need to conduct studies that contrast and compare different CFS case definitions and to further refine the criteria based on the results of this research. One universally accepted case definition, both for diagnostic and research purposes, would help uncover the face of CFS.

How many Americans have CFS?

In the United States, we have been trying to paint an accurate epidemiological picture of CFS since 1988, less than 20 years. Early studies, including physician-based surveillance studies, significantly underestimated the prevalence of CFS. Over time, new epidemiology studies were undertaken, leading to dramatic increases in prevalence estimates and refinements in study methodology. Here is a rundown of key first- and second-generation studies:

▶ The first widely publicized study of CFS epidemiology was done by the CDC in the late 1980s. Prevalence rates of CFS were found to range from 4.0 to 8.7 individuals per 100,000 cases, but the study only included information from physicians in four cities who identified patients with specific fatigue-related symptoms.[6]

▶ In 1993 DePaul University researchers interviewed a random community-based sample of adults in Chicago.[7] The research team found 200 individuals per 100,000 with CFS, which was considerably higher than the rate originally reported by the CDC. The sample size for this study, however, was relatively small, with only 1,031 participants.

▶ The CDC conducted a community-based survey in San Francisco in 1994.[8] Investigators contacted 8,004 random households by phone, obtaining information on 6,970 adult and minor residents. Researchers estimated the prevalence of CFS-like illness to be between 76 and 233 per 100,000. Unfortunately, medical and psychiatric evaluations weren't included in this study, so it's not known how many of the people who reported the symptoms of CFS would actually meet the criteria after completing a medical evaluation.

▶ In 1995 Buchwald and associates found rates from 75 to 267 per 100,000 in a sample of individuals enrolled in an HMO.[9] Because respondents all had access to an HMO, individuals lacking access to the health care system were underrepresented.

▶ The DePaul research team conducted a larger community-based study from 1995 to 1998, contacting households in Chicago by telephone.[10] Some 18,675 individuals were screened for CFS symptoms, and individuals who self-reported symptoms of CFS were asked to complete a medical workup to determine whether they fully met the 1994 Fukuda criteria for CFS. A prevalence rate of 420 per 100,000 was found. Given U.S. Census data of the time, investigators estimated that approximately 800,000 American adults had CFS in 1999.

▶ In the largest population-based prevalence study to date, nearly 25% of the population of Sedgewick County (Wichita), Kansas was surveyed, with 34,000 households called.[11] Data from this Wichita cohort led CDC investigators to increase estimates of CFS prevalence rates to 235 per 100,000.

▶ In 2001 Herrell examined CFS-like illness in American Indian tribes and in Mexican American populations of Fresno County, California, finding prevalence rates of 200 to 400 per 100,000.[12] Unfortunately, medical examinations didn't occur with these surveys, so it's unclear whether similar rates would have been found for CFS.

Because the Fukuda case criteria are very strict, people with CFS-like illness are excluded from prevalence estimates. Even though those individuals don't meet the strict case definition,

Fast Facts

- As many as 900,000 Americans have CFS according to the Centers for Disease Control and Prevention (CDC) and research conducted by DePaul University.
- The phrase yuppie flu, coined in the 1980s to describe CFS, turned out to be wrong on almost all counts. The illness occurs most often in people aged 40-59, and it's more common in lower-income than affluent individuals. While most patients aren't young, affluent professionals, many do experience severe flu-like symptoms, so that part of the name was correct.
- Approximately 3 to 5 times more women have CFS than men.
- CFS occurs in all ethnic and racial groups, and in countries around the world.
- Although CFS is less common in children than in adults, very little is known about the occurrence of this illness in children. Studies suggest CFS is more prevalent in adolescents than younger children.
- Between 63% and 77% of adult CFS patients in community-based samples experience gradual onset of the illness, while the remainder become ill suddenly and can often name the exact day their lives changed because of this illness.
- According to a CDC study, only 16% of Americans with CFS have been diagnosed, a staggering statistic. In a community-based study in Chicago, the rate was even lower, with only 9% diagnosed.

International Prevalence of CFS

Chronic fatigue syndrome is found all over the world. Just like in the United States, CFS prevalence estimates vary dramatically. Here are some representative samples.

Japan: 0.85 cases per 100,000 (Minowa and Jiamo, 1996)
1,500 cases per 100,000 (Kawakami, Iwata, Fujihara & Kitamura, 1998)

Hong Kong: 3,000 cases per 100,000 (Lee et al, 2000)

Australia: 37.1 cases per 100,000 (Lloyd, Hickie, Boughton, Spencer, Wakefield, 1990)
1,500 cases per 100,000 (Hickie, Koschera, Hadzi-Pavlovic, Bennett & Lloyd, 1999)

New Zealand: 127 cases per 100,000 (Murdoch, 1987)

Brazil: 2,000 cases per 100,000 (prolonged and severe fatigue, not CFS; Nacul et al, 1998)

Great Britain: 160 cases per 100,000 (David et al, 1990)
130 cases per 100,000 (Ho-Yen & McNamara, 1991)
2,500 cases per 100,000 (McDonald, David, Pelosi & Mann, 1993)
6 cases per 100,000 (Pawlikowska et al, 1994)
560 cases per 100,000 (Lawrie & Pelosi, 1995)
2,600 cases per 100,000 (with comorbid disorders; Wessely et al, 1997)
500 cases per 100,000 (excluding comorbid disorders; Wessely et al, 1997)
740 cases per 100,000 (Lawrie, Manders, Geddes & Pelosi, 1997)
800 cases per 100,000 (Viner & Hotopf, 2004)

Netherlands: 112 cases per 100,000 (Bazelman et al, 1999)

Iceland: 1,400 cases per 100,000 (Lindal, Stefansson & Bergmann, 2002)

Italy: 9,500 cases per 100,000 (Conti et al, 1994)

they are frequently as ill as people with the formal diagnosis. The CDC currently estimates there are up to 900,000 Americans with CFS and another 2.5 million with CFS-like illness.

While there is still a wide variation in prevalence estimates depending on study setting, methodology and other factors, it's clear that CFS is a common chronic illness and poses a significant public health burden on the United States. In fact, CFS is more common in this country than cervical cancer, AIDS or lung cancer.

Demographic profile

Chronic fatigue syndrome is more common among adults than children. Both the Chicago and Wichita studies estimate much lower prevalence in children and adolescents than among adults. In fact, the Chicago study didn't find any cases of CFS in the group of children aged 5 to 12, and the prevalence for adolescents (aged 13 to 17) was 181 per 100,000. Among the pediatric sample in the Wichita study, researchers estimated the weighted prevalence of CFS to be 49 per 100,000 and found CFS-like prevalence rates to be 338 per 100,000.[11] Many other estimates of child and adolescent CFS have not included medical examinations to appropriately diagnose the illness. (See page 42 for more on pediatric CFS.)

Among adults, women appear to be at much greater risk for CFS than men. In the Wichita study, prevalence estimates of both CFS and CFS-like illness for women were significantly higher than those for men. This supports previous findings in both the San Francisco and Chicago studies, as well as many others. In fact, it's estimated that women are three to five times more likely to have CFS than men. Furthermore, both the Wichita and Chicago studies estimate CFS prevalence to be highest among women aged 40 to 59, contrary to early studies which suggested younger women were more likely to have the illness.[10,11]

The first generation of prevalence studies obtained their samples by asking physicians and clinics to identify patients who had specific fatigue-related symptoms. Consequently, the majority of CFS cases identified were Caucasian women who were well-educated and middle- or high-income earners. Minorities and low-income individuals seem to have been underrepresented because these groups tend to have less access to the health-care system.[13]

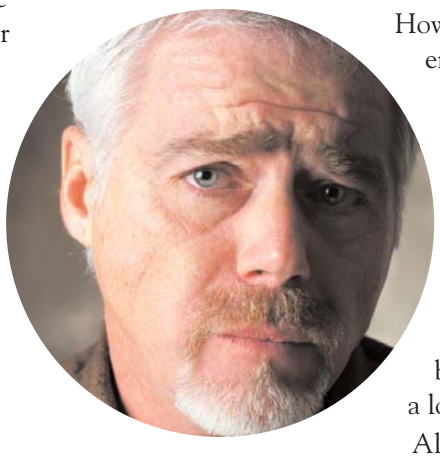
However, later randomized community-based studies consistently show comparable or higher levels of CFS prevalence among minorities. For example, in the San Francisco study, Steele et al found that, relative to Caucasians, CFS-like illnesses were significantly elevated among African Americans and Native Americans.[8] In the Chicago study, investigators found that the prevalence of CFS was higher for Latinos and African Americans, with older Latino women reporting the highest relative severity of fatigue.[10]

The most recent U.S. studies also support these findings. For instance, in the CDC's Wichita cohort, rates of CFS were higher among African Americans than Caucasians.[11] Similarly, when Herrell examined CFS-like illness in American Indian tribes and in Mexican American populations, the resulting prevalence rates of 200

to 400 per 100,000 clearly demonstrate this illness is found among different ethnic groups at levels at least equal to Caucasians.[12]

Socioeconomic factors also appear to play a role in the disease. The San Francisco study found that people with annual household incomes below $40,000 had a higher prevalence of CFS-like illness.[8] Similarly, in the Chicago study investigators found that individuals with lower educational and occupational status reported higher levels of fatigue than those with higher educational and occupational status.[14] In fact, this study showed that subjects from the lowest socioeconomic group had significantly higher disability ratings than those from the highest group. More recently, Bierl et al reported on a national study suggesting that lower income and education were associated with higher levels of chronic fatigue.[15]

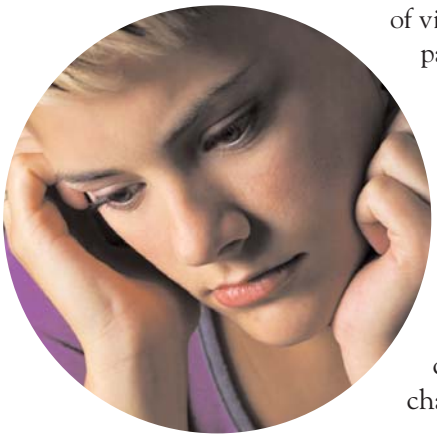
Interestingly, the data from the Chicago study also revealed no significant relationship between ethnicity and socioeconomic status (SES) among those with CFS, suggesting that ethnicity and SES are independent risk factors. In fact, when the effects of SES, gender, age, marital status and parental status were controlled, ethnicity alone didn't play a significant role in fatigue severity.[10] Thus, higher prevalence rates and higher fatigue levels among low-income groups might be due to environmental or psycho-social risk factors—such as limited medical access, poor nutrition, unemployment, discrimination and other documented stressors—more than strict ethnicity.



Illness presentation

Chronic fatigue syndrome seems to present in two distinct ways—sudden (acute) or gradual onset. Interestingly, patients with sudden onset can often name the exact day they became ill, while patients with gradual onset become ill over a period of weeks, even months. Patients with sudden onset are more likely to experience symptoms of an infectious nature, including fever, sore throat, chills and tender lymph nodes.[13,16] This suggests that sudden onset may be indicative of a viral/infectious illness in this subset of CFS patients.

Research data on the percentage of patients who experience sudden versus gradual onset varies somewhat, but it's more consistent than some of the other epidemiological data. In the Chicago study, for instance, we found that 63% reported gradual onset of symptoms, while the Wichita cohort showed 77% of CFS patients with gradual onset.[10,17] Population-based studies like these appear to have a higher percentage of gradual onset than tertiary care settings, where sudden onset is more common. There is also some evidence to suggest that the rate of acute onset may be higher in pediatric CFS than adult CFS.[18,19]



What's the prognosis?

How many people recover from CFS? Of those who fully recover, what characteristics do they have in common? How long does the illness last? Is there hope of recovery for people who have been sick a long time?

All these questions are of vital interest to patients who are struggling with CFS and with uncertainty about the future. Although clinicians and researchers are also engaged with these questions, very few studies have taken place to give us a full picture of the long-term course of the illness. CFS is characterized by a pattern of relapse

Demographic characteristics of CFS in the U.S.

CHICAGO COHORT (1999)
Prevalence per 100,000

AGE	
18-29	315
30-39	412
40-49	805
50-59	413
60+	354
RACE	
White	318
Latino	726
African American	337
Other	491
OCCUPATION	
Unskilled/semiskilled	486
Skilled worker	701
Professional	325

WICHITA COHORT (2003)
Prevalence per 100,000

AGE	
18-29	50
30-39	183
40-49	465
50-59	501
60-69	130
RACE	
White	224
Nonwhite	300
HOUSEHOLD INCOME	
$20,000 or less	202
$20,000-$40,000	280
$40,001 or more	233

The High Cost of CFS

With an illness as prevalent as CFS, the economic cost can be staggering. According to a 2004 CDC study, the illness costs every American with CFS about $20,000 a year in lost earnings and productivity. This means CFS costs the United States $9.1 billion a year, not counting the cost of health care or disability benefits.

The study authors conclude, "The extent of the burden indicates that continued research to determine the cause of and potential therapies for CFS could provide substantial benefit both for individual patients and for the nation."

and remission over long periods of time, making it even more difficult to assess recovery rates, illness duration and factors that may contribute to better health outcomes.

It's still not clear how long the illness lasts in most people. What we do know is that some people are sick with CFS for less than 2 years, while others are ill for decades. The median duration of CFS was 2.9 years in the Chicago study, while CFS subjects in the CDC's Wichita cohort had been sick anywhere from 8 months to 44 years, with a median illness duration of 7.3 years.[10,11,16]

Full recovery from CFS appears to be rare in adults, with an average of only 5% to 10% of subjects sustaining total remission.[17] The picture for partial remission and improvement in symptoms is not as bleak, although the percentage of CFS patients who experiences partial remission varies from study to study. A 2005 article published in *Occupational Medicine*, which reviewed 28 CFS studies, found that improvement rates varied from 8% to 63%, with a median of 39.5% of CFS patients improving during follow-up.

One of the reasons the data varies so much is that there is still no standard definition of short versus long duration, or of recovery. Some studies use self-reported recovery, others measure vitality, level of physical functioning and/or symptom severity to define recovery or improvement. Recovery rates may also vary according to the duration of the follow-up period. The 2005 review of CFS studies mentioned above reveals that the duration of follow-up may be quite important in recovery data. Given the relapsing-remitting pattern of the illness, some patients may be in remission at follow-up, suggesting their illness duration is shorter than it actually is unless the follow-up period extends for a period of years and detects any relapses.

"The literature on prognosis of adult CFS has been contradictory because of differing diagnostic criteria before 1988 and variations in the definition of improvement," says David Bell, MD, of Primary Care Pediatrics. "Because CFS has no objective markers to validate symptom severity, subjective impressions are relied on to assess outcome and are subject to both exaggeration and denial, depending on the coping style of participants."

Even murkier are determinations about what factors influence prognosis. Older age at illness onset, greater symptom severity, gradual onset, longer duration of illness, depression, less education, being unemployed, higher use of sedating and anti-depressant drugs, poor coping skills and a belief that the illness is due to physical not psychological causes have all been implicated as possible risk factors for a poorer outcome.

Unfortunately, results haven't been consistent across studies. Perhaps the most which can be said at this time is that the most consistent factors identified so far that *may* lead to a better prognosis

include shorter duration of illness, younger age at onset, milder fatigue/illness severity and the absence of psychiatric illnesses.

As sketchy as this prognosis data is, there are important clinical implications. For instance, enough studies agree that illness/symptom severity is a risk factor for clinicians to conclude that helping CFS patients manage symptoms is an important goal. Similarly, clinicians may want to consider evidence from studies such as the CDC's 2003 population-based study, which found that delayed diagnosis may be a risk factor for poor prognosis.[11] James Jones, MD, of the CDC explains, "In the CDC's research to date on the clinical course of CFS, patients who were ill for two years or less were more likely to improve, making early detection and treatment of CFS of utmost importance. The longer a person is ill before diagnosis, the more complicated the course of the illness appears to be."

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—DR. JAMES JONES, CENTERS FOR DISEASE CONTROL AND PREVENTION

Moving forward

We can now see the basic shape of the face of CFS in the United States, but the features need to come into sharper focus for us to understand CFS and formulate an effective response to an illness that constitutes a major public health concern.

For instance, research suggests that subtyping individuals with CFS for research purposes may be particularly useful in understanding CFS (see page 5). There is also a vital need to examine the course of CFS over time, particularly in random, community-based, multiethnic populations. We need to determine the natural history of CFS in longitudinal cohorts that include socioeconomically diverse samples so we can determine the long-term course of the illness and identify risk factors for poor prognosis. We also need community-based studies to better estimate the prevalence and incidence of pediatric CFS and determine how it compares to adult CFS in onset, symptom severity, psychosocial factors, prognosis and other variables.

We have learned an enormous amount about the epidemiology of CFS in the past two decades. First- and second-generation studies have led us to continually assess and refine the face of CFS. Now it's time for the next generation of studies. ■

ON THE FRONTIER

New Studies Will Advance Understanding of CFS

DePaul University researchers and the CDC are responsible for much of what we know about the epidemiology of CFS in the U.S. They are again on the frontier of research with two new studies.

Dr. Leonard Jason and his DePaul University colleagues were recently awarded an NIH grant to revisit their community-based Chicago cohort to conduct a follow-up study of CFS progression and prognosis. Research began in the fall of 2005 on this first large study to focus specifically on the long-term course of CFS.

In September 2005 the CDC finished gathering data from 13 counties in Georgia. More than 7,000 people completed a telephone survey and 700 of them visited the CDC's clinics in northeast Atlanta or Macon to provide investigators with a rich set of data on the CFS patients identified. The CDC and Emory University researchers will use the data to estimate the prevalence of CFS, better pinpoint the exact nature of symptoms and develop control and prevention strategies.

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