



A new study suggests that the number of Americans with CFS may be much higher than previously thought. But some people question the study's methods and results. Here's insight into the study, the questions raised about it and the implications.

Prevalence Figures

BY K. KIMBERLY MCCLEARY, CFIDS ASSOCIATION PRESIDENT & CEO

What's in a number? And why does prevalence matter? The number of people affected by a condition is an important indicator of its scope and magnitude. It can also drive policy and business decisions, one of several factors that determine priorities for important endeavors like research funding and drug development.

So, how many people have CFS? That's a question researchers have been trying to answer since CFS was first defined in 1988. In the absence of a diagnostic marker that clearly indicates who has it, and given the waxing and waning pattern of symptom severity most patients experience, counting the people who have CFS is harder than you might think. For the past 20 years, estimates of CFS prevalence (how many people have it at a single point in time) have varied

greatly. This variability is due largely to the study design and methods employed to identify CFS patients and the criteria used to define whether they have the illness or not. Early studies, based on asking *doctors* to refer CFS cases, estimated that 3,000-10,000 U.S. adults had CFS. Community-based studies put the number higher. The most recent study, published in June, offers the highest figure yet: four million estimated CFS cases among adults age 18-59.

In this article, we'll look into how case definitions and study methods influenced this latest estimate and why it has sparked controversy among researchers and patients in the CFS community. We'll also try to share some insights as to what this ongoing debate over the number of CFS cases means.

Community-based prevalence studies

The most recent studies of CFS prevalence have come from two research groups: DePaul University researchers led by Dr. Leonard Jason and the U.S. Centers for Disease Control & Prevention (CDC) researchers led by Dr. William Reeves. This generation of studies has employed some similar methods, taking a broad, population-based approach by surveying different communities by telephone for symptoms of CFS and then conducting more thorough medical and psychiatric examinations to rule out other conditions and verify CFS. These studies have been nicknamed for the geographic regions that were surveyed: San Francisco (published in 1998), Chicago (1999), Wichita (2003) and Georgia (2007).

The Chicago and Wichita studies generated estimates of 400,000-800,000 CFS cases in the U.S. Both screened respondents for the symptom of fatigue, then applied the 1994 international criteria to define CFS and performed similar exclusions for medical and psychiatric conditions that might otherwise explain the subject's symptoms.

At the time, one weakness of these methods was the use of fatigue as the only screening symptom for identifying possible cases. Many people in the CFS community felt that cases were being missed by not also asking about other features of CFS during the first contact with respondents.

As these studies were evolving, ongoing dialogue about how CFS was being defined led CDC to convene a series of three-day workshops between 2000 and 2002 to identify problems applying the 1994 criteria in a consistent fashion across research settings. The recommendations arising from these workshops were published in 2003 and represent a consensus of many prominent CFS researchers across the globe. The group, dubbed the "International CFS Study Group," suggested the use of standardized questionnaires to identify and score CFS symptoms and their impact on daily function, rather than simply asking questions like, "Do you have a sore throat" or "Are you impaired by your symptoms?" and trying to make sense of answers like "always," "sometimes" and "never."

This paper also clarified some ambiguities about overlapping and exclusionary conditions and made recommendations for subgrouping patients within the CFS population for greater comparability between studies. These guidelines were widely endorsed and have been used by most CFS research groups to refine the selection of CFS cases and controls for their studies.

A new approach to classifying CFS

In 2003, CDC researchers conducted a study that attempted to "operationalize" the recommendations from the International CFS Study Group. First, they determined cut-off points for scores on a set of standard questionnaires, a process they referred to as an "empiric" approach to the CFS case definition. Then they compared the clinical status and diagnosis of a group of 227 subjects recruited between 1997 and 2000 during the Wichita prevalence study to

determine their clinical status in 2003. They specifically looked at the 46 patients originally classified as CFS to see whether they still met CFS criteria using the traditional method (by asking simple questions about symptom occurrence) and by the new approach, using standardized questionnaire instruments. When published in 2005, this analysis provided some interesting data.

Of the original 46 CFS patients who enrolled in this later study, only 6 still met CFS criteria by the traditional methods, but another 10 patients previously categorized in other ways now fit CFS criteria. Five patients had improved significantly; 8 now had exclusionary conditions. The other 27 remained ill but didn't have symptoms severe enough to meet traditional CFS criteria. According to study authors, this "could reflect the cyclic nature of CFS and changes over time." Since 3 to 6 years had passed between assessments, some change would be expected.

When the researchers evaluated all 227 subjects, comparing the traditional method with the empiric one, using the standardized instruments to assess symptom severity and impact on daily function, they classified a total of 43 people as having CFS. Only 10 of these 43 were the patients who at the same time fulfilled CFS criteria using the traditional approach, although 14 others came from the group of 46 diagnosed with CFS in the original Wichita study. So, while the numbers of CFS patients—46 vs. 43—were roughly the same between the initial Wichita report of CFS cases and the latter comparison paper using the new empiric method, the individuals who fit that classification were somewhat different. Nonetheless, 42% of the group identified as CFS by the empiric approach had also met CFS criteria by the traditional approach in the original study. The authors suggest, "the clinically empirical case definition may be less affected by the day-to-day fluctuation of the illness and rather reflect the underlying chronic illness process."

The Georgia prevalence study

This brings us to the 2007 prevalence study. CDC researchers surveyed 19,381 respondents in three geographically distinct areas of Georgia between September 2004 and July 2005. In response to criticisms of earlier studies that screened only for fatigue, this time they asked about

Variability [in prevalence estimates] is largely due to the study design and methods employed to identify CFS patients and the criteria used to define whether they have the illness or not.

“unwellness,” defined by at least one of the classic CFS symptoms (fatigue, cognitive impairment, unrefreshing sleep, muscle or joint pain, sore throat, tender lymph nodes or headache).

When brought into the clinic for evaluation, all study subjects completed the questionnaires utilized in the empiric approach to the case definition in addition to having thorough medical and psychiatric evaluations to rule out exclusionary conditions. The researchers employed the empiric approach to determining who had CFS, using the same cut-off points published in the 2005 paper. They found 113 subjects who met the criteria for CFS. When weighted for relevant demographic factors, this translates to a rate of 2.54% of the adult population age 18-59 for these regions of Georgia.

In addition to a prevalence rate that is 6-10 times higher than earlier estimates, this study contained other important findings. The rate of CFS didn't vary in the metropolitan area (Atlanta) compared to a smaller city (Macon) and rural areas surveyed. While women were affected at higher rates compared to men, these rates varied widely by the size of community. The reasons why warrant more study. Rates among Hispanics were significantly higher than Caucasians and African-Americans, even though the screening questionnaires were only conducted in English. This finding demands more investigation, too.

Another important outcome was that 48% of those who had the symptoms of CFS by telephone interview alone were found in the clinic to have an undiagnosed medical condition other than CFS. Most of these, including thyroid disease, anemia, diabetes, heart disease and primary psychiatric disorders, were treatable. According to CFS expert Dr. Nancy Klimas of University of Miami, “This makes it even more critical for people who have symptoms of CFS to be thoroughly evaluated by a clinician.”

Evaluating the Georgia study

If the figures from Georgia are expanded to the U.S. population, the prevalence of CFS is estimated to be four million adult cases. That's a big jump from earlier estimates. But it doesn't mean there is an explosion of cases. According

to the study's lead author, Dr. Reeves, “We don't think the number of Americans with CFS is dramatically increasing. What is increasing is our knowledge base about the illness. We know so much more about this illness than we did 10 or 15 years ago. This increased knowledge has led to better diagnostic and measurement tools for estimating the number of people who have CFS.”

But others feel that the latest study employed unsound methods for screening telephone respondents and defining CFS, and therefore the new estimate should be discounted, if not discarded. When the study was published on June 8 in the journal *Population Health Metrics*, it ran with an editorial by CFS researcher Dr. Peter D. White titled, “How common is CFS; how long is a piece of string?” The other major critique has come from Dr. Leonard Jason, who posted a lengthy statement on the website of the International Association of CFS/ME, of which he is an officer. The study also drew criticism from some patient advocates who expressed concern that CDC had cast the net too wide and loosened the CFS criteria, including people with psychiatric conditions.

So, why is the new estimate so much larger, and are the critics justified? One of the major changes made, to screen for all the case-defining symptoms instead of fatigue alone, accounted for just 13 (11.5%) of the 113 CFS cases identified. This would suggest that the “wider net” isn't a huge factor in the increase.

The stickiest debate centers as much on the empiric approach outlined in the 2005 paper (described on the previous page), as it does the 2007 study of Georgia. However, the 2005 paper attracted little attention at the time it was published. Now there's concern

that this approach to classifying cases may be too liberal.

Of the 43 CFS patients identified in the 2005 Wichita case-comparison paper using the empiric approach, one-third of them (14 cases) had not been classified as CFS (at either point in time) using the traditional approach. However, 14 others who had been classified as CFS in the original Wichita study, but whose symptoms were not sufficiently severe in the 2005 comparison study by the traditional approach, *did* fit CFS criteria using the empiric approach. So, it seems that the empiric approach may “adjust” for the waxing and waning features of the illness

This study is important because it reports that CFS may be more common than previously estimated. This could have important implications for public policy, interest from pharmaceutical companies and for general awareness.

better than traditional questioning methods, but that it also lets in some cases that wouldn't otherwise be counted as CFS using the traditional approach alone.

Dr. Jason takes particular issue with the selection of questionnaire subscales used and the cut-off points established for the standardized instruments, stating, "The overall level of symptoms seems relatively low for patients with classic CFS symptoms." He also points out that symptoms on one of the questionnaires are rated according to severity in the month prior to interview, rather than six months as required in the 1994 case definition. He notes, "This change has the potential [to include] more individuals." However, CDC used the one-month timeframe for the symptom questions in the traditional approach as well. Only fatigue was required to be present for six months or more.

In both the 2005 paper and the 2007 Georgia study, the authors acknowledge that the choice of specific subscales and cutoffs can be debated. In the Georgia paper, Reeves, et al, write, "In the end, we decided to use these cutoffs because we believe they make sense, because we used them in the Wichita study and can compare findings in similarly ill individuals; and, because others can replicate the findings if they use the same cutoffs and stratify their populations based on variations of the cutoffs." It seems likely that this issue will be the focus of future studies, hopefully leading to consensus guidelines for appropriate inclusion of questionnaire subscales and cutoffs.

While critics have charged that the estimates are inflated through the inclusion of people with psychiatric disorders, it's not clear how well-founded that charge may be. The methods described in the paper state that psychiatric evaluations, a standardized evaluation tool and review by a committee of physicians and psychologists were employed to exclude subjects with primary psychiatric conditions. The number of CFS subjects in the Georgia study with a current or lifetime history of depression, allowable under the 1994 criteria, is not reported in the paper. However, past studies of prevalence have reflected individuals with CFS and certain forms of concurrent or past depression. In fact, Dr. Jason and colleagues reported in the 1999 study of Chicago prevalence that a "significantly higher frequency of individuals in the CFS [and other fatigue-related groups] received current and lifetime . . . psychiatric diagnoses compared with controls." So this confound may be present in past prevalence studies as well.

Finally, it's possible, as Dr. White writes, that "Georgia may not be representative of the U.S. as a whole" and that the estimates from this study should not be applied to the

country's population because of differences in demographics and other regional features. This is another limitation of earlier studies as well, with the possible exception of Wichita which was selected because of its demographic similarity to the total U.S. population at that time.

Does the Georgia study matter?

In spite of the rather anticlimactic reception this study has received, Dr. Anthony Komaroff, a leading CFS expert, feels this study merits attention. "Only a few years ago, chronic fatigue syndrome was viewed as a rare condition. This study is important because it reports that CFS may be more common than previously estimated." This could have important implications for public policy, interest from pharmaceutical companies in CFS as a potential market and for general awareness. It also signals a need to reassess the economic impact of CFS, currently estimated to be \$17-25 billion a year, based on lower prevalence figures.

As Dr. White concludes in his editorial, this study underscores the need for individuals with the symptoms of CFS to receive appropriate diagnosis and medical care. In another CDC study, early intervention was shown to contribute to higher recovery rates and better long-term health outcomes. Expanded education of health care professionals and the public is warranted.

The Georgia study is also a call to action to increase research funding for CFS, enabling a large cadre of scientists to intensify the search for markers that identify meaningful patient subgroups and targeted therapies. Disagreements over the specifics of the empiric approach to classifying CFS cases will need to be resolved since studies of CFS patients identified in the Georgia study and further analysis of the data accumulated from it will be the basis for future research and will shape funding priorities.

So, how many people have CFS?

After 20 years, it's fair to say "millions." Earlier estimates of one million people arising from the Chicago and Wichita studies represent minimum figures, due to the strict definition used and the tight survey methods employed. The Georgia study cast a wider net yielding an upper boundary of four million, demonstrating how common these chronic symptoms are in communities of all sizes—and how many people need appropriate care and medical treatment. Formal estimates will likely be revised with further study. ■

