Title: Prevalence of Chronic Fatigue Syndrome in Metropolitan, Urban, and Rural Georgia

Authors:

William C Reeves (wcr1@cdc.gov)
James F Jones (jaj9@cdc.gov)
Elizabeth Maloney (evm3@cdc.gov)
Christine Heim (cmheim@emory.edu)
David C Hoaglin (dave_hoaglin@abtassoc.com)
Roumiana S Boneva (rrb5@cdc.gov)
Marjorie Morrissey (Marjorie_Morrissey@abtassoc.com)
Rebecca Devlin (Rebecca_Devlin@abtassoc.com)

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Author's response to reviews: see over
Before responding to the reviewers’ critiques, the authors would like to express our appreciation for the time the reviewers put into the manuscript and for their well thought-out and incisive comments. It’s never particularly fun to realize that one’s masterpiece has some flaws, but their comments were all on the mark and the exercise of responding to them has greatly improved the manuscript. Reviewers’ critiques are in italics followed by our response in normal font.

The most important major criticisms of both referees involved how we chose to apply the internationally accepted 1994 CFS research case definition. Both, in particular, questioned our choice of cut-off values and we completely re-wrote the initial section of Discussion to address their comments. Bottom-line, the article is not important because the 2.5% prevalence it reports is considerably larger than other estimates; because, CFS isn’t like cancer, birth defects, AIDS that have a gold standard for diagnosis. CFS is defined by symptoms, there are no diagnostic signs or lab tests, so the sensitivity and specificity of any study cannot be measured. CFS is also a moving target, which depends on the survey methodology and case definition. What’s important is that using these standard validated instruments and specific cutoff scores we have defined CFS in a manner that can be replicated by other investigators.

Further analysis of the impact of the operational decisions on the prevalence estimates should be added to resolve the higher prevalence estimate reported here than in all previous studies. The fatigue criterion in the CFS case definition was operationalised as "those with a score ? well-population median" - this implies substantial overlap between the cases and the healthy control subjects in this variable. This deserves careful justification and further discussion - what would be the impact on the prevalence figures of a more conservative threshold??? Similarly, what influence would a change to the 10th percentile for the SF36 definition of functional impairment have? or a change to a more conservative score on the Symptom Inventory.

This is addressed in the revised Discussion. Of note, although a proportion of “well” persons will score well below population norms on any individual scale, we did not evaluate solely individual scores and no study participant could be classified as CFS unless she/he met SF-36 AND MFI AND Symptom Inventory criteria. We are not willing to change the criteria, because we wish to compare findings in persons with CFS identified in this study with those identified in similarly diagnosed subjects in our earlier Wichita clinical study.

The authors state that, “Functional impairment was assessed by the medical outcomes survey short form-36 (SF-36) [13]. For classification as CFS, those with a score ? 25th percentile of population norms in the physical function or role physical, or social function, or role emotional subscales of the SF-36 were considered to have substantial reduction in activities as specified in the 1994 definition.” The same criticism as in the paragraph above applies to their choice of SF36 subscales. The use of physical function, role physical and social function sub-scales is consistent with the International Study criteria for CFS, which states that the illness “results in substantial reduction in previous levels of occupational, educational, social, or personal activities...” The use of role emotional is not, since it specifically asks about change in function “as a result of any emotional problems”. I note that “role emotional” had the lowest correlation coefficient of any of the SF36 subscale scores with any of the three measures of CFS in one of the authors’ previous studies.

This is addressed in the revised Discussion. Of note, we specifically chose the physical function, role physical, social function, and role emotional subscales because we believe these four best encompass functional impairment in occupational, educational, social and personal activities.

The authors state that, “...those with a score ? well-population medians on the general fatigue or reduced activity scales of the MFI were considered to meet fatigue criteria of the 1994 case definition.” This means that it would be possible to meet the fatigue criterion without significant fatigue; i.e. with reduced activity alone. This is inconsistent with the international study criteria...
for CFS, which require: “clinically evaluated, unexplained, persistent or relapsing chronic fatigue (of least 6 months duration) that is of new or definite onset”

This is addressed in Discussion. We believe that the general fatigue and reduced activity scales of the MFI are consistent with the international study criteria for fatigue.

Furthermore the authors need to refer to the studies from which they took these population norms. I am aware of several population studies of working age adults using the SF36, but they give slightly different results, and the readers need to know which one they chose and why. I am not aware of any population studies of working age adults using the MFI. This reference should be given.

This is addressed in the revised Discussion. This was a particularly rough one because there is no answer. There are many publications all reporting slightly different norms for the SF-36, so we used those published by the company that markets the instrument. Similarly to Dr. White, we know of no population studies reporting MFI norms for working age adults, so we used the same cutoffs as we used in the study in which we first published this clinically empirical method of classifying CFS.

The authors state that, “For classification as CFS, those reporting < 4 case defining symptoms and who scored > 25 on the SI case definition subscale were considered to meet accompanying symptom criteria of the 1994 case definition.” Having read the relevant paper, I am still uncertain by both what is meant by the “SI case definition subscale” and what a score of 25 means. This needs both clarifying and justifying.

In the preceding comments, both referees had reference to things like “a score < 25th percentile” “a score < well-population medians”

I think this may reflect some sort of glitch with our use of MS Word symbols in the manuscript. We have now specified => and =< rather than the symbols.

Are the discussion and conclusions well balanced and adequately supported by the data? I think the authors need to be more cautious in their interpretation of their findings of a much higher prevalence than previously found. They should also refer to similar findings of prevalence found in other countries.

We have extensively rewritten the Discussion, in particular our interpretation of the prevalence estimate reported in this manuscript. This includes reference to prevalence estimates from other countries. The only problem is that we do not know of similar population-based surveys for CFS. Most of the good papers reporting prevalence do so based on primary care patients (albeit in countries with government-supported free medical care).

The methods leave out non-English speaking people, which may have led to an under-sampling of ethnic minority groups, and possibly CFS, if there is a difference in those who do not speak the majority language. I note the authors weighted the sample to allow for ethnic differences. The authors should mention this in discussion.

We added a paragraph concerning this to the discussion

The authors describe similar findings across black and white people, but do not describe the ethnic groups adequately. What do they mean by “black”? We added text explaining how we assigned race and ethnicity (Hispanic non-Hispanic) in the Detailed telephone interviews paragraph of Methods.

What proportion of the three different geographical sample households did not have a working telephone at the time of sampling? This is important information in order to approximate the
selection bias towards greater economic income. I would assume that this data would be available.

We have added a paragraph in the section on weighting to explain this.

What proportion of those screened by telephone was fatigued but not "unwell"? This should be reported.

None of those who were screened by telephone or who completed the detailed telephone interview were fatigued but not unwell. We defined unwell as being fatigued or cognitively impaired, or unrefreshing sleep, of muscle pain, or joint pain, or sore throat, or tender lymph nodes, or headache, or any combination. If a person had at least fatigue, he/she was considered unwell fatigued and if any of the symptoms but not fatigue she/he was unwell not fatigued. We have added text to the Methods clarifying this.

How did they work out the numeric value of the weightings? It would help the reader to give more details about this.

We went through considerable angst writing the Weighting section of Methods. Weighting is complex and Dr. Hoaglin is an internationally recognized expert in this area. We are uncertain as to how we might change this to make it clearer to those readers who are not familiar with this rather arcane field.

The authors give mainly univariate analyses results with limited interaction data. We need to see multivariate analyses to model all the examined factors that may influence the prevalence of CFS, so that confounding and interactions can be excluded or explored.

The objective of this manuscript was to estimate the prevalence of CFS in racial/ethnic groups representative of defined metropolitan, urban, and rural populations and to provide a core reference to the methodology that can be referenced in more specific manuscripts that deal with issues such as severity of illness and CFS phenotypes, economic impact, access to and utilization of health care, associations of CFS stress over the lifetime and stress reactivity/resiliency. To maintain the focus of the manuscript, we intentionally did not present multivariate or other analyses of interaction because we believe they are beyond the scope of this manuscript. However, the core data concerning CFS prevalence (Table 3) is weighted, which we believe is adequate.

Reference 12 needs revision.

We fixed the citation so that it is now Smets EMA not Smets EM

The description of the numbers and proportions found in sampling, telephone assessment and clinical assessment is complicated and it is hard to follow the numerators and denominators. I think readers would be helped by an algorithmic figure with the numbers (%) at each stage, with both true and false negatives and positives given at each stage of assessment.

See our comment under weighting. We went through considerable angst trying to write this and it’s even hard for me to work through it. But, numerators and denominators are largely weighted numbers and we do not feel they can be easily improved nor do we believe a figure will help. We did not modify text to accommodate this criticism.

The difference between metropolitan and urban areas seems somewhat arbitrary to this non-American referee. I suspect some further justification would help non-American readers

Metropolitan, urban and rural are defined by the U.S. Office of Management and Budget and the U.S. Census and I agree with the referee that the definitions seem not only arbitrary, but do not necessarily coincide between the two agencies. However, they are the official U.S. Government definitions. We tried to summarize these terms in the second paragraph of Methods.