Author's response to reviews

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

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Author's response to reviews:

Thank you for the outstanding critical attention that the editors and reviewers have provided our manuscript.

Dr. White remains concerned that the manuscript does not provide information allowing a side-by-side comparison with our previous study of CFS in the Wichita population and Dr. Jason's study in Chicago. We cannot provide such a comparison.

These earlier studies screened households for fatigued and non-fatigued residents. Then, fatigued residents were evaluated in more detail by means of a detailed telephone interview and a random selection of non-fatigued residents completed the same interview. This detailed interview was used: a) to classify fatigued persons (identified in screening) as CFS-like, fatigued but not meeting criteria for CFS, or non-fatigued; and, to confirm that those identified as non-fatigued were, in fact, non-fatigued. Then, all who were classified as CFS-like, a random selection of fatigued not CFS-like, and a random selection of non-fatigued were invited for detailed clinical evaluation, which confirmed CFS, other fatigued, and non-fatigued status. Prevalence was estimated utilizing weights based on the sampling strategy. The study design of the Georgia survey precludes estimating prevalence based on fatigued individuals detected by household screening because the Georgia study screened households for unwell and well residents. Unwell was defined as fatigue, problems with cognition, problems with sleep, musculoskeletal pain; well was defined as none of these. Every person identified as unwell with fatigue was eligible for the detailed telephone interview. An equivalent number of randomly selected residents identified as unwell but not fatigued, and an equivalent number of residents identified as well (none of the unwell criteria) were asked to participate in the detailed telephone interview. As in the other surveys, the detailed interview was used to identify persons with CFS-like illness, chronically unwell with fatigue not CFS-like, chronically unwell not fatigued, and well. A substantial proportion of those interviewed because they had been identified as unwell not fatigued personally reported fatigue on the detailed interview and were classified as CFS-like. These individuals were not included in previous surveys. Then, as in earlier studies, everyone classified as CFS-like was invited for clinical evaluation. Unlike other studies, random selections of unwell (with or without fatigue) and well were also invited for clinical evaluation. The unwell were not specifically identified and were not evaluated clinically in previous surveys. As with the detailed interview, some individuals brought to clinic because they were thought to be chronically unwell not fatigued were found to have CFS. Prevalence was calculated based on weights determined by the sampling strategy.

Even before Dr. White suggested it, the authors discussed this issue in detail. We have continued to worry about it and still cannot figure out how to dissect-out something that can be used to estimate prevalence based on the screening criteria that were utilized in Wichita or Chicago. Dr. White's query and our attempts to accommodate it notwithstanding, CFS is not fatigue. Rather, CFS is a complex disabling illness that comprises fatigue and accompanying symptoms and frequently these accompanying symptoms are more prominent for the affected individual than is fatigue. Thus, studies based on fatigue alone to screen for CFS lack sensitivity. The second paragraph in Discussion represents our attempt to succinctly present this issue. If we have failed we can redraft it.

The editors requested that we "follow Dr. White's suggestion to recalculate prevalence using the case
The editors believe "there are major issues with the case definition and that prevalence estimates from this study are rather high as a result." The editors misunderstood Dr. White's review. Fatigue was mandatory for the diagnosis of CFS in this study.

Based on the detailed telephone interview we classified all respondents who fulfilled verbatim criteria of the 1994 case definition as CFS-like. In brief, they reported that they were fatigued, had been fatigued for at least 6-months and that rest did not relieve their fatigue. They further reported that they suffered at least 4 of the 8 accompanying symptoms specified by the 1994 case definition (this is detailed in Methods). As discussed above, everyone identified as CFS-like was invited to clinic. This manner of screening individuals for more detailed clinical evaluation is similar to Pap smear screening for cervical cancer (sensitive but not terribly specific). In clinic we used internationally standardized and validated instruments to apply impairment, fatigue, and accompanying symptom criteria of the 1994 case definition (look upon it as a colposcopically directed biopsy to follow-up a LSIL Pap smear). As detailed in methods, based on the clinical evaluation individuals who met specified SF-36 criteria for functional impairment AND met MFI criteria for fatigue severity, AND met CDC Symptom Inventory criteria, AND had no exclusionary medical or psychiatric conditions were diagnosed as CFS. Clinic participants who met at least one BUT not all criteria were considered unwell. Finally, those who met none of the criteria were considered well. This approach was recommended by an international group after 3 annual 3-day meetings to discuss the issues of defining CFS. Their subsequent peer reviewed publication of these recommendations has received an unusually high number of citations, indicating its utility to the scientific community.

Again, we elaborated (hopefully not too succinctly) on these issues in paragraphs three and four of the Discussion. The authors have discussed the current critiques and have not changed it. We could add more discussion if the editors request it.

The crux of Dr. White's, the editors' and others' comments is that the manuscript needs to allow fair comparisons with previous prevalence rates. The authors believe that comparing prevalence rates ascertained in earlier studies for an illness like CFS is silly at this point in the game. There have really only been three population based studies and CDC conducted two of them. We designed the current study to move forward from what we and others had learned and not to use the same old methods in a new population. The first sentence in Discussion states what we believe is the most important aspect of the study; namely, that we screened defined metropolitan, urban, and rural populations for unwellness and used internationally standardized and validated instruments to define CFS.

Finally, thank you Dr. White, we corrected the incorrect reporting of point prevalence in Wessely et al's 1997 publication.