Author’s response to reviews

Title: An Evaluation of Exclusionary Medical/Psychiatric Conditions in the Definition of Chronic Fatigue Syndrome

Authors:

James F Jones (jaj9@cdc.gov)
Jin-Mann S Lin (dwe3@cdc.gov)
Elizabeth M Maloney (evm3@cdc.gov)
Roumiana S Boneva (rrb5@cdc.gov)
Urs M Nater (u.nater@psychologie.uzh.ch)
Elizabeth R Unger (eru0@cdc.gov)
William C Reeves (wcr1@cdc.gov)

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Author’s response to reviews: see over
Reviewer 2’s report:
Minor Essential Revisions

The authors thank the reviewers and the editor for the careful reading of our manuscript. Omission of previously reported valued observations was certainly unintended. It is tempting to attribute the oversight to very specific literature search paradigms.

In the Background section, the comment about excluding certain psychiatric illnesses because patients may not be competent to participate in studies really should be removed. Any participant who cannot give informed consent, regardless of the diagnosis should not be included in research. The diagnosis of a psychiatric illness should not be equated with incompetence.

Some psychiatric diseases are considered exclusionary diagnoses. The sentence was intended to provide an explanation for these exclusions, but it was not clear. We did not intend to suggest that any psychiatric illness is equated with incompetence. The reviewer is correct that truly incompetent subjects could not be enrolled as they could not provide informed consent. We have re-worded this sentence to clarify this point (page 3, 2nd paragraph).

In that same paragraph… Why would MMD with melancholic features be exclusionary but non-melancholia would not?

During the deliberations regarding the criteria for the definition of the syndrome, there was great concern raised by our UK and other European colleagues that MDD with melancholia overlapped too much with CFS and it would be difficult to separate the 2 entities. They won the day regarding this point in the definition and MDD with melancholia is an exclusionary condition. This emphasizes the somewhat arbitrary nature of how exclusions are determined and applied.

There is too little information about Table 1 in the Results section. There is a very limited discussion of the odds ratios and no comment on the use of adjusted or unadjusted odds ratios.

The data in Table 1 is derived from subjects chosen to come to clinic based on the detailed telephone interview; hence the CFS-like, unwell and well categories. The data are collected in the clinic, but no final classification has taken place. The table is divided into 2 parts. The first part (Part A) describes demographic variables and adjusted odds ratios for only those variables. This section is discussed in the first paragraph on page 8. Because we wanted to characterize the data derived from the three definitional questionnaires in the same manner, Part B describes those results. The text expanding those results is on page 9 in the first paragraph. The text explains that when all of the variables in parts A and B are considered, only the Vitality score is associated with exclusionary diagnoses.
What does bold font indicate in the table?

ORs with p-values <0.05 are in bold font. We have added this description in the footnote of Table 1.

Abbreviations need to be spelled out in a footnote and the text of the Results section should really highlight what is important in the table.

The footnotes now describe all abbreviations. As mentioned above the text highlights the meaningful tabular material.

All of the Tables need to have abbreviations defined in a footnote.

See above note.

Why were other psychiatric illnesses evaluated by telephone, but not MDD? Is Anxiety or Trauma included in the Other category or was it evaluated? Did the telephone interview query symptoms or diagnosed illness?

The telephone interview was used to collect information only on conditions that could be reliably self-reported. Only the psychotic exclusionary psychiatric illnesses fall into this category. While the telephone interview did query symptoms and information on current depression, post trauma stress disorder, and anxiety, these data were used only for recruitment to the clinic. All clinic subjects were evaluated on the SCID interview in the clinic for a more rigorous diagnostic process.

It might be useful to identify the form of the questions used in telephone interview.

The questionnaire is 34 pages in length. It can be provided as an electronic supplement if deemed appropriate.

Does the Sleep Disorders category also include insomnia?

The Sleep Disorders category does not include insomnia.

What is the n in each group in Table 4?

The n for each group is now included in Table 4.

The organization of the table is rather difficult to follow. Clearly, the goal is to define the most prevalent exclusions in each category, but the reader is also
going to be interested in comparing across categories. It might be easier to order the conditions across group.

As noted by the reviewer, Table 4 is designed to describe the most prevalent exclusions in each category. We reviewed the table and feel that the current format best allows the reader to compare diagnoses of interest by scanning across the table.

Table 5: it would be helpful to bold the font on significant differences. The meaning of the p adjustment in the footnote is not clear. Adjusted for the number of variables or the comparisons between groups or both, i.e. an experiment-wise p<.05? It would seem to be most meaningful to adjust for all comparisons and highlight those that are significant by an experiment-wise p<.05.

The bottom panel of Table 5 summarized the p-values from ANOVA for the overall comparison of measures across three categories of exclusionary conditions. Subsequently, post-hoc comparison with Tukey p-adjustment for multiple group comparison was used to examine the pair-wise differences among three groups. We have clarified this in the footnotes. The table footnotes also use a, b, and c to indicate different pair-wise comparison; a indicates the p-value for an post-hoc comparison between Both and Med types, b indicates the p-value for an post-hoc comparison between Both and Psych types, c indicates the p-value for an post-hoc comparison between Med and Psych types with Tukey p-adjustment less than 0.01 for multiple group comparison. For mult-test on multiple variables, the significance was set at 0.01 instead of the standard, 0.05.

Table 6 seems unnecessary since only BMI remained significant after adjustment.

Table 6 presents the factors associated with the presence of exclusionary conditions among subjects (n=210) classified as CFS at clinical evaluation while Table 5 describes the characteristics of subjects (n=280) with exclusionary conditions and both types of exclusions. BMI did not differ by type of exclusions in Table 5. We feel that Table 6 is important because it shows that 6 variables are either positively or negatively associated with exclusionary diagnoses among CFS subjects unless the appropriate adjustments are made.

The first sentence on page 15 is awkward and should be broken into two separate sentences.

The sentence (now in the last paragraph on page 15) in question now reads “Since people with CFS suffer from personal, social, workplace [1], and observed financial losses [20], should not all individuals fulfilling CFS inclusion criteria with or without exclusionary diagnoses be considered in future public health planning?”

Response to Suggestions by the Editors
A paragraph has been added to the discussion on pages 13 and 14 to address the editor’s concern that similar studies were not cited. We found the references suggested of interest, although the focus of both were different from our study addressing differences in CFS subjects with and without exclusionary conditions. The references clearly document the frequency of co-morbid psychiatric and medical conditions in subjects with CFS. We also found one reference cited by these papers to be of interest. We have incorporated this information as follows:

“Although not emphasizing differences between subjects who fulfill definitional requirements for exclusionary diagnoses and those who do not, previous studies of chronic fatigue and CFS have shown high rates of psychiatric morbidity and functional morbidity, and documented these outcomes to be an important public health burden [18-19]. Another study included 98 subjects with chronic fatigue and compared disability and psychosocial distress in those that met criteria for CFS and those that had medical or psychiatric exclusions, failed to meet the definition in use, or were using medications specific to the study [20]. The study results showed that the CFS subjects could not be differentiated from the excluded subjects based on the study variables that addressed symptoms of depression, general health, impairment, symptom perception, and somatic and psychological stress.”