Author's response to reviews

**Title:** Replication of an empirical approach to delineate the heterogeneity of chronic unexplained fatigue

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**Author's response to reviews:** see over
Reviewer-1

1) The two study populations are totally different and the authors fail to adjust for some key variables such as education, income, marital status, and other health conditions that influence their findings. Moreover, the methodology and questions are not the same in both studies.

Response: The purpose of the study was to replicate our previous findings in an independent and different population sample. We acknowledge that there may have been differences in demographic features between the two samples, but there is no current evidence that income, marital status et cetera influence the endophenotypes of CFS. We believe that finding some classes the same in different population samples supports both the heterogeneity of CFS and some of its previously described class contents.

We agree there were differences in methods and questions used or variables measured, which we have made clear in the revised Methods. We think this strengthens rather than weakens the study, since finding similar or the same classes as in the previous study suggests that the replication is robust. At the same time, we have used proxy measures when the same measure was not used (e.g. salivary cortisol on waking rather than 24 hours urinary free cortisol) as a way of measuring similar variables.

2) The authors used a telephone survey to recruit their sample. They report a screening response rate of 79%. They need to report their CASRO rate. The methodology excludes those with no telephone and cell phone only (about 35% of the population). In addition, out of their screened sample, they had 63% complete a detailed interview. Basically, 10,837 households were screened with 21,105 residents and only 3,189 completed the interviews. Who are the folks who refused to participate? How comparable are they to the study population in terms of the variables of interest? Basically, is there some self-selection in this study?

Response: Several comments of both reviewers addressed our poor description of the study population. We apologize for the poor writing and thank the reviewers for pointing this out. We have completely rewritten the section of Methods that describes the study population and have added a figure to add further clarity. Due to the stratified method of sampling a simple CASRO rate was not appropriate to this study. We did not expound upon this in this manuscript but we believe the rewritten manuscript will make it clear and those with more interest can refer to the cited manuscript, which was published in Population Health Metrics and is readily and freely available online.
Reviewer-2

1. Is the question posed by the authors new and well defined?

The two research questions posed by authors are not new but well defined. The topic of heterogeneity of chronic unexplained fatigue syndrome is still unresolved, thus it is justified pursuit of replications of past studies that add more information and expand our understanding of the research area.

Response: We agree and this is why we wrote the paper.

2. Are the methods appropriate and well described, and are sufficient details provided to replicate the work?

The Method and Result sections need improvement to allow more clarity of what is being analyzed and better understanding of results/findings.

Response: This is similar to the comment #2 by Reviewer-1 and as noted above we have completely rewritten Methods and added a figure to clarify our study population.

3. Are the data sound and well controlled?

Overall, data is sound but better explanation of study population and sub-sets, as well as the screening and diagnostic methods applied to define subsets will make paper clearer with regard to limitations and conclusions.

Response: As noted in responses to Reviewer-1 Comment # 2 and Reviewer-2 Comment #2, we have revised the paper to better explain these points.

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?

Overall, the manuscript adheres to relevant standard for reporting and data depositions. Improvement in Methods, Results, and discussion on limitations and conclusion are necessary though.

Response: We have done this.

5. Are the discussion and conclusions well balanced and adequately supported by the data?

Discussion and conclusion will have to address concerns in methodology and Results sections to become well balanced.

Response: As noted above Methods has been completely revised to explain the study population. We have revised the discussion and conclusion to take in the referee’s concerns in methods and results. In particular, we have toned down the implications to make it clear that these data “support” rather than “confirm” the heterogeneity of CFS.
6. **Do the title and abstract accurately convey what has been found?**

Yes they do!

7. **Is the writing acceptable?**

The writing is acceptable. Revisions in text are strongly recommended to clarify methodology, results and discussion.

**Response:** We have done this.

**Reviewer's report**

- **Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached)**

1. Authors need to clearly identify subpopulations (potential and analytic) involved in the study because of potential to limit findings and conclusions:

   1.1. **On page 6, under Study Participants, 1st paragraph** authors need to clearly say whether a 79% screening rate needs to be applied to the 21,105 residents to obtain the quantity 16,673 or 21,105 represents 79% of a population size not shown/described in text (26, 715)?

   **Response:** As noted in responses above we have rewritten Methods and included a Figure, which clarifies all these queries.

   1.2. **On page 6, under Study Participants, 1st paragraph.** From the screened population of 16,673 or 21,105 (whichever quantity is correct depending on answer to question/issue 1.1 above), authors should describe the proportion and numbers of individuals who are a) “Unwell but not fatigued”, and b) “Well”, both identified through detailed telephone interview? Only the number of “Unwell with Fatigue” is provided (N=3851).

   **Response:** We have included all these figures in the methods.

   1.3. **On page 7, under Study Participants, 2nd and 3rd paragraphs.** The authors describe random samples selection of 2,136 and 3,116 from those who were “Unwell but not Fatigued” and the “Well” respectively, and selection of “all” those who were “Unwell and Fatigued” so that a detailed phone interview would be offered to provisionally classify individuals into three categories of CFS-likeness: CFS-like illness, Chronically Unwell not CFS-like, or Well. However, it is not clear if detailed phone interview to classify CFS-likeness were offered/collected only to/from those who were classified during screening as “Unwell but not fatigued” and “Unwell and Fatigued” or involved the “Well” individuals as well.

   **Response:** We have written in the text that we did a detailed phone interview of all three groups.
2. Page 15, under “Limitations of this replication”. Need to address two other limitations: 1) cannot generalize findings to men- only women in analysis; 2) needs to recognize potential misclassification of provisory classification based on CFS-likeness introduced by bias in selection of “illness” identification subgroups for completed detailed phone interviews (56% for “well”, 67% for “Unwell but not fatigued”, and 63% for “unwell and fatigued”) and acceptance to participate in final analytical samples (53% for “chronic unwell but not CFS like” and 62% for “CFS-like”). What could have happened to study if non-participants were different from participants in each sub-group defined after screening (unwell without fatigue, unwell with fatigue and ) and after detailed interview-provisory classification based on CSF-likeness?

**Response:**

1) We have revised the limitations to mention that these data cannot be generalised to men. That having been said, this was a replication study and the original Wichita study was of women only for the purposes of exploring heterogeneity.

2) We have added a sentence to make clear that an unknown response bias may have affected our results.

- **Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)**

3. Page 8, under Independent Variables used to delineate the Sub-Groups, 1st paragraph. Define variables in text or in Table 1: whether categorical, ordinal or continuous. For continuous and ordinal provide cut-off for dichotomization, if done.

**Response:** Although we can supply this information, we respectfully suggest that readers will already know what type of data each variable is since all these variables are so well known (e.g. heart rate, haemoglobin concentration, BMI, age). We have explained that all non-categorical data was dichotomised by median split (necessary for a latent class analysis), which we would suggest is sufficient information to allow replication of our work (since other studies will have different values for their median splits). We would be happy to add that this information is available from the authors if required.


**Response:** We have added a sentence to do that.

5. page 10, under Results, 1st paragraph. Add words “data not shown” between parenthesis, right after AIC values.

**Response:** We have added a clarification that the 4 class and 6 class solutions’ data are not shown.

6. page 10, under Results, 2nd paragraph. Add words “data not shown” between parenthesis, right after AIC values – consistency of data presentation is needed.

**Response:** We have added a clarification that the 4 class and 6 class solutions’ data are not shown.
7. Page 11, under “Validation against independent variables not included in the model”. The description of the ANOVA analysis with Kruskal-Wallis testing in Table 4, and that of Mann-Whitney U tests for fatigue and disability scores across classes should have been better described in Methods, to facilitate flow of writing and reading of results.

Response: The statistics shown in the Table are from the Kruskal Wallis overall test. This is a non-parametric ANOVA test and uses a statistic that is a form of Chi-square; where normally ANOVA uses the F statistic; Kruskal Wallis uses Chi-square to indicate significance of differences between groups. We then followed-up with Mann Whitney U tests for individual group comparisons. We have added a paragraph to the analysis section to describe this analysis.

8. Page 11, Under “Validation against independent variables not included in the model”. Add words “data not shown” in parenthesis to first description of M-W U test results and class number between parenthesis when describing “three unwell classes”.

Response: The data are given in table 3.

9. Page 11, Under “Validation against independent variables not included in the model”, 2nd paragraph. It is not clear to reader which class is authors referring to when they say “subjects in class 4 reported significantly lower physical functioning and physical fatigue”.

Response: This pertains to the comparison between the two well classes (4 and 5) and we have omitted this paragraph to simplify our results.

10. Page 11, Under “Validation against independent variables not included in the model”, 2nd paragraph. In next sentence they say “these differences in the reported level of disability and fatigue between these two ‘well’ groups… Which two ‘well’ groups are authors referring to? I assume the “well” groups are the same as classes 4 and 5?

Response: This pertains to the comparison between the two well classes (4 and 5) and we have omitted this paragraph to simplify our results.

11. Page 12, Under “Validation against independent variables not included in the model”, 1st paragraph. Statement “there is no …remaining measures listed in table 4” seems unnecessary.

Response: We agree, and we have omitted this paragraph to simplify our results.

12. Page 12, Under “Validation against independent variables not included in the model”, 2nd paragraph. First mention in the manuscript of the SF-36 and MFI subscales. These should have been clearly presented in methods with clear indication when they were used: detailed telephone interview? Or another opportunity not described in methods?

Response: We agree and have added a brief paragraph in methods to describe their use as external validators.
13. Page 12, Under “Validation against independent variables not included in the model”, 3rd paragraph. First time term “Criterion based Diagnoses used– also first time term “CDC Research Criteria”m used in Table 5. Are these terms the same? Need to write a description of Criterion in Methods.

**Response:** We have added this description of validation against the CDC criteria for CFS, which are referenced, in the methods section.

14. Page 12, Under “Validation against independent variables not included in the model”, 4th paragraph. Statement “As can be seen there was close similarity across all four classes” is not accurate for data referred to in Wisconsin: Class 4(16%) and Class 1 (32%).

**Response:** We have revised this interpretation to clarify that we are referring to the content of the four classes rather than their prevalence.

- *Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)*

15. Conclusion needs to be toned down given limitations. For example, authors could consider substitution of statements such as “provides strongest support yet published of the heterogeneous nature of CFS” by “provides additional support to heterogeneity of CFS”

**Response:** We have qualified our interpretations as requested.