Author’s response to reviews

Title: A Logistic Regression Analysis of Risk Factors in ME/CFS Pathogenesis

Authors:

Eliana Mattos Lacerda (Eliana.Lacerda@lshtm.ac.uk)
Keith Geraghty (KeithGeraghty2@gmail.com)
Caroline Kingdon (Caroline.Kingdon@lshtm.ac.uk)
Luis Nacul (Luis.Nacul@lshtm.ac.uk)

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Author’s response to reviews:

Dear Darren Byrne,

Please see our revised manuscript, which we believe has now addressed all the requests from you and the distinguished reviewers.

We take this opportunity to thank the reviewers for their comments and suggestions, which helped us to improve our manuscript by clarifying our recruitment procedures, acknowledging the limitations of our findings, while being able to report a structured model of looking at risk factors that helps to better identify them.

Please see the following point-by-point answers.

Yours sincerely,

Dr Eliana Lacerda

RESPONSE TO EDITOR AND REVIEWERS
Response to editor comment

1) We have amended the way we report the P values
Response to Reviewer 1
We appreciate your comments and corrected the extra “return line breaks” as advised.

Response to Reviewer 2

We are very grateful for your comments and suggestions, which help us to improve our manuscript by clarifying our recruitment procedures, acknowledging the limitations of our findings, while being able to report a structured model of looking at risk factors in ME/CFS research, which helps to better identify them. We address your comments in the following paragraphs.
1. DEFINITION OF CASES: All cases have been clinically diagnosed previously to invitation to be part of the study. Those consenting to participate were assessed through a combination of a self-completed questionnaire addressing symptoms that form part of both CDC-1994 and Canadian Consensus Criteria. Those whose symptoms were compatible with a diagnosis of ME/CFS were further assessed face to face by trained clinical researchers, including clinical examination. Additionally, we run laboratory test to exclude other medical conditions that could explain the symptoms and screen for psychiatric conditions. These procedures are contained in Figure 1 from the reference 17 (Lacerda et al, 2017), whose description was taken out in compliance with the editorial limits of that journal. These procedures are now described in pages 5 (lines 10 – 26) and 6 (lines 1 – 25).

2. Fraction of cases who agreed to participate: The proportion of patients with ME invited by the NHS services, who responded positively to the invitation to participate in the study was 32%, and the distribution by sex and age-group from non-participants was similar to the consenting participants. As both participants and non-participants were from the same catchment areas of the NHS health services, we believe the recruits to be a fairly representative sample from the study population, this is now reported in page 6, lines 19-22.

3. DEFINITION OF RISK FACTORS: We now present the questions on risk factors as supplementary material (Participant Questionnaires), as per reviewer’s suggestion. The information is by “self-report” and the retrospective period, for most questions, is of 6 months (as indicated in the questionnaire).

4. We do have information on the family member for whom the “other neurological disease” was reported. For severe cases of ME/CFS, dementia and Parkinson’s were the most commonly reported diseases, and most of these were reported for the father or mother. The small numbers with family history of other neurological diseases precludes meaningful conclusions. This is elaborated in lines in page 10 (lines 14 – 17).

5. Medical records: We did not have access to medical records to confirm information on risk factors. This is now explained in page 7 (lines 4 and 5).

6. History of vaccinations: Again this was obtained by self-report. We edit the text to highlight this limitation, including recall bias as a potential determinant of this finding. We totally agree this should not be over-read, and we believe the text now reflects more strongly the limitations of this information. See pages 13 (lines 22-24) and page 16 (line 19).

7. STATISTICAL QUESTION - We did not adjust for multiple comparisons, as per description of original methodology (reference 18). However, the use of a more stringent cut-off point for statistical significance, would virtually not change the interpretation of results. We now mention this on page 16 line 23 to page 17 line 3.

MINOR ISSUES

8. Tables 3-5. We have edited the table to indicate that risk refers to additional years of age (at survey for comparison with non-diseased controls, and at disease onset for comparisons with MS and between ME/CFS groups with distinct groups of severity. Additionally, we clarified that the variable sex in the final models refer to female sex.
9. Female predominance: We agree that our data is limited in demonstrating female predominance, due to the non-randomised recruitment procedures; however, considering the NHS primary care services have an almost universal coverage, we consider that the ratios between female to male in the ME/CFS and MS groups recruited, fairly represent the population distribution, which is similar to those reported in the literature. Despite these differences had not been significant in the first level of the multivariate models, we maintained the variables sex and age group in the subsequent hierarchical models to control for potential confounding. (Please see in the text on pages 8 and 9 (lines 12-16 and 1-4, respectively)

10. Report of common infections before developing symptoms of ME/CFS: We entirely agree with the observation, and we amended the text to reflect that on page 12 (lines 19-21)

11. Kaposi is now correctly spelled (page 13, line 2)

12. Anxiety in the family: We have now corrected the text, reinforcing the negative finding on previous history of anxiety in cases compared to controls (page 14, lines 10-12)

13. Recall bias: we now emphasise this limitation as a major issue (page 16, line 19)

Response to Reviewer 3

We are very grateful for the useful comments from this reviewer. Some of the issues are similar to those mentioned by reviewer 2 and have been addressed as above

Literature review: We have included more references, including those suggested by the reviewer Please see references 16, 29, and 31.

Interaction with environmental factors: We have now added a note to emphasise the importance of environmental factors. Please see page 4, lines 20-22.

Child abuse and HPA axis: We added information on these on page 4, lines 26-27.

Details of methods: These have been amended with more detailed information. Please see replies to comments from 2nd reviewer which cover diagnosis confirmation, sampling frame and numbers approached and response rates. Please refer to pages 5 (lines 10 – 26) and 6 (lines 1 – 25).

Recall and response bias: These are given more emphasis throughout the text (see response to reviewer 2 and page 16, line 20)