**PEER REVIEW HISTORY**

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**ARTICLE DETAILS**

| TITLE (PROVISIONAL) | An Exploratory Study into the relationship between the symptoms of Chronic Fatigue Syndrome (CFS)/ Myalgic Encephalomyelitis (ME) and Fibromyalgia (FM), using a quasi-experimental design. |
|---------------------|----------------------------------------------------------------------------------------------------------------------------------|
| AUTHORS             | Mckay, Pamela; Walker, Helen; Martin, Colin; Fleming, Mick                                                                     |

**VERSION 1 – REVIEW**

| REVIEWER            | Dr Kristy Themelis  |
|---------------------|---------------------|
|                     | University of Warwick  |
|                     | United Kingdom       |
| REVIEW RETURNED     | 23-Aug-2020          |

| GENERAL COMMENTS     | The manuscript reports interesting results with respect to the similarity in symptoms experience of patients with CFS/ME and Fibromyalgia. This study adds new information that could have important clinical applications. |
|----------------------|----------------------------------------------------------------------------------------------------------------------------------|
|                      | I only have some minor comments:                                                                                               |
| Abstract             | - Participants: I would suggest adding the number of participants recruited, mean demographics and diagnostic criteria.       |
|                      | - Results- from just reading the abstract, it would not be clear to the reader what the sentence "It may have been erroneous to conclude that CFS/ME and FM were different based on 5 questions out of 400" means out of context. It might just need a bit more context and generally slight rephrasing of the results section (i.e. The sentence “The Syndrome Model was created to comprise these 3 questionnaires and incorporated the ACR criteria for FM, pain points” could be slight rephrased). |
| Aims and objectives   | - The mention of a "Phase 1" and "Phase 2" is slightly confusing and I wonder if this could be rephrased to clarify what has already been investigated in phase 1, what the findings are and how it informed the research described in this study. |
| Results              | - I would suggest using inferential statistics for differences in age and other demographics to strengthen the case that the groups share similar characteristics at baseline. |
|                      | - Similarly, for completion it would be informative use a statistical test to compare group difference, i.e. the percentage of participants that were diagnosed between groups, number of symptoms experienced. |
- Similar to the report that both groups fulfilled the CFS/ME criteria, it would be interesting to report the number of CFS/ME participants fulfilling the ACR criteria.
- It was not entirely clear to me why the ACR Criteria for FM points was now included as part of the Syndrome model.

Discussion
- Perhaps relevant to the discussion of the finding that the CFS/ME group recorded lower than the required number of pain points to meet the 1990 FM Criterion are other diagnostic criteria used for CFS/ME such as the Canadian Consensus Criteria that acknowledge pain as a criteria, but not a requirement for diagnosis.

REVIEWER
Dr Keith Geraghty
Centre for Primary Care and Health Services Research
Division of Population Health
Faculty of Biology Medicine and Health
University of Manchester

REVIEW RETURNED
04-Sep-2020

GENERAL COMMENTS
Thank you for the opportunity to review this paper. The idea to check symptom profiles between ME/CFS and FM is not a new one, perhaps the type of model you use is. The key finding from your paper, if I am correct, is the symptom profile overlap between CFS and FM, again not a new finding, thus perhaps some further explanation is required to highlight the importance of your findings. Overall, I am happy with the paper, there are a few points that need to be addressed.

As follows:

Background
While authors suggest aetiology of CFS is unknown, research data has long shown that infections tend to initiate the illness
Eg Lacerda EM, Geraghty K, Kingdon CC, et al. (2019) A logistic regression analysis of risk factors in ME/CFS pathogenesis. BMC Neurol 19: 275.

There is a break at the end of background into two short paragraphs that don’t follow well from the prior paragraphs and are difficult to fully understand, perhaps join and expand explanation for reader to know what you really mean “The evidence presented was evaluated, within the context of advances in clinical management and investment in research………..!”

“The purpose of this phase was to assess the current relationship between CFS/ME and FM, and to establish whether a relationship exists.” – I understand what you mean from later sections, but at this point the word “relationship is too vague and unspecified – you must present a clearer case of what you mean…..eg symptom presentation similarity or what?

Aims
This sort of line is rather frustrating – “Phase two, now reported is based on the findings published from phase one 2” – ok (the reader doesn’t care about phases, you can report there was two phases to the current study, phase 1 did x,y,z and here are results from phase 2, where we did j,h,t). I encourage you to edit this section, it could be one shorter paragraph that sets out the aims
and how this part of the research links to the other – don’t make
the reader have to go off and read another paper to understand
this one, give them the salient information here.

Sample: why choose 16+ - any rationale for that: teenagers with
CFS for instance usually have rapid recovery and almost 95%
recover within 2 years, often due to mild post-viral fatigue
associated with EBV – whereas mean onset of CFS is mid 30s
and rates of recovery are lower and disease tends to become
chronic; you are looking at teens to adults – just wondered why?

Sample size: there is gaps between text on html format – check
spacing is correct between words.

Discussion section: use of comma missing across many
sentences, check punctuation.
This argument/conclusion is presented based on the evidence
which highlights that to date, the aetiologies for both these groups
have not been identified and therefore CFS/ME and FM, manifest
as a single reality based on their responses to the questionnaires
4, (no need for comma here – and then commas missing in other
sentences).
“In this instance when there is no cause, test or cure for CFS/ME
and FM, it is the experience of the complex constellation of
debilitating symptoms that is important and should be considered
and managed appropriately, to enhance the patients’ recovery and
quality of life.” --- clearly there is a cause right, and the literature
points to viral infections as key and neurological and
immunological events, brain inflammation and possible CNS
inflammation (not mentioned much in your paper) – what is not
known is the exact way in which infection induces fatigue, pain and
so on, but in FM causation has often been linked to traumatic
events, physical trauma for instance (as far as some of the papers
I have read) v CFS whereby infections are commonly the most
reported trigger. This needs to be covered a little bit more.
“The findings presented raise questions which complement
research into the biomedical aspects of the syndromes,” -- please
elaborate on what you mean by this, it’s not clear to me.
“all the management options” – you have to take on that NICE
recommend CBT and GET for CFS, so what
management options
are you talking about, do you suggest other options and why –
make this point clearer.

Conclusion
Don’t like opening with “it may be concluded” – best to just
conclude – this is your conclusion.
Don’t like the word “impossible” – I would argue that it is possible
to differentiate CFS from FM, however I accept there is a high
degree of overlap, eg your finding that many if not most CFS
cases might meet new criteria for FM< and perhaps vice versa.
This is the main finding of your paper I believe. If so, this
conclusion needs to be made clearer with reference to NICE
guidelines, treatment guidelines, benefits, management and
diagnosis eg GP care.
“same management” – again you need to state in text above what
those area and then conclude that FM and CFS should be offered
similar management – are you suggesting CBT for FM and CFS or
not? Pain, what is the best management for pain in CFS and FM?
1. **Abstract**

1.1 Participants: I would suggest adding the number of participants recruited, mean demographics and diagnostic criteria.

- I have made the necessary changes as requested, to the sections on participants. I hope this is more informative now. I added in the statistics I had, but had to sacrifice other words to meet the 300-word limit.

1.2 Results: from just reading the abstract, it would not be clear to the reader what the sentence "It may have been erroneous to conclude that CFS/ME and FM were different based on 5 questions out of 400" means out of context. It might just need a bit more context and generally slight rephrasing of the results section (i.e. The sentence "The Syndrome Model was created to comprise these 3 questionnaires and incorporated the ACR criteria for FM, pain points" could be slight rephrased).

- I have changed the wording in this section, to improve the meaning of what was previously written. Please see marked copy for changes.

2. **Aims and objectives**

2.1 The mention of a "Phase 1" and "Phase 2" is slightly confusing and I wonder if this could be rephrased to clarify what has already been investigated in phase 1, what the findings are and how it informed the research described in this study.

- I have now added a section, which I hope makes the purpose of phase one clearer, and what was achieved. I appreciate the comments, this study was on the large side and it is challenging to decide what to omit. I have provided the explanation/summary which should make it clearer what was reported in phase one and published in the first paper.

2.2 **Results**

2.2.1 I would suggest using inferential statistics for differences in age and other demographics to strengthen the case that the groups share similar characteristics at baseline.

- Changes have been made to address the questions raised by the results section. This has resulted in amending a table and including Mann Whitney tests for the CDC Criteria to confirm that the participants were similar at their baseline, before additional testing was performed. No formal statistical tests were used on the demographic data, as there was so much additional data which confirmed that the groups were similar using other statistics on their symptoms. Therefore, I included the results from the Mann Whitney U test for the CDC criteria for CFS/ME, as this would provide evidence that the groups were similar at baseline. I hope this is acceptable.

2.2.2 Similarly, for completion it would be informative use a statistical test to compare group difference, i.e. the percentage of participants that were diagnosed between groups, number of symptoms experienced.

- Table 3 has now been amended to include the percentage and mean scores of the participants on the CDC Criteria to highlight the number of people who experienced each symptom, and to provide further evidence of what the groups symptoms were at baseline.

2.2.3 Similar to the report that both groups fulfilled the CFS/ME criteria, it would be interesting to report the number of CFS/ME participants fulfilling the ACR criteria.
• Following Table 3 I have added more information from the results from the ACR criteria to show evidence of the pain points.

2.2.4 It was not entirely clear to me why the ACR Criteria for FM points was now included as part of the Syndrome model.

• The rationale for including the ACR pain point in the Syndrome Model was also made clearer, in the text. It could not have been tested in a model by itself, as it only involves one data point, which a model cannot be created from.

3. Discussion
- Perhaps relevant to the discussion of the finding that the CFS/ME group recorded lower than the required number of pain points to meet the 1990 FM Criterion are other diagnostic criteria used for CFS/ME such as the Canadian Consensus Criteria that acknowledge pain as a criteria, but not a requirement for diagnosis.

• Yes, it was interesting that the participants reported lower than the number of pain points, but they had a number of areas of pain, which was extensive. Due to the limitations of this paper it is difficult to include all this data. I acknowledge that there are a number of different criteria which add or take away from the symptoms. However, it was the CDC symptom Inventory that was used and the criteria I refer to in the paper. It acknowledges muscle aches and pain. I have changed the text to emphasise that Pain is a defining symptom in FM, whereas it is Fatigue in CFS/ME, however it is problematic for both groups. Furthermore, the pain does not need to be on the pain points highlighted by the FM criteria, to cause issues for the patients.

Reviewer: 2 Dr Keith Geraghty

1.1 Background
1.1.1 While authors suggest aetiology of CFS is unknown, research data has long shown that infections tend to initiate the illness.

Eg Lacerda EM, Geraghty K, Kingdon CC, et al. (2019) A logistic regression analysis of risk factors in ME/CFS pathogenesis. BMC Neurol 19: 275.

• Thank you for this comment. Yes, I totally agree that the possible cause of this illness is due to viral illness. I have changed the wording to take away ‘unknown’ to ‘unclear’. I have also added in a section in the discussion to refer to the possible causes of CFS/ME and FM.

1.1.2 There is a break at the end of background into two short paragraphs that don’t follow well from the prior paragraphs and are difficult to fully understand, perhaps join and expand explanation for reader to know what you really mean “The evidence presented was evaluated, within the context of advances in clinical management and investment in research.........!

• I have amended this section and rewritten it to make the information/meaning clearer.

1.1.3 The purpose of this phase was to assess the current relationship between CFS/ME and FM, and to establish whether a relationship exists.” – I understand what you mean from later sections, but at this point the word “relationship is too vague and unspecified – you must present a clearer case of what you mean…..eg symptom presentation similarity or what?
• I have reviewed the text and amended it to make it clearer that it is the relationship between the symptoms that is being explored.

2. Aims
This sort of line is rather frustrating – "Phase two, now reported is based on the findings published from phase one 2" – ok (the reader doesn’t care about phases, you can report there was two phases to the current study, phase 1 did x,y,z and here are results from phase 2, where we did j,h,t). I encourage you to edit this section, it could be one shorter paragraph that sets out the aims and how this part of the research links to the other – don’t make the reader have to go off and read another paper to understand this one, give them the salient information here.

• I have now added in a paragraph to address what was achieved in phase one.

3. Sample
3.1 Why choose 16+ - any rationale for that: teenagers with CFS for instance usually have rapid recovery and almost 95% recover within 2 years, often due to mild post-viral fatigue associated with EBV – whereas mean onset of CFS is mid 30s and rates of recovery are lower and disease tends to become chronic; you are looking at teens to adults – just wondered why?

• I understand why you ask this question. I have not added this explanation into the article, but address this question here. It is interesting that 95% of teenagers with a diagnosis of CFS/ME recover within 2 years. I have read this in papers, and for the patient this is brilliant, but then could it be argued that they have something different, and raises questions again about the criteria/ guidelines. However, the > 16 age limit was an issue raised by the ethics committee and they wanted this age (adults) to be included. As recruitment was done using online methods the chief investigator would have had little control over the participants recruited. Participants had to confirm that they were over the age of 16 to participate, as in Scotland this is the age that a person is deemed an adult and as such the ethics committee asked this to be added. It was also considered, as this would make it more likely that the questionnaire would be completed by the patient rather than a carer or guardian.

3.2 Sample size: there is gaps between text on html format – check spacing is correct between words.

• This has been addressed in the main document.

4. Discussion section:
4.1 Use of comma missing across many sentences, check punctuation. This argument/conclusion is presented based on the evidence which highlights that to date, the aetiologies for both these groups have not been identified and therefore CFS/ME and FM, manifest as a single reality based on their responses to the questionnaires 4, (no need for comma here – and then commas missing in other sentences).

• The grammar has been revised and proof read. Please see main document.

4.2 "In this instance when there is no cause, test or cure for CFS/ME and FM, it is the experience of the complex constellation of debilitating symptoms that is important and should be considered and managed appropriately, to enhance the patients' recovery and quality of life," — clearly there is a cause right, and the literature points to viral infections as key and neurological and immunological events, brain inflammation and possible CNS inflammation (not mentioned much in your paper) – what is not known is the exact way in which infection induces fatigue, pain and so on, but in FM causation has often
been linked to traumatic events, physical trauma for instance (as far as some of the papers I have read) and CFS whereby infections are commonly the most reported trigger. This needs to be covered a little bit more.

- I have addressed the issues raised here by adding in some sections to the discussion to acknowledge the possible causes for CFS/ME and FM. Please see main document. As you will appreciate CFS/ME and FM is a huge subject and I have so much written on this. But due to the constraints the word count imposes it was challenging to be selective of what could be included.

4.3 “The findings presented raise questions which complement research into the biomedical aspects of the syndromes,” -- please elaborate on what you mean by this, it's not clear to me. “all the management options” -- you have to take on that NICE recommend CBT and GET for CFS, so what management options are you talking about, do you suggest other options and why – make this point clearer.

- I have addressed the issues raised here by adding in some sections to the discussion to acknowledge that there is controversy in the management options selected by NICE for the management of CFS/ME and FM, and how some management may be potentially damaging to patient’s recovery. Please see main document. Again, I had to be selective on what to include here as there is so much that could be included.

5. Conclusion
Don't like opening with “it may be concluded” – best to just conclude – this is your conclusion. Don't like the word “impossible” – I would argue that it is possible to differentiate CFS from FM, however I accept there is a high degree of overlap, eg your finding that many if not most CFS cases might meet new criteria FM< and perhaps vice versa. This is the main finding of your paper I believe. If so, this conclusion needs to be made clearer with reference to NICE guidelines, treatment guidelines, benefits, management and diagnosis eg GP care. “same management” – again you need to state in text above what those areas and then conclude that FM and CFS should be offered similar management – are you suggesting CBT for FM and CFS or not? Pain, what is the best management for pain in CFS and FM?

- I have changed the wording of the conclusion to make it clearer and amended the words that were not satisfactory. Please see main document.

Once again, I would like to thank you all for taking the time to review my paper, and for all the constructive comments. I hope I have addressed all the recommendations to your satisfaction. It would have been great to have a discussion with you both regarding the research. Dr Themelis, thank you for your comments regarding the ACR pain points. I feel there is so much that could be written on this, now that there are revised guidelines. Dr Geraghty, I have read much of your work during the process of writing my PhD, and it has been an honour to have you review my work. I agree with many aspects of the approach you have to CFS/ME especially the viral aspect of it. I also understand the controversy that surrounds the syndrome and the difficulties with the recommendations of PACE, GET, and CBT. Having experienced this all first hand, it is challenging at times to write about things when trying to remain impartial. Let’s hope one day there is a cure.

I am happy to discuss any questions you have regarding the changes to the paper. I hope this process has resulted in a paper that you now find acceptable. Thank you.
**GENERAL COMMENTS**

Thank you for the opportunity to review the paper and for addressing the previous suggestions.

Some further comments:

**Abstract:**
There is not enough information on the outcome measures in the abstract. I appreciate word count is restricted but would expect at least some general information on what kind of diagnostic criteria/questionnaires (i.e. to measure function/disability/pain?).

**Abstract/manuscript**
- The mention of The syndrome model requires more context.
  
  "This presented an opportunity to include the pain point questions from the ACR criteria for FM, as it comprised only one data point." This could benefit from more background in both the manuscript and the abstract.

**Data analysis**
- Again the mention of Phase one remains confusing - it seems to be both referring to a previous paper and a specific step of the current research.

**Discussion**
- Paragraph 1: Consider rephrasing the following sentence: The results confirmed that the characteristics of the participants, such as age and gender are supported by historical findings of CFS/ME and FM"

**Minor comments:**
- Please make sure the formatting is consistent throughout the abstract and manuscript (i.e. adding years, use of italics for statistical symbols)

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**VERSION 2 – AUTHOR RESPONSE**

Reviewer: 1.

**Abstract:**
There is not enough information on the outcome measures in the abstract. I appreciate word count is restricted but would expect at least some general information on what kind of diagnostic criteria/questionnaires (i.e. to measure function/disability/pain?).

Based on the tight word count restrictions, I have now reworded my abstract to address these suggestions, as can be seen in the tracked changes document and as outlined here. This should now make it clearer for the reader. I have not added in the names of the questionnaires used as this impacts on the word count, but I have added in the subject areas to be investigated.
Outcome measures: Diagnostic Criteria: The American Centre for Disease Control (CDC) for CFS/ME, and the American College of Rheumatology (ACR) Criteria for FM. Additional symptom questionnaires measuring: Pain; Sleep Quality; Fatigue; Quality of Life; Anxiety and Depression; Locus of Control and Self Esteem.

- The mention of The syndrome model requires more context. "This presented an opportunity to include the pain point questions from the ACR criteria for FM, as it comprised only one data point." This could benefit from more background in both the manuscript and the abstract.

I have addressed this issue again that can be see in the tracked changes in the abstract and main document. In the abstract I have made it clearer the reason why the ACR could not be measured on its own and expand on this in the main text. In the abstract…

Results: Invariance was confirmed with the exception of the American CDC Symptom Inventory, FIQ and HADS ($p < 0.05$), based on 5 questions. Consequently, it was erroneous to conclude differences. Therefore, the Syndrome Model was created. SEM couldn’t have tested the ACR previously, as it comprised a single data point. Therefore, it was combined with these 3 questionnaires, increasing the data points, to create this new measurable model. Results confirmed no significant differences between groups ($p = 0.07$ ($p <0.05$)).

Main text

Instead, the Syndrome Model was created comprising the 3 questionnaires responsible for Non Invariance, which now incorporated the ACR Criteria for FM pain points (Figure 1). The ACR criteria could not have been previously tested using SEM, because an independent model could not be created and tested as it only comprised one data point. Incorporating the ACR with these 3 questionnaires, increased the data points to create a testable model, where the sample size was appropriate to generate meaningful data. Invariance testing confirmed no differences between groups ($p \leq 0.05$) (Table 4).

Data analysis
- Again the mention of Phase one remains confusing- it seems to be both referring to a previous paper and a specific step of the current research.

The use of phase one has now been removed from the paper. Instead, wording has been changed to say that some preparatory work had to be performed to be able to create the research that is reported.
This will remove any confusion for the reader, as this paper is stand alone. This may be viewed on page 12 of the tracked changes.

**Discussion**
- Paragraph 1: Consider rephrasing the following sentence: The results confirmed that the characteristics of the participants, such as age and gender are supported by historical findings of CFS/ME and FM

The wording has been changed to read:

The results confirmed that the characteristics of the participants, such as age and gender, concur with previously reported characteristics of patients with CFS/ME and FM \(^{11, 25}\).

**Minor comments:**
- Please make sure the formatting is consistent throughout the abstract and manuscript (i.e. adding years, use of italics for statistical symbols)

I have been through the document paying close attention to this and checked the symbols. Italics were used to highlight a question from a questionnaire. I have also checked for consistency in the reporting.

Once again, I would like to thank you for taking the time to review my paper, and for all the constructive comments. I hope I have addressed all the recommendations to your satisfaction.

I am happy to discuss any questions you have regarding the changes to the paper. I hope this process has resulted in a paper that you now find acceptable. Thank you.