PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Impact of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) on the quality of life of people with ME/CFS and their partners and family members: an online cross-sectional survey
AUTHORS	Vyas, Jui; Muirhead, Nina; Singh, Ravinder; Ephgrave, Rachel; Finlay, Andrew

VERSION 1 – REVIEW

REVIEWER	Araja, Diana Riga Stradins University
REVIEW RETURNED	18-Nov-2021

GENERAL COMMENTS	The study demonstrates a significant ME/CFS population coverage, however the sample of the study is not completely homogeneous, and the question arises as to whether there were any plans to compare data from different regions. For the reflection of data, parameters such as Mean, Standard Deviation and Confidence Interval could contribute the reliability of the results.

REVIEWER	Friedman, Kenneth New Jersey Medical School Department of Pharmacology and Physiology
REVIEW RETURNED	24-Dec-2021

GENERAL COMMENTS	This is a well written, thoughtful paper on the social and society impact of ME/CFS as an example of a severely limiting chronic disease with little or no remedial treatment currently available. It is more timely to publish this manuscript in this time of COVID pandemic and hopefully soon post-pandemic, as the impact of Longhaul COVID is making its presence known. While the chronic illness of ME/CFS and Longhaul COVID are not identical, they are similar. Soon, the numbers of persons suffering ME/CFS-like illness will dramatically increase with the commensurate burden of social and societal impact increasing as well.

REVIEWER	Thomas, Marie Bath Spa University, Psychology
REVIEW RETURNED	24-Jan-2022

GENERAL COMMENTS	This is a well written piece of work that has taken the views of the CFS/ME comunities into consideration when designing and conducting the research. This topic is clearly of importance to patients and their familes and as such is an important peice of research.

REVIEWER	Kumah, Emmanuel University of Education Winneba Faculty of Science Education, Healthcare Management
REVIEW RETURNED	15-Feb-2022

GENERAL COMMENTS	The paper is very interesting and has a lot of strengths, considering the large sample size drawn from over 30 countries. It addresses a very important issue, and thus publishable. My suggestions are provided below for further improvement. 1. In my view, the introduction is not sufficiently grounded in the literature. For example, does the study aim to fill a specific gap, and if so what is this gap? Or it is just to add to and extend what is already known on the topic? The introduction should tell readers what is already known on the topic, and what is not known that the study intends adding. 2. According to the authors "Microsoft Excel, SPSS and GraphPad Prism v9 were used for data handling and statistical analysis, involving descriptive statistics and parametric statistical tests including Item-total correlations, inter-item correlations and Spearman rank correlation coefficient". I have three key issues: a) there are no displayed outputs for the Item-total correlations, and inter-item correlations in the paper; b) Spearman rank correlation is a non-parametric test used to measure the degree of association between two variables (i.e. the strength and direction of the association), and thus not a parametric statistical test as stated; and c) In place of Spearman rank correlation coefficients at the results section, I see linear regression analysis. 3. The authors state "In order to determine the relationship between the person with ME/CFS and their family members quality of life, we used linear regression analysis". Two key assumptions of linear regression analysis are: Linearity and normality (normally distributed residuals). However, the points in the scatter plots in Figure 6 and Figure 7 do not seem to me falling along a straight line. Thus, the question is: is there a linear relationship for the linear regression to be an appropriate model for the analysis? If the model could not satisfy the assumption of linearity, the authors may consider using a non-parametric test which does not require these assumptions. Minor comments 1. In Table 1, I think "Age" should be "Mean Age" 2. By convention, table titles are placed on top of the table and not beneath it, unless specified by the journal 3. By convention, we don't begin a sentence with a figure. I see a lot of sentences in the paper beginning with figures e.g. 160 family members reported having…………………………., 80 participants did not have one, . 604 (42.6%) of the ME/CFS participants reported having another chronic health condition, etc. The authors may check and make the necessary corrections throughout he paper.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Diana Araja, Riga Stradins University
Comments to the Author:

The study demonstrates a significant ME/CFS population coverage, however the sample of the study is not completely homogeneous, and the question arises as to whether there were any plans to compare data from different regions.

RESPONSE
Because of the inherent biases in the method of recruitment to this study, we did not consider that comparing data from different regions would result in any meaningful data. It was not a study aim to compare different regions as the methodology required would have been different. However as you have raised this interesting question we have examined the mean FROM-16 scores from UK (mean17.79 SD=6.99, n=834), Europe (mean=18 SD=6.99, n=228), North America (mean=18.38 SD=6.92, n=230) and Rest of World (mean=17.96 SD=6.68, n=126). The mean EQ5D Index scores from the UK (mean=0.359 SD=0.218), Europe mean=0.351 SD= 0.205). North America (mean=0.341 SD= 0.201). Rest of World (Mean =0.389 SD=0.217). We have added the following text to the Results:

The inherent biases in the method of recruitment to this study make it difficult to draw any meaningful comparison between FROM-16 scores from different countries or regions of the world. However, when examined, the mean FROM-16 score from UK was 17.79 (SD=6.99, median=18 , n=834), Europe 18 (SD=6.99, median=18, n=228), North America 18.38 (SD=6.92, median=18.5, n=230) and Rest of World 17.96 (SD=6.68, median=18, n=126). The mean EQ5D value from the different regions were also similar with the UK mean of 0.359 (SD=0.218 ,median= 0.301), Europe mean 0.351 (SD= 0.205, median=0.267), North America mean 0.341 (SD= 0.201, median=0.264) and Rest of World mean EQ-5D value 0.389 (SD=0.217, median=0.264).

COMMENT
For the reflection of data, parameters such as Mean, Standard Deviation and Confidence Interval could contribute the reliability of the results.

RESPONSE
Thank you for this suggestion, we have checked that these parameters (Mean, Standard deviation, and where appropriate, p values) have been given at all appropriate points.

COMMENT
Reviewer: 2
Dr. Kenneth Friedman, New Jersey Medical School Department of Pharmacology and Physiology
Comments to the Author:
This is a well written, thoughtful paper on the social and society impact of ME/CFS as an example of a severely limiting chronic disease with little or no remedial treatment currently available. It is more timely to publish this manuscript in this time of COVID pandemic and hopefully soon post-pandemic, as the impact of Longhaul COVID is making its presence known. While the chronic illness of ME/CFS and Longhaul COVID are not identical, they are similar. Soon, the numbers of persons suffering ME/CFS-like illness will dramatically increase with the commensurate burden of social and societal impact increasing as well.

RESPONSE
Thank you for these positive and insightful comments, with which we fully agree.

COMMENT
Reviewer: 3
Dr. Marie Thomas, Bath Spa University
Comments to the Author:

This is a well written piece of work that has taken the views of the CFS/ME communities into consideration when designing and conducting the research. This topic is clearly of importance to patients and their families and as such is an important piece of research.

RESPONSE
We appreciate these kind comments.

COMMENT
Reviewer: 4
Mr. Emmanuel Kumah, Scuola Superiore Sant'Anna
Comments to the Author:
The paper is very interesting and has a lot of strengths, considering the large sample size drawn from over 30 countries. It addresses a very important issue, and thus publishable.

RESPONSE
Thank you for these encouraging comments.

COMMENT
My suggestions are provided below for further improvement.
1. In my view, the introduction is not sufficiently grounded in the literature. For example, does the study aim to fill a specific gap, and if so what is this gap? Or it is just to add to and extend what is already known on the topic? The introduction should tell readers what is already known on the topic, and what is not known that the study intends adding.

RESPONSE
Thank you for this suggestion. There is remarkably little information about this topic in the literature. We made changes in the Introduction to address these points:

Original:
"Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a chronic, complex, debilitating disease, with a negative impact on health-related quality of life (QoL) 1, worse than for many other diseases 2. There is growing international acknowledgement of the impact of ME/CFS on caregivers 3: a pilot study, using the Family Reported Outcome Measure (FROM-16), showed that QoL of partners and other family members is greatly impaired, suggesting that ME/CFS impact goes far beyond the affected person 4"

Revised
"Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a chronic, complex, debilitating disease, with existing literature demonstrating a negative impact on health-related quality of life (QoL) 1, worse than for many other diseases 2. There is growing international acknowledgement of the impact of ME/CFS on caregivers 3, but there is only a small scale pilot study using the Family Reported Outcome Measure (FROM-16) which showed that QoL of partners and other family members is greatly impaired, suggesting that ME/CFS impact goes far beyond the affected person 4. There is therefore very little information about the partner/family impact, a gap in ME/CFS knowledge which this study aims to address".

In addition we have made changes to the last paragraph in the introduction

Original:

"This study's aim was to measure the impact of ME/CFS on the QoL of those affected and their partners or family members."

Revised:
"This study's aim was to measure the impact of ME/CFS on the QoL of those affected and expand knowledge by conducting a large-scale international study on the impact on QoL of their partners or family members. In addition we aimed to determine correlation of QoL data between the persons with ME/CFS and their family members."

COMMENT
2. According to the authors "Microsoft Excel, SPSS and GraphPad Prism v9 were used for data handling and statistical analysis, involving descriptive statistics and parametric statistical tests including Item-total correlations, inter-item correlations and Spearman rank correlation coefficient". I have three key issues: a) there are no displayed outputs for the Item-total correlations, and inter-item correlations in the paper;

RESPONSE
Thank you for your comment, which we agree with. We did not carry out these tests and have therefore removed reference to them.

COMMENT
b) Spearman rank correlation is a non-parametric test used to measure the degree of association between two variables (i.e. the strength and direction of the association), and thus not a parametric statistical test as stated;

RESPONSE
We appreciate this comment and have added the word 'non' in front of parametric.

COMMENT
and c) In place of Spearman rank correlation coefficients at the results section, I see linear regression analysis.

RESPONSE
Please see below for response to this comment.

COMMENT
3. The authors state "In order to determine the relationship between the person with ME/CFS and their family members quality of life, we used linear regression analysis". Two key assumptions of linear regression analysis are: Linearity and normality (normally distributed residuals). However, the points in the scatter plots in Figure 6 and Figure 7 do not seem to me falling along a straight line. Thus, the question is: is there a linear relationship for the linear regression to be an appropriate model for the analysis? If the model could not satisfy the assumption of linearity, the authors may consider using a non-parametric test which does not require these assumptions.

RESPONSE
Thank you for this comment. We agree as the data is not normal, Spearmans Rank is the most appropriate test to use to look for the degree of correlation between FROM-16 scores and the VAS. We found the 2 data sets to have a moderate but significant negative correlation of -0.411 (R value), in that the higher the FROM-16 score, the lower the VAS/EQ5D. The residual plots have been removed and Spearmans Rank data has been presented in Figure 6.

The wording has been changed:

Original:
"In order to determine the relationship between the person with ME/CFS and their family members quality of life, we used linear regression analysis. We found a significant negative correlation between the total FROM-16 score of family members and the patients VAS score (P<0.0001, R=-0.3467, R2=0.1146) (Figure 6). Furthermore, a similar negative correlation was calculated using the total FROM-16 score and the EQ-5D value of patients (P<0.0001, R=-0.411, R2=0.1668) (Figure 7), supporting the fact that family member quality of life is significantly impacted by a ME/CFS. "

Revised:
"In order to determine the relationship between the person with ME/CFS and their family member's quality of life, we used Spearmans Rank Correlation as the data was not normally distributed. We found a significant negative correlation between the total FROM-16 score of family members and the patients VAS score (P<0.0001, R=-0.3467) (Figure 6). Furthermore, a similar moderate but significant negative correlation was calculated using the total FROM-16 score and the EQ-5D value of patients (P<0.0001, R=-0.411) (Figure 6), supporting the fact that family member quality of life is significantly impacted by a family member's ME/CFS. "

COMMENT
Minor comments
1. In Table 1, I think "Age" should be "Mean Age"

RESPONSE
Thank you for spotting this, we have added the word "mean". In table 1

COMMENT
2. By convention, table titles are placed on top of the table and not beneath it, unless specified by the journal

RESPONSE
Thank you for your comment, this has been amended.

COMMENT
3. By convention, we don't begin a sentence with a figure. I see a lot of sentences in the paper beginning with figures e.g. 160 family members reported having………………………….., 80 participants did not have one, . 604 (42.6%) of the ME/CFS participants reported having another chronic health condition, etc. The authors may check and make the necessary corrections throughout he paper. [NOTE FROM THE EDITORS: Please feel free to rebut this final comment - it is fine to start sentences with numbers]

RESPONSE
We agree that this convention has in the past been generally accepted. However, the restructuring of sentences necessary to comply with this convention can sometimes result in an increase in word count and no greater clarity for the reader. We would be grateful if you would allow our sentences to remain unaltered.

VERSION 2 – REVIEW

REVIEWER	Kumah, Emmanuel

	University of Education Winneba Faculty of Science Education, Healthcare Management
REVIEW RETURNED	21-Mar-2022

GENERAL COMMENTS	Thank you for sending me a revised version of this paper to review. The paper is a great improvement over the previous version. All the issues I raised have been addressed. However, I am not satisfied with the explanation offered for beginning a sentence with numerals. This is not used in scientific and academic writing. I therefor insist that the necessary revision is done, However, if BMJ Open will allow it, then I have no problem, But in my entire experience, I am yet to read a scientific or academic paper that has sentences starting with numerals. Each area has its own conventions and style of writing which must be followed.