PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Is the Association between Health -Related Quality of Life and Fatigue Mediated by Depression in Patients with Multiple Sclerosis? A Spanish Cross Sectional Study
AUTHORS	Fernández-Muñoz, Juan J; Cigarán-Méndez, Margarita; Navarro-Pardo, Esperanza; Perez-de-Heredia, Marta; Paras-Bravo, Paula; Fernández-de-las-Peñas, César

VERSION 1 – REVIEW

REVIEWER	Tatjana Pekmezovic Faculty of Medicine, University of Belgrade, Serbia
REVIEW RETURNED	22-Feb-2017

GENERAL COMMENTS	In this study authors aimed to investigate direct and indirect effects of depression and health-related quality of life on fatigue in patients with multiple sclerosis. Results of the study showed that depression indirectly mediated the association between some health-related quality of life domains, such as bodily pain and mental health, with fatigue, suggesting that depression contributes to worse perception of fatigue via these factors. Major points: • Title should be changed because, in given form, it does not reflect core of the hypothesis tested. • There are several serious methodological weaknesses: o Time frame of the study: Authors did not mention period in which the study was conducted. o Sample size: How did the authors calculate the sample size? o Selection of participants: Authors did not note inclusion criteria. Hospitalized patients are not appropriate for investigation of HRQoL because of strong influence of hospitalization and potential presence of depression (depression is well established confounding factor in HRQoL studies). This fact compromised obtained results! o Regarding BDI, authors stated that ‘’The score ranges from 0 to 21 points where higher score suggests higher level of depressive symptoms’’, which is wrong because BDI comprises 21 statements (range 0-3). o Authors used the SF-36 questionnaire, however they did not mention which version (Spanish, English, others) was used, whether validation process was performed. o Demographic and clinical data are not outcome measures. • The manuscript should be edited by native English speaker. Also, there are many typing errors that have to be corrected. For example, affiliation should be in English.

REVIEWER	Judit Füvesi MD, PhD Department of Neurology University of Szeged Hungary
REVIEW RETURNED	07-Mar-2017

GENERAL COMMENTS	The manuscript entitled “Direct and indirect effects of depression and health-related quality of life on fatigue in patients with multiple sclerosis” deals with the increasingly important question of patient reported outcome measures and their correlations. Assessing the effect of chronic neurological disorders such as multiple sclerosis on health-related quality of life and exploring the relationship between common symptoms and comorbidities like fatigue and depression is of high priority in order to improve the well-being of our patients. The manuscript is generally very well written and logical. However, there are some spelling and language mistakes that should be corrected. I believe the study could be strengthened by addressing the following points: Introduction: What is the prevalence of multiple sclerosis in Spain? Methods: The modified McDonald criteria are cited in the first sentence, but the reference does not point to the paper describing it. Were the instruments used for the study (the Fatigue Impact Scale and the SF-36) previously validated in Spanish? If yes, these references should be cited. Results: As described in the methods section, the FIS includes 3 subscales assessing cognitive, physical and social fatigue. It would be interesting to know these subscale scores and include them in Table 1. Were the correlation between the subscales of SF-36 and the subscales of FIS examined? If yes, was there any difference in the effect of the assessed variables on the different aspects of fatigue (social, physical, cognitive)? How many of the patients involved in the study were considered to be depressed based on the BDI? Why the authors chose the SF-36 for quality of life assessment? There are more disease-specific instruments like the MSQoL-54 developed from the SF-36. As far as I know, MSQoL-54 is available in Spanish. Discussion There are more recent references on fatigue, depression and quality of life in MS, among others: 1. Fatigue and depression predict quality of life in patients with early multiple sclerosis: a longitudinal study. Nourbakhsh B, Julian L, Waubant E. Eur J Neurol. 2016 Sep;23(9):1482-6. doi: 10.1111/ene.13102. 2. The effects of fatigue, depression and the level of disability on the health-related quality of life of glatiramer acetate-treated relapsing-remitting patients with multiple sclerosis in Hungary. Fricska-Nagy Z, Füvesi J, Rózsa C, Komoly S, Jakab G, Csépány T, Jobbágy Z, Lencsés G, Vécsei L, Bencsik K. Mult Scler Relat Disord. 2016 May;7:26-32. doi: 10.1016/j.msard.2016.02.006. 3. Associations Between Fatigue and Disability, Functional Mobility, Depression, and Quality of Life in People with Multiple Sclerosis. Garg H, Bush S, Gappmaier E. Int J MS Care. 2016 Mar-Apr;18(2):71-7. doi: 10.7224/1537-

	2073.2015-013. 4. Fatigue, depression, and health-related quality of life in patients with multiple sclerosis in Isfahan, Iran. Kargarfard M, Eetemadifar M, Mehrabi M, Maghzi AH, Hayatbakhsh MR. Eur J Neurol. 2012 Mar;19(3):431-7. doi: 10.1111/j.1468-1331.2011.03535.x. Overall I think this is an important analysis that will be of interest to readers.

REVIEWER	Alessio Signori Italy-University of Genoa
REVIEW RETURNED	01-Jun-2017

GENERAL COMMENTS	Authors performed the correct statistical analysis to address their objectives. Results are clinically meaningful and are well summarised in the Conclusions.

REVIEWER	Gemma Hammerton University of Bristol, UK
REVIEW RETURNED	05-Aug-2017

GENERAL COMMENTS	This interesting paper examines whether the association between health-related quality of life and fatigue is mediated by depression in a cross-sectional sample of patients with multiple sclerosis (MS). My suggestions for improvement are mainly methodological and are meant constructively, outlined below by section. Abstract: It is not clear from the objectives which construct is the exposure and which is the mediator, this could be re-worded, for example: 'to determine the direct and indirect effects of health-related quality of life, via depression, on fatigue in multiple sclerosis.' This is also the case for the title of the manuscript, the study aims in the introduction, and in parts of the discussion. Additionally, the wording of the results suggests that higher levels of fatigue are associated with lower levels of bodily pain, and lower levels of mental health. From reading the rest of the manuscript, I realise that this is not the case and is due to the naming of the sub-scales in the quality of health questionnaire; however, this should be clarified in the abstract. Introduction: A thorough review of the literature has been provided in the introduction; however, the authors could provide a stronger rationale for why they hypothesise depression to lead to fatigue rather than fatigue leading to depression in MS (this is especially important given the cross-sectional design). Methods: I have concerns over the mental health sub-scale of the SF-36 being used as an exposure in the path model. What is the overlap between questions in this sub-scale and the BDI-II? Items used from SF-36 could be provided in supplementary material.

	Finally, what is the rationale for specifically examining effects of physical function, bodily pain and mental health as exposures over the other sub-scales? Statistical analysis: The description of the path model is confusing in places; for example, it is not clear what is meant by quality of life domains being 'independent outcomes', or by the phrase 'arrows connect the error terms with their respective intermediary variables'. The authors state that the chi-square statistic is largely independent of sample size – this is not the case. However, a wide range of fit statistics are reported, some of which are largely independent of sample size. It is not clear whether missing data were treated using full information maximum likelihood estimation (which doesn't involve imputation), or via an imputation method. Standard errors or confidence intervals should be reported for effect estimates in addition to p-values. For indirect effects, these should be derived using bootstrapping given that the product of coefficients is unlikely to be normally distributed. This is especially important with a small sample size. Results: It would be helpful to see the results from the path analysis in a table (i.e. showing direct, indirect and total effects for each exposure (bodily pain, mental health, and physical function) on fatigue) to give a better idea of how important depression is as a mediator for each aspect of quality of life examined. Discussion: Again, the wording used in the discussion sometimes indicates that depression is the exposure with its effects being mediated by the quality of life constructs, for example p10, lines 34, 43, 50 and p12 line 25. The discussion also indicates in places, that it is fatigue that likely leads to increased depression, for example p11, lines 4, 39. Given the inconsistency in the literature, and the cross-sectional design, the discussion should not overstate the implications of the findings. Additional comments related to STROBE checklist: Item 1 – the design of the study has not been included in the title (i.e. cross-sectional design) Item 9, 16, 19 – all sources of bias have not been considered; for example, potential confounders of the paths in the mediation model (i.e. exposure to mediator, exposure to outcome, and mediator to outcome). This should be addressed, and if there are no potential confounders, or none have been assessed this should be stated.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 - Tatjana Pekmezovic

In this study authors aimed to investigate direct and indirect effects of depression and health-related quality of life on fatigue in patients with multiple sclerosis. Results of the study showed that depression indirectly mediated the association between some health-related quality of life domains, such as bodily pain and mental health, with fatigue, suggesting that depression contributes to worse perception of fatigue via these factors.

Major points:

Comment 1: Title should be changed because, in given form, it does not reflect core of the hypothesis tested.

Response: We have edited the title as requested. The new proposed title is as follows:

The Association between Health-Related Quality of Life and Fatigue is Indirectly Mediated by Depression in Patients with Multiple Sclerosis: A Cross Sectional Study

Comment 2: There are several serious methodological weaknesses:

- Time frame of the study: Authors did not mention period in which the study was conducted.

Response: We have included the period of the study on page 6 as follows:

“Patients diagnosed with definite MS according to the modified McDonald criteria21 by experienced neurologists, recruited from a local regional hospital in Madrid (Spain) between September 2013 and December 2014, were screened for eligibility criteria.”

- Sample size: How did the authors calculate the sample size?

Response: We included the highest number of participants that we could recruit during the study period. Since this is a cohort study searching for potential associations, which have not been previously assessed in the literature, there is no specific data for applying a specific sample size calculation. We could not develop a probabilistic sampling for the study and finally we did an incidental sampling in order to get a higher sample. In this sense, we calculate with a 95% of confidence level with several errors for obtaining a proper sample size. Thus, we assumed a finite population and according to this criterion we calculated possible numbers of participants (size of sample) for this research. During the fieldwork we tried to get that number for the study. When we finished the time for the fieldwork we just got 108 participants. We have included this topic in the limitation section on page 13 as follows:

“Further, we used a non-probabilistic sampling for a finite population for calculating our sample size. This was conducted applying a 95% confidence level and a sampling error for the final set of participants under 5%. Although we could not estimate a priori sample size, we believe that our sample is representative of the population”

- Selection of participants: Authors did not note inclusion criteria. Hospitalized patients are not appropriate for investigation of HRQoL because of strong influence of hospitalization and potential presence of depression (depression is well established confounding factor in HRQoL studies). This fact compromised obtained results!

Response: All of our patients were diagnosed according to the McDonald criteria as it is stated in the methods on page 6. We did not expand the criteria since this is the common way reported in all studies of MS, so we believe that this info is enough.

We have clarified we did not include hospitalized patients. This is an important topic as the reviewer has pointed out. Patients were recruited during routine medical visit and this is specified in the methods section on page 6 as follows:

“Patients were recruited during their routine neurological visits and were screened and explored during a stationary phase of the disease.”

- Regarding BDI, authors stated that ‘’The score ranges from 0 to 21 points where higher score suggests higher level of depressive symptoms’’, which is wrong because BDI comprises 21 statements (range 0-3).

Response: We would like to thank to the reviewer for advising us of this typo. We have edited it in the text and tables, thanks

- Authors used the SF-36 questionnaire, however they did not mention which version (Spanish, English, others) was used, whether validation process was performed.

Response: We have clarified that we used the validated Spanish version of the SF-36 on page 7 as follows:

“In the current study, the validated Spanish version of the SF-36 questionnaire was used.33”

33. Alonso J, Prieto L, Antó JM. [The Spanish version of the SF-36 Health Survey (the SF-36 health questionnaire): an instrument for measuring clinical results]. Med Clin (Barc) 1995; 104: 771-6.

- Demographic and clinical data are not outcome measures.

Response: We do not understand this comment from the reviewer since clinical and demographic data are referred as clinical and demographic data and not as outcomes.

- The manuscript should be edited by native English speaker. Also, there are many typing errors that have to be corrected. For example, affiliation should be in English.

Response: A native English speaker has carefully edited all the text. We would like to comment to the reviewer that Spanish affiliations cannot be translated to English, since they are proper names.

Reviewer 2 - Judit Füvesi MD, PhD

General comment: The manuscript entitled “Direct and indirect effects of depression and health-related quality of life on fatigue in patients with multiple sclerosis” deals with the increasingly important question of patient reported outcome measures and their correlations. Assessing the effect of chronic neurological disorders such as multiple sclerosis on health-related quality of life and exploring the relationship between common symptoms and comorbidities like fatigue and depression is of high priority in order to improve the well-being of our patients. The manuscript is generally very well written and logical.

Response: We would like to thank to the reviewer for this positive comment

Comment 1: However, there are some spelling and language mistakes that should be corrected.

Response: A native English speaker has carefully edited all the text.

I believe addressing the following points could strengthen the study:

Comment 2: Introduction: What is the prevalence of multiple sclerosis in Spain?

Response: We had included prevalence data from Spain as requested in the introduction section as follows:

“In Spain, the prevalence of MS has been found to be 125 cases/100,000 habitants;2 however, some recent studies have observed an increase prevalence in the last decade.3,4

2. Fernández O, Fernández V, Guerrero M et al E. Multiple sclerosis prevalence in Malaga, southern Spain estimated by the capture-recapture method. Mult Scler 2012; 18: 372-6
3. Otero-Romero S, Roura P, Solà J et al. Increase in the prevalence of multiple sclerosis over a 17-year period in Osona, Catalonia, Spain. Mult Scler 2013; 19: 245-8.
4. Candeliere-Merlicco A, Valero-Delgado F, Martínez-Vidal S et al. Prevalence of multiple sclerosis in Health District III, Murcia, Spain. Mult Scler Relat Disord 2016; 9: 31-5

Comment 3: Methods:

The modified McDonald criteria are cited in the first sentence, but the reference does not point to the paper describing it.

Response: We have included the original reference about McDonald diagnostic criteria as requested on page 6 in the methods section:

“Patients diagnosed with definite MS according to the modified McDonald criteria21 by experienced neurologists, recruited from a local regional hospital in Madrid (Spain) between September 2013 and December 2014, were screened for eligibility criteria.

21.Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol 2011; 69: 292-302

Were the instruments used for the study (the Fatigue Impact Scale and the SF-36) previously validated in Spanish? If yes, these references should be cited.

Response: Yes, we have clarified that we used the validated Spanish version of the FIS and SF-36 questionnaires on pages 6 and 7, respectively, as follows:

“In this study, the validated Spanish version of the FIS was used.26”

26. Benito-León J, Martínez-Martín P, Frades B, et al (2007). Impact of fatigue in multiple sclerosis: The fatigue impact scale for daily use (D-FIS). Mult Scler 2007; 13: 645–651

“In the current study, the validated Spanish version of the SF-36 questionnaire was used.33”

33. Alonso J, Prieto L, Antó JM. [The Spanish version of the SF-36 Health Survey (the SF-36 health questionnaire): an instrument for measuring clinical results]. Med Clin (Barc) 1995; 104: 771-6.

Comment 4: Results:

As described in the methods section, the FIS includes 3 subscales assessing cognitive, physical and social fatigue. It would be interesting to know these subscale scores and include them in Table 1.

Response: We did not consider each subscale of the FIS; we only considered the total score. We have included this on page 7 as follows:

“We considered as main outcome the total FIS score.”

Were the correlation between the subscales of SF-36 and the subscales of FIS examined? If yes, was there any difference in the effect of the assessed variables on the different aspects of fatigue (social, physical, cognitive)?

Response: As we have previously stated, we only considered the total score of the FIS questionnaire.

How many of the patients involved in the study were considered to be depressed based on the BDI?

Response: Based on our scores on the BDI-II, the depressive levels were low in our sample. In fact, we could not considered the presence of depression in any patient. The topic of the low levels of depression is discussed on pages 10-11. We have included a comment on this topic in the limitation section on page 13 as follows:

“Third, the level of depressive symptoms in our sample of patients with MS was lower than expected. In fact, scores showed that almost all participants exhibited small depressive levels. It is possible that the presence of higher symptoms of depression can lead to further associations or effects. “

Why the authors chose the SF-36 for quality of life assessment? There are more disease-specific instruments like the MSQoL-54 developed from the SF-36. As far as I know, MSQoL-54 is available in Spanish.

Response: We preferred to use a general health-related quality of life outcome instead of a specific one because probably a more specific questionnaire would lead to more restrictive associations. We have included this topic in the limitation section on page 13 as follows:

“Fourth, we should consider that health-related quality of life was assessed with a general, but not disease-specific, questionnaire. It is possible that the use of a MS-specific quality of life questionnaire, i.e., MSQoL-54, would lead to other potential associations”

Comment 5: Discussion

There are more recent references on fatigue, depression and quality of life in MS, among others:

Nourbakhsh B, Julian L, Waubant E. Fatigue and depression predict quality of life in patients with early multiple sclerosis: a longitudinal study. Eur J Neurol. 2016 Sep;23(9):1482-6.

Fricska-Nagy Z, Füvesi J, Rózsa C, Komoly S, Jakab G, Csépány T, Jobbágy Z, Lencsés G, Vécsei L, Bencsik K. The effects of fatigue, depression and the level of disability on the health-related quality of life of glatiramer acetate-treated relapsing-remitting patients with multiple sclerosis in Hungary. Mult Scler Relat Disord. 2016 May;7:26-32.

Kargarfard M, Eetemadifar M, Mehrabi M, Maghzi AH, Hayatbakhsh MR. Fatigue, depression, and health-related quality of life in patients with multiple sclerosis in Isfahan, Iran. Eur J Neurol. 2012 Mar;19(3):431-7.

Response: We have included these 3 references in the introduction or discussion section where appropriate (references number 9, 10, and 14).

Overall I think this is an important analysis that will be of interest to readers.

Response: We would like to thank to the reviewer for this positive comment

Reviewer 3 - Alessio Signori

Authors performed the correct statistical analysis to address their objectives. Results are clinically meaningful and are well summarized in the Conclusions.

Response: We would like to thank to the reviewer for this positive comment

Reviewer 4 - Gemma Hammerton

General comment: This interesting paper examines whether the association between health-related quality of life and fatigue is mediated by depression in a cross-sectional sample of patients with multiple sclerosis (MS). My suggestions for improvement are mainly methodological and are meant constructively, outlined below by section.

Response: We would like to thank to the reviewer for this positive comment

Comment 1: Abstract:

- It is not clear from the objectives which construct is the exposure and which is the mediator, this could be re-worded, for example: ‘to determine the direct and indirect effects of health-related quality of life, via depression, on fatigue in multiple sclerosis.’

Response: The mediator factor is depression so we believe that the current text reflects the objective. The proposed objective of the reviewer is a different construct, that the mediated factor is quality of life.

- This is also the case for the title of the manuscript, the study aims in the introduction, and in parts of the discussion.

Response: The title has been edited as previous comments (see new proposed title). We have also edited the introduction and all the text for clarifying this topic, since we have observed that confusion can be related to some typos. For instance, the current objective is as follows (page 5):

“Therefore, the aim of the current study was to further determine the direct and indirect effects of depression on the association between health-related quality of life and fatigue in individuals with MS. Since depression is the psychological disorder most commonly experience by subjects with MS;11,12 we hypothesized that the relationships between health-related qualify of life domains and related-fatigue would be mediated by depressive symptoms.”

- Additionally, the wording of the results suggests that higher levels of fatigue are associated with lower levels of bodily pain, and lower levels of mental health. From reading the rest of the manuscript, I realise that this is not the case and is due to the naming of the sub-scales in the quality of health questionnaire; however, this should be clarified in the abstract.

Response: The reviewer is quite right, since the SF36 domains are positive. We have avoided in the abstract the words negative or positive in relation to the associations for avoiding this confusion.

Comment 2: Introduction: A thorough review of the literature has been provided in the introduction; however, the authors could provide a stronger rationale for why they hypothesized depression to lead to fatigue rather than fatigue leading to depression in MS (this is especially important given the cross-sectional design).

Response: We have included a sentence in the hypothesis as follows (page 5):

“ Since depression is the psychological disorder most commonly experience by subjects with MS;11,12 we hypothesized that the relationships between health-related qualify of life domains and related-fatigue would be mediated by depressive symptoms.”

Comment 3: Methods:

- I have concerns over the mental health sub-scale of the SF-36 being used as an exposure in the path model. What is the overlap between questions in this sub-scale and the BDI-II? Items used from SF-36 could be provided in supplementary material.

Response: Since the SF36 questionnaire is a worldwide outcome used for assessing the quality of life, we do not believe that it should be included as supplementary material. The items used for the mental health domain covers different aspects than those used in the BDI-II.

- Finally, what is the rationale for specifically examining effects of physical function, bodily pain and mental health as exposures over the other sub-scales?

Response: As it is stated in the statistical analysis, only those domains showing a direct correlation with fatigue can be included in the path model. Therefore, we have only included in the analysis and in the results those domains and not the remaining. We had now clarified this in the statistical analysis section on page 8 as follows:

“Secondly, a path model with maximum likelihood estimation was conducted to evaluate the direct and indirect effects of depression between the variables significantly associated with fatigue using AMOS computer program.34”

Comment 4: Statistical analysis:

- The description of the path model is confusing in places; for example, it is not clear what is meant by quality of life domains being ‘independent outcomes’, or by the phrase ‘arrows connect the error terms with their respective intermediary variables’.

Response: We have changed the meaning of the arrows in the model and explaining with other words the conceptual characteristics of the path models and we have omitted several sentences of the manuscripts in order to show clearer the characteristics of the path diagram. We believe that the information about the path is explained according to the current literature on the topic and that it is properly expressed in the current version of the manuscript.

- The authors state that the chi-square statistic is largely independent of sample size – this is not the case. However, a wide range of fit statistics are reported, some of which are largely independent of sample size.

Response: We agree with the reviewer according to the Chi-square statistic, although we thought that it would be better add more information for the readers. Moreover, we have included some fit statistics and we will be able to add more fit statistics. Anyway, Chi-square statistic has been removed as suggested and we have now included other fit indexes, e.g., some of the set of incremental index (TLI, NFI and so on). Therefore, we have removed from the text previous information related to the chi square statistic.

- It is not clear whether missing data were treated using full information maximum likelihood estimation (which doesn’t involve imputation), or via an imputation method.

Response: For this study we used maximum likelihood estimation because it does not involve imputation; anyway we did statistics proofs with others estimation methods, for instance generalized least square, in order to check if the fit index were similar and we get the same results. Finally, we decided to use the data from the final sample of 108. We have clarified this on pages 8-9 as follows: “Missing data were removed to the first recollected sample of participants and just the sample was composed by the final subjects who satisfied all inclusion criteria (n=108).”

- Standard errors or confidence intervals should be reported for effect estimates in addition to p-values. For indirect effects, these should be derived using bootstrapping given that the product of coefficients is unlikely to be normally distributed. This is especially important with a small sample size.

Response: We agree with the referee; therefore, we have included confidence intervals for the effect estimates (in all cases 95%) in addition to p values. Anyway, we think that for this study with p-values and also with the confidence intervals would be enough statistics information to check the fit of the conceptual path model. In our opinion, the bootstrapping could be a great option for the indirect effects; but not necessary in this study. The standard errors were between.035 and .070.

Comment 5: Results: It would be helpful to see the results from the path analysis in a table (i.e. showing direct, indirect and total effects for each exposure (bodily pain, mental health, and physical function) on fatigue) to give a better idea of how important depression is as a mediator for each aspect of quality of life examined.

Response: We believe that a table could be slightly confusing for the readers since the relationships explained in a path model are direct and indirect. We believe that the text and the data included in the legend of figures explain appropriately the associations.

Comment 6: Discussion:

Again, the wording used in the discussion sometimes indicates that depression is the exposure with its effects being mediated by the quality of life constructs, for example p10, lines 34, 43, 50 and p12 line 25. The discussion also indicates in places, that it is fatigue that likely leads to increased depression, for example p11, lines 4, 39. Given the inconsistency in the literature, and the cross-sectional design, the discussion should not overstate the implications of the findings.

Response: We have carefully revised the discussion and editing places that the reviewer suggested us for avoiding any confusion. We have also revised some expressions for avoiding any overestimation of the comments.
Comment 7: Additional comments related to STROBE checklist:

Item 1 – the design of the study has not been included in the title (i.e. cross-sectional design)

Response: The new proposed title includes the study design (see previous comments)

Item 9, 16, 19 – all sources of bias have not been considered; for example, potential confounders of the paths in the mediation model (i.e. exposure to mediator, exposure to outcome, and mediator to outcome). This should be addressed, and if there are no potential confounders, or none have been assessed this should be stated

Response: No potential cofounders were assessed since all are self-reported outcomes.

We hope that the current version satisfies all comments from the reviewers and can be accepted for publication in BMJ Open

Sincerely yours - The authors

VERSION 2 – REVIEW

REVIEWER	Tatjana Pekmezovic Faculty of Medicine, University of Belgrade, Serbia
REVIEW RETURNED	28-Aug-2017

GENERAL COMMENTS	Despite some improvements, the manuscript is still suffering from serious methodological shortcomings.

REVIEWER	Judit Füvesi MD, PhD Department of Neurology University of Szeged Szeged Hungary
REVIEW RETURNED	13-Sep-2017

GENERAL COMMENTS	I accept the authors' responses to my questions and the corrections to the text. Now I recommend the manuscript for publication.

REVIEWER	Gemma Hammerton University of Bristol, UK
REVIEW RETURNED	06-Sep-2017

GENERAL COMMENTS	This is the second review of a manuscript examining whether the association between health-related quality of life and fatigue is mediated by depression in a cross-sectional sample of patients with multiple sclerosis. The paper is improved following response to reviewers, however, I still have some outstanding concerns regarding the analyses and some additional minor comments. 1. The wording throughout the manuscript regarding the exposure and mediator is still confusing. It is the exposure that exerts a direct effect or indirect effect via the mediator on the outcome. The mediator cannot exert an indirect effect on the outcome (unless it is through a second mediator). 2. The authors have provided a rational for why they focus on depression (as opposed to another psychological disorder) but not why they specifically hypothesise that depression leads to fatigue, rather than fatigue leading to depression. With a cross-sectional design, a clear rationale for the ordering of exposure, mediator and outcome is especially important. 3. The authors state that 95% confidence intervals are now included for the effect estimates, but I cannot see these in the text. Standard errors, or confidence intervals, should be provided for all effect estimates. The statement: 'all standard errors were between .035 and .070 with a confidence level of 95%' doesn't make sense. 4. The authors note that confounders were not assessed because outcomes were self-reported. A confounder is a variable that is associated with the exposure and a risk-factor for the outcome (but not on causal pathway between exposure and outcome), which may explain the observed association between exposure and outcome. In a mediation model potential confounders may exist for the association between exposure and mediator, between mediator and outcome, or between exposure and mediator. Therefore, even with self-reported outcomes, potential confounders still need to be considered. Minor comments: 5. The statistical analysis section still states that 'missing data were treated with maximum likelihood imputation'. This should be removed. 6. In the abstract under 'outcome measures', only the outcomes in the analyses should be listed (specifically, fatigue and depression). 7. In the strengths and limitations section it is not clear what is meant by 'restrictive indexes' 8. The manuscript still contains typos that need to be corrected.

VERSION 2 – AUTHOR RESPONSE

Reviewer 1 - Tatjana Pekmezovic

Despite some improvements, the manuscript is still suffering from serious methodological shortcomings.

Response: We do not understand this comment from the reviewer since we answered all questions proposed in the first revision.

Reviewer 2 - Judit Füvesi MD, PhD

I accept the authors' responses to my questions and the corrections to the text. Now I recommend the manuscript for publication.

Response: We would like to thank to the reviewer for her positive comments

Reviewer 4 - Gemma Hammerton

This is the second review of a manuscript examining whether the association between health-related quality of life and fatigue is mediated by depression in a cross-sectional sample of patients with multiple sclerosis. The paper is improved following response to reviewers; however, I still have some outstanding concerns regarding the analyses and some additional minor comments.

Comment 1: The wording throughout the manuscript regarding the exposure and mediator is still confusing. It is the exposure that exerts a direct effect or indirect effect via the mediator on the outcome. The mediator cannot exert an indirect effect on the outcome (unless it is through a second mediator).

Response: We agree with the reviewer that some wording can be confusing. We have deleted the words indirect mediator effect since it is confusing and refer only to mediator effect of depression as the reviewer suggests us.

Comment 2: The authors have provided rational for why they focus on depression (as opposed to another psychological disorder) but not why they specifically hypothesize that depression leads to fatigue, rather than fatigue leading to depression. With a cross-sectional design, a clear rationale for the ordering of exposure, mediator and outcome is especially important.

Response: We decided to include depression as mediator leading to fatigue instead the opposite since fatigue is a disease-related symptom provoked by the own condition (in this case multiple sclerosis). Therefore, we wanted to determine if depression (which is not an intrinsic symptom of the disease) can mediate the associations between of quality of life and a specific symptom of MS. We have briefly included the following sentence at the end of the introduction as follows:

“Since depression is the psychological disorder, not intrinsically provoked by the disease, most commonly experienced by individuals with MS;11,12 we hypothesized that the relationships between health-related qualify of life and the MS associated-fatigue would be mediated by depressive symptoms.”

Comment 3: The authors state that 95% confidence intervals are now included for the effect estimates, but I cannot see these in the text. Standard errors, or confidence intervals, should be provided for all effect estimates. The statement: ‘all standard errors were between .035 and .070 with a confidence level of 95%’ doesn’t make sense.

Response: We have removed the general sentence about standard errors and we have now included the standard error for all effect estimates as the reviewers requested. We agree with the reviewer that with this information and with the fit of the model, the results can be better understood.

“According to the direct effects, a significant path was noted from mental health (B=-.53, P<0.01) to depression with a Standard Error (SE) of.035. Likewise, significant paths were also indicated between physical function (B=-.23, P<0.01, SE=.054) bodily pain (B=-.36, P<0.01, SE=.070) and depression (B= .29, P<0.01, SE=.025) on fatigue. The direct effect from bodily pain on depression did not reach the significance (B=-.15, P=0.07, SE=.024). Furthermore, significant indirect effects in the path analysis model from bodily pain to fatigue mediated by depression (B=-.04, P<0.01, SE=.031) and from mental health to fatigue, also mediated by depression (B=-.16 P<0.01, SE=.015) were observed. Overall, the amount of fatigue explained by all predictors in the model was R2 0.37.”

Comment 4: The authors note that confounders were not assessed because outcomes were self-reported. A confounder is a variable that is associated with the exposure and a risk-factor for the outcome (but not on causal pathway between exposure and outcome), which may explain the observed association between exposure and outcome. In a mediation model potential confounders may exist for the association between exposure and mediator, between mediator and outcome, or between exposure and mediator. Therefore, even with self-reported outcomes, potential confounders still need to be considered.

Response: We are confused to which is referring the reviewer with the term confounder. If the reviewer is asking about other variables that could affect fatigue, such as sleep or anxiety, the limitation section clearly describes that these variables were not assessed. If the reviewer asked us for other variables affecting the exposure such as the other quality of life domains, we would like to comment to the reviewer that all these variables were obviously included in the analysis, but no significant association with the final outcome was observed, so they were consider in the analysis but not showed in the text since no influence on the analysis was found. We hope that this explanation answers the comment from the reviewer.

Minor comments:

Comment 5: The statistical analysis section still states that ‘missing data were treated with maximum likelihood imputation’. This should be removed.

Response: This sentence has been removed

Comment 6: In the abstract under ‘outcome measures’, only the outcomes in the analyses should be listed (specifically, fatigue and depression).

Response: We have removed statistical analysis as requested leaving only the outcomes included in the analysis.

Comment 7: In the strengths and limitations section it is not clear what is meant by ‘restrictive indexes’

Response: The words restrictive indexes had been removed since they are not necessary

Comment 8: The manuscript still contains typos that need to be corrected.

Response: The paper has been again carefully reviewed by an English naïve speaker

We hope that the current version satisfies all comments from the reviewers and can be accepted for publication in BMJ Open

Sincerely yours - The authors

VERSION 3 – REVIEW

REVIEWER	Gemma Hammerton University of Bristol
REVIEW RETURNED	31-Oct-2017

GENERAL COMMENTS	My comments have been addressed by the authors and I believe the paper is improved following revisions. The cross-sectional design is a limitation given the research question, however the implications of this have been acknowledged in the discussion. A few typos still remain and some sentences which are slightly confusing for the reader, therefore the paper will need to be proofread carefully before publication.