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Direct and Indirect Effects of Depression and Health-Related Quality of Life on Fatigue in Patients with Multiple Sclerosis

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Keywords: multiple sclerosis, depression, fatigue, quality of life.

Abstract

Objectives: To determine the direct and indirect effects of depression and health-related quality of life on fatigue in multiple sclerosis (MS). **Design:** A cross-sectional study. **Setting:** Tertiary urban hospital. **Participants:** One hundred and eight patients (54% women) with definite MS participated. **Outcome measures**: Demographic and clinical data (weight, height, medication, and neurological impairment), fatigue (Fatigue Impact Scale - FIS), depression (Beck Depression Inventory - BDI/II) and health-related quality of life (Short-Form Health Survey 36-SF36) were assessed. Correlation and path model analysis with maximum likelihood estimations were conducted to assess the direct and indirect effects of depression on health-related quality of life and MS-related fatigue. **Results**: Fatigue was negative associated with bodily pain, physical function and mental health, and positive associated with depression. Depression was negatively associated with bodily pain and mental health. The path analysis found direct effect from physical function, bodily pain and depression to fatigue (all, P<0.01). The path model analysis revealed that depression exerted an indirect effect from bodily pain to fatigue (*B*=-0.04, P<0.01) and from mental health to fatigue (*B*=-0.16 P<0.01). The amount of fatigue explained by all predictors in the path model was 37%. **Conclusions**: Our study found that depression mediates the relationship between some health-related quality of life domains and fatigue in people with MS. Future longitudinal studies focusing on proper management of depressive symptoms in individuals with MS will help to determine the clinical implications of these findings.

Keywords: multiple sclerosis, depression, fatigue, quality of life.

Strengths and limitations of this study

- Depression mediated the relationship between mental health and bodily pain with fatigue in a sample of people with multiple sclerosis.
- Clinicians should be aware that depression was directly related with fatigue and that can indirectly mediate the effects of health-related quality of life in MS.
- Early identification and proper management of depression should be clinically considered in patients with multiple sclerosis.
- This was a cross-sectional study; therefore, cause and effect relationships cannot be inferred.
- The sample was composed of patients with multiple sclerosis recruited from different urban hospitals, not from the general population
- Some potential variables such as anxiety or sleep disturbances which could give a broader vision of the biopsychosocial model approach were not included

Conflict of Interest

The authors declare no conflicts of interest with the content of this article.

Funding

No funds were received for the study.

Patient consent

Obtained

Ethics approval

This study was approved by the local ethical research committee of the Hospital Universitario Fundación Alcorcón, Madrid, Spain

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Introduction

Multiple sclerosis (MS) is a chronic demyelizing disease of the central nervous system including a variety of symptoms which interfere with daily life activities, social, and working life, disturb emotional well-being and reduce quality of life. A recent study has reported a worldwide incidence of 5.2 per 100,000 person-years and a prevalence of 112 per 100,000 person-years for MS.[1]

Among all symptoms experienced by people with MS, fatigue is probably one of the most disabling.[2] The prevalence of fatigue in MS ranges from 53% to 80%.[3] Fatigue is a risk indicator for conversion to confirmed moderate-severe disability in relapsing-remitting MS.[4]In fact, fatigue is a complex symptom influenced by several aspects such as psychological status, social relationships, personal beliefs, as well as interaction with environment.[5]Among all potential relationships, depression and health-related quality of life are those aspects showing more impact on fatigue in people with MS.

Depression is the most prevalent comorbid situation reported by individuals with MS.[6,7] A recent study found that the presence of depression is an important determinant of cognitive performance in subjects with MS.[8] In fact, the relationship between fatigue and depression is bidirectional: fatigue can promote the development of depression, but depression may also contribute to worse self-perceived fatigue. Nevertheless, the results from current literature are somehow conflicting. Bakshi et al reported that fatigue was associated with depression independently of disability.[9] In the same direction, a recent study has shown that fatigue and sleep disturbances may contribute to the development

of depression.[10] Other authors have investigated the opposite, the role of depression in fatigue. Kroencke et al found that depressed mood was a significant predictor of fatigue accounting for approximately 23% of its variance.[11] Nevertheless, others have reported that depression is independently related to the presence of fatigue.[12] Due to multiple interactions between depression and fatigue can exist, more studies are needed.

Finally, fatigue and depression can also influence self-perceived quality of life. Tanriverdi et al observed that fatigue and depression strongly influence quality of life in MS.[13] A recent study has reported that depression and fatigue, in addition to disability and physical co-morbidities, were associated with health-related quality of life in people with MS.[14] Further research investigating the association between depression, health-related quality of life and fatigue in MS is needed. In fact, a better understanding of the possible interaction between these multidimensional aspects associated with fatigue can potentially assist clinicians in determining better therapeutic programs for individuals with MS. Therefore, the aim of the current study was to further determine the direct and indirect effects of depression and health-related quality of life on fatigue in people with MS. We hypothesized that relationships between health-related qualify of life variables and fatigue would be mediated by depressive symptoms.

Methods

Patients diagnosed with definite MS according to the modified McDonald criteria[15] by experienced neurologists were screened for eligibility criteria. The exclusion criteria included comorbid neurological diseases including herniated disk and other disorders of the spine, renal diseases, cancer, diabetes mellitus, other psychiatric diseases and a Mini Mental State Examination score<25.[16] Written informed consent was obtained from all participants prior to their inclusion in the study. The study design was approved by the Ethics Committee of Hospital Universitario Fundación Alcorcón (HUFA 11/087) in Madrid (Spain). All procedures were conducted according to the Declaration of Helsinki

Patients were recruited during their routine neurological visits and were screened and explored during a stationary phase of the disease. Patients completed a demographic and clinical questionnaire including age, sex, weight, height, medication, and history of pain, if existed. All participants underwent a neurological examination and neurological impairment was rated with the Expanded Disability Status Scale (EDSS).[17]

Multiple Sclerosis Related Fatigue

MS-related fatigue was assessed with the Fatigue Impact Scale (FIS).[18] The FIS consists of a 40-items questionnaire including 3 subscales assessing the impact of self-perceived fatigue on cognitive functioning (10 items), physical functioning (10 items), and psychosocial functioning (20 items). Patients rate on a 5 points Liker scale if fatigue causes problems during the previous month (0: no problem; 4: extreme problem). The total score ranges from 0 to 84 points, where higher scores represent higher level of self-rated fatigue. This questionnaire has obtained good test-retest reliability and validity in MS.[19]

Depression

Depression was assessed with the Beck Depression Inventory (BDI-II). It consists of 21-items assessing affective, cognitive and somatic symptoms of depression.[20] Patients choose from a group of sentences which best described how they had been feeling in the preceding two weeks. The score ranges from 0 to 21 points where higher score suggests higher level of depressive symptoms.[21] This questionnaire has exhibited good internal consistency and good convergent and divergent validity in MS.[22]

Health-Related Quality of life

The Short-Form Health Survey 36 (SF-36) was used to assess health-related quality of life. This questionnaire assesses 8 domains including physical function, physical role, bodily pain, general health, vitality, social function, role-emotional, and mental health.[23] Each domain is standardized on scores ranging from 0 to 100points where higher scores represent better quality of life. The SF-36 has shown the ability to discriminate between individuals with health problems and healthy people.[24,25]

Statistical analysis

Means, standard deviations, and confidence intervals were calculated to describe the sample. The Kolmogorov-Smirnov test revealed that all quantitative data exhibited a normal distribution. To determine the relationship between fatigue and the remaining variables, i.e., depression and health-related quality of life domains, different Pearson product-moment correlation coefficients were firstly assessed.

Secondly, a path model with maximum likelihood estimation was conducted to evaluate the direct and indirect effects of depression between the variables using AMOS computer program.[26] A path model is a diagram relating independent, intermediary, and dependent variables.[27] In the hypothesized model, fatigue was the dependent variable,

quality of life domains (independent outcomes) were the predictors of depression, and depression (intermediate variable) was a predictor of fatigue. In a path analysis, single arrows indicate causation between intermediary and dependent variable. Further, arrows also connect the error terms with their respective intermediary variables. Double arrows indicate correlation between pairs of independent variables. The path coefficient is a standardized regression coefficient (beta) showing the direct effect of an independent variable (health-related quality of life) on a dependent (fatigue) variable. These path coefficients may be used to decompose correlations in the model into direct and indirect effects, corresponding to direct and indirect path reflected in the arrows in the model. Indirect effects occur when the relationship between 2 variables (e.g. fatigue and mental health) is mediated by one or more variables (i.e., depression).

Previous conditions from data were assessed: linearity, additivity, interval level data, recursivity, low multicollinearity and adequate sample size.[28] Confirmation of the adequacy of the model was conducted within absolute fit indices.[29,30] AMOS provides several fit indices that are largely independent of the sample size: the chi-square statistic (X^2);[31] the goodness of fit index (GFI) and adjusted goodness of fin index (AGFI) whose value reference is at 90 to consider an acceptable model;[32] and the Comparative Fit Index (CFI), Normed Fit Index (NFI) and Tucker-Lewis Index (TLI) which are also adequate if their values are over 0.90.[33] Finally, within parsimony adjustment indices, the error of the Root Mean Square Approximation (RMSEA) whose values<0.08 or less are good.[34] Missing data were treated with maximum likelihood imputation.

Results

One hundred and twenty (n=120) consecutive subjects with MS were screened for eligibility criteria. Finally, one hundred and eight (n=108, 90%), 54% women, mean age: 44±8 years; height: 170±9 cm; weight: 71±15 kg satisfied all the eligibility criteria, agreed to participate, and signed the informed consent. The reasons for exclusion were as follows: previous surgery (n=6), pregnancy (n=2), and older than 65 years old (n=4). Demographic and clinical data of the total sample are listed in **Table 1**.

Correlation Analysis

Table 2 shows the Pearson's correlation coefficients between variables included in the path model. Fatigue was significantly negative associated with bodily pain (r=-0.48, P<0.01), physical function (r=-0.31, P<0.01), and mental health (r=-0.42, P<0.01), and significantly positive associated with depression (r=0.47, P<0.01): the higher the self-perceived fatigue, the worse physical function and mental health, the higher bodily pain, or the higher depressive symptom. Depression was also negatively associated with bodily pain (r=-0.40, P<0.01) and mental health (r=-0.61, P<0.01): the worse mental health or higher presence of bodily pain, the higher the level of depression.

Path analysis

The hypothesized model fit of the data was excellent with X^2=6.47 - X^2/df=1.71; Goodness of Fit Index (GFI): 0.98; Adjusted Goodness of Fit Index (AGFI): 0.91; Comparative Fit Index (CFI): 0.98; Tucker-Lewis Index: 0.94; Normed Fit Index: 0.97. Further, Root Mean Square Error of Approximation (RMSEA) was 0.08. **Fig. 1** displays the parameter estimates (standardized solution).

According to the direct effects, a significant path was noted from mental health (*B*=-.53, P<0.01) to depression. Likewise, significant paths were also indicated between physical function (*B*=-.23, P<0.01), bodily pain (*B*=-.36, P<0.01) and depression (B=

.29, P<0.01) on fatigue. The direct effect from bodily pain on depression did not reach the significance (*B*=-.15, P=0.07). Furthermore, significant indirect effects in the path analysis model from bodily pain to fatigue, exerted through depression (*B*=-.04, P<0.01) and from mental health to fatigue, exerted through depression (*B*=-.16 P<0.01) were observed. Overall, the amount of fatigue explained by all predictors in the model was R^2 = 0.37.

Discussion

The present study demonstrated that depression mediates the relationship between some health-related quality of life domains, such as mental health and bodily pain, and fatigue in individuals with MS. These results support the assumption that depression is directly related with fatigue and that can indirectly mediate the effects of health-related quality of life in MS.

The findings from our study show, firstly, and in accordance with prior literature[9-11] that depression is a psychological factor directly associated with fatigue in people with MS. However, previous studies did not investigate the potential indirect effects of depression on other variables. Our 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. The relevance of depression was further supported by the fact that we observed direct and indirect effects on self-perceived fatigue in our sample of subjects with MS, that is, depression has a direct influence on fatigue, but also other indirect influence on other outcomes. This finding is quite interesting if we consider that depression symptoms of our sample of people with MS was small since scores reflected minimal or mild signs of depression.[21] It is probable that higher levels of depression may reveal other relationships.

The association between mental health and fatigue in MS is not also new since some studies have reported that fatigue contributes to mental fatigue, worse emotional well-being, and worse cognitive performance.[35,36] The novelty of the current study was that the effect of mental health on fatigue was indirectly mediated by depression. This is an expected finding, since depression has been found to contribute to worse cognitive performance.[8] It would be reasonable that MS patients suffering fatigue experience worse cognitive function, which may in turn provoke depressive symptoms, and hence increasing the self-perceived fatigue. Bidirectional reinforcement between mental health and depression can create a vicious cycle by promoting self-perceived fatigue in people with MS.

Another health-related quality of life domain which was directly associated with fatigue was bodily pain. This seems to be expected since the presence of pain can also contribute to fatigue.[37] Nevertheless, similarly than mental health, the effect of pain on fatigue was indirectly mediated by depression. It can be hypothesized that pain induces depression and that the latest will promote a worse fatigue self-perception. In fact, this hypothesis has been supported by a study, which used a similar analysis that our study, where higher pain levels were associated with fatigue, which in turn were associated with higher depressive symptoms.[38] Current and previous findings suggest that proper management of depressive symptoms would be a key element in the treatment of pain in individuals with MS.

The path model also identified that physical function was associated with self-perceived fatigue in our sample of individuals with MS. In this case, the association of physical function and fatigue was not mediated by depression, supporting a direct effect between these variables. These findings agree with the results by Turpin et al who found that MS patients with greater fatigue and disability exhibited poorer physical activity.[39]

Again, it is expected that subjects reporting greater fatigue has lower physical activity. Nevertheless, this association could influence on other psychological outcomes included in our path, since fatigue may contribute to depression by reducing physical function as the result of lack of energy.[40] These associations support a complex interaction between physical outcomes, depressive symptoms, and fatigue.

Uncertainty over biological mechanisms withstanding in these interactions, the current results have important clinical implications. Our results indicate that depression, that is, an emotional status, plays a relevant role in the relationship between fatigue and health-related quality of life in people with MS. Therefore, current results suggest that proper management of depression can be effective for improving self-perceived fatigue in people with MS by acting on mental health and bodily pain. In such scenario, proper management of fatigue by indirectly treating depressive symptoms would lead increase of physical activity in these individuals. This hypothesis is supported by a recent review reporting that psychological treatment produced improvement in both psychological and physiological outcomes in patients with MS.[41]

There are a number of limitations that should be recognized. First, we used a cross-sectional design; therefore, cause and effect relationships between the variables cannot be inferred. Second, the sample was composed of patients with MS recruited from different urban hospitals. Therefore, extrapolation of our results to more diverse populations should be conducted with caution. Finally, other potential variables such as anxiety or sleep disturbances which could give a broader vision of the biopsychosocial model approach were not included. This study would benefit from longitudinal data to further determine the impact of proper management of depressive symptoms on the identified associated factors over time in patients with MS.

Conclusions

This study found that depression mediated the relationship between mental health and bodily pain, but not the association of physical activity, and fatigue in people with MS. These results support the assumption that depression is directly related with fatigue and that can indirectly mediate the effects of health-related quality of life in MS. Future longitudinal studies will help to determine the clinical implications of these findings.

Author contributions

All authors contributed to the study concept and design. JJFM and CFdlP did the main statistical analysis and interpretation of data. CFdlP and MCM contributed to draft the report. CFdlP obtained funding. MGC and ENP provided administrative, technical, and material support. ENP and MPHT supervised the study. All authors revised the text for intellectual content and have read and approved the final version of the manuscript.

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Legend of Figure

Figure 1: Path analyses relating mental health, bodily pain and physical function with fatigue with the intermediate effect of depression. Standardized direct path coefficients are presented. In this model mental health predicts depression, while the independent variable (fatigue) is predicted by depression and also directly by physical activity. The straight arrows represent regression paths for presumed causal relationships, which the curved double-headed arrows represent assumed correlations among the variables.

TABLE 1: Demographics and specific disease clinical data for the total sample (n = 108)*

Gender (male / female) n (%)	49 (45%) / 59 (55%)
Age (years)	44 ± 8 (42 - 45)
Height (cm)	170 ± 9 (168-172)
Weight (kg)	71.5 ± 15 (68-75)
Disease course n, (%) Relapsing remitting Secondary progressive Primary progressive	 80 (74%) 19 (18%) 8 (8%)
Disease duration (years)	12.5 ± 8.0 (11.0-14.2)
EDDS (0-10)	3.4 ± 1.7 (3.1-3.8)
FIS (total score, 0-84)	38.7 ± 19.2 (34.9-42.5)
Physical Function (SF-36, 0-100)	55.5 ± 27.8 (49.9-60.9)
Physical role (SF-36, 0-100)	49.5 ± 40.7 (41.4-57.6)
Bodily pain (SF-36, 0-100)	66.2 ± 23.5 (62.5-70.8)
General health (SF-36, 0-100)	44.8 ± 21.1 (40.6-49.1)
Vitality (SF-36, 0-100)	44.9 ± 19.8 (40.9-48.8)
Social function (SF-36, 0-100)	71.2 ± 24.2 (66.4-76.0)
Emotional role (SF-36, 0-100)	78.3 ± 35.9 (71.2-85.4)
Mental health (SF-36, 0-100)	68.6 ± 16.4 (65.4-71.9)
BDI - II (0-21)	10.2 ± 6.7 (8.8-11.5)

FIS: Fatigue Impact Scale; EDSS: Expanded Disability Status Scale; BDI - II: Beck Depression Inventory

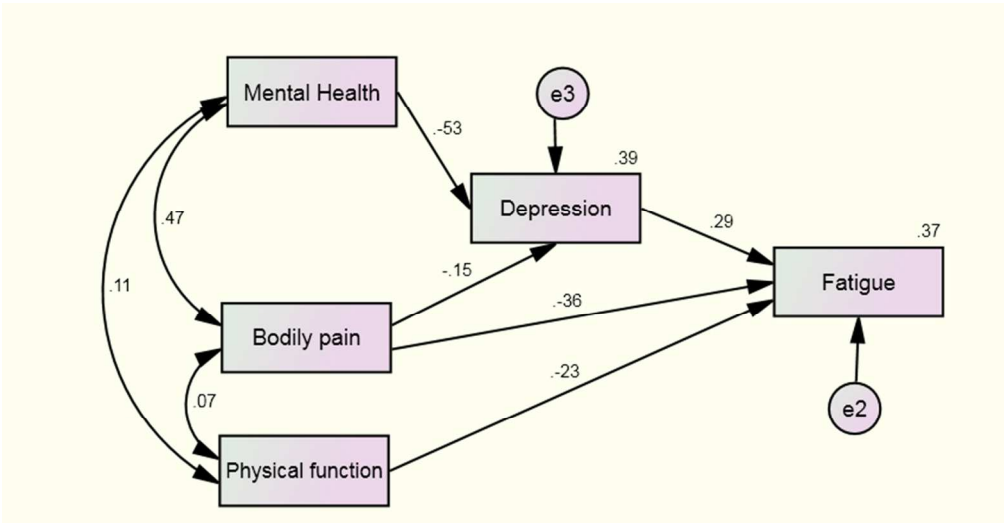
*Data are mean ± SD (95% confidence interval).

TABLE 2: Pearson-Product Moment Correlation Matrix for the Study Variables Included in the Path Model

	Mean	SD	95%CI	Kurtosis	Skewness	1	2	3	4
1. Fatigue (FIS, 0-84)	38.7	19.2	34.9 - 42.5	-.48	.22				
2. Bodily pain (0-100)	66.2	23.5	62.5 - 70.8	-.46	-.28	-.488**			
3. Physical function (0-100)	55.5	27.8	49.9 - 60.9	-1.20	.00	-.308**	.072		
4. Mental Health (0-100)	68.6	16.4	65.4 - 71.9	-.70	-.15	-.424**	.468**	.106	
5. Depression (0-21)	10.2	6.7	8.8 - 11.5	.33	.72	.475**	-.403**	-.184	-.606**

SD: Standard deviation; 95%CI: 95% confidence interval

[1] Skewness standard error = .23; [2] Kurtosis standard error = .46: ** P<.01; *P<.05 (two tailed)



STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any pre-specified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	7-8
		(*c*) Explain how missing data were addressed	7-8
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	7-8
		(*e*) Describe any sensitivity analyses	7-8

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9, table 1
		(b) Indicate number of participants with missing data for each variable of interest	
Outcome data	15*	Report numbers of outcome events or summary measures	9-10, table 2, Fig. 1
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-10, table 2, Fig. 1
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	N/A

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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

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

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Keywords: multiple sclerosis, depression, fatigue, quality of life.

Abstract

Objectives: To determine the direct and indirect effects of depression on health-related quality of life on fatigue in multiple sclerosis (MS). **Design:** A cross-sectional study. **Setting:** Tertiary urban hospital. **Participants:** One hundred and eight patients (54% women) with definite MS participated. **Outcome measures**: Demographic and clinical data (weight, height, medication, and neurological impairment), fatigue (Fatigue Impact Scale - FIS), depression (Beck Depression Inventory - BDI/II) and health-related quality of life (Short-Form Health Survey 36-SF36) were assessed. Correlation and path model analysis with maximum likelihood estimations were conducted to assess the direct and indirect effects of depression on health-related quality of life and MS-related fatigue. **Results**: Fatigue was associated with bodily pain, physical function and mental health, and with depression. Depression was associated with bodily pain and mental health. The path analysis found direct effect from physical function, bodily pain and depression to fatigue (all, $P<0.01$). The path model analysis revealed that depression exerted an indirect effect from bodily pain to fatigue (B=-0.04, $P<0.01$) and from mental health to fatigue (B=-0.16 $P<0.01$). The amount of fatigue explained by all predictors in the path model was 37%. **Conclusions**: The current study found that depression mediates the relationship between some health-related quality of life domains and fatigue in people with MS. Future longitudinal studies focusing on proper management of depressive symptoms in individuals with MS will help to determine the clinical implications of these findings.

Keywords: multiple sclerosis, depression, fatigue, quality of life.

Strengths and limitations of this study

- This study using a path model with restrictive indexes observed that depression levels mediated the relationship between mental health and bodily pain with fatigue in a sample of 108 individuals with multiple sclerosis.
- Clinicians should be aware that depression was directly related with fatigue and that can indirectly mediate the effects of health-related quality of life in multiple sclerosis; early identification and management of depression should be clinically considered in this population.
- Since this was a cross-sectional study, cause and effect relationships cannot be inferred. In addition, the sample was composed of patients recruited from urban hospitals, not from the general population
- The level of depressive symptoms in this sample of patients exhibiting multiple sclerosis was lower than expected, so we do not know if the presence of higher symptoms of depression can lead to further associations or effects.

Conflict of Interest

The authors declare no conflicts of interest with the content of this article.

Funding

No funds were received for the study.

Patient consent

Obtained

Ethics approval

This study was approved by the local ethical research committee of the Hospital Universitario Fundación Alcorcón, Madrid, Spain

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

Introduction

Multiple sclerosis (MS) is a chronic demyelizing disease of the central nervous system including a variety of symptoms, which interfere with daily life activities, social, and working life, disturb emotional well-being, and reduce quality of life. It has been reported a worldwide annual incidence of 5.2 per 100,000 persons and an prevalence of 112 cases per 100,000 habitants.[1] In Spain, the prevalence of MS has been found to be 125 cases/100,000 habitants;[2] however, some recent studies have observed an increased prevalence in the last decade.[3,4]

Among all symptoms experienced by people with MS, fatigue is probably one of the most disabling.[5] The prevalence of fatigue in MS ranges from 53% to 80%.[6] Fatigue is a risk indicator for conversion from moderate-severe disability to relapsing-remitting MS.[7] In fact, fatigue is influenced by several aspects such as psychological status, social relationships, personal beliefs, as well as personal interaction with environment.[8] Among all potential relationships, depression and health-related quality of life are those aspects showing more impact on fatigue in people with MS.[9,10]

Depression is the most prevalent comorbid situation reported by individuals with MS.[11,12] It has been recently reported that the presence of depression is an important determinant of cognitive performance[13] and quality of life[14] in individuals with MS. In fact, the relationship between related-fatigue and depression is bidirectional: fatigue can promote depression, but depression may also contribute to worse self-perceived fatigue.

Nevertheless, the results from current literature are sometimes conflicting. Bakshi et al observed that fatigue was associated with depression, but independently of disability.[15] Similarly, a recent study found that both fatigue and sleep disturbances contribute to the development of depression.[16] Other authors have investigated the role of depression on fatigue. Kroencke et al found that depressed mood was a significant predictor of fatigue accounting for approximately 23% of its variance.[17] Nevertheless; others reported that depression was not directly related to fatigue.[18]

Since depression and fatigue can be related thought multiple interactions, more studies including other cofounders such as health-related quality of life are needed. In fact, fatigue and depression can also influence self-perceived quality of life. Tanriverdi et al observed that fatigue and depression strongly influence the quality of life in MS.[19] Some recent studies reported that depression and fatigue, as well as related-disability and physical co-morbidities, were associated with health-related quality of life in people with MS.[9,10,20] Further studies investigating the association between depression, health-related quality of life and fatigue in MS are needed. In fact, a better understanding of the possible interaction between these multidimensional aspects associated with fatigue can potentially assist clinicians in determining better therapeutic programs for individuals with MS. 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.

Methods

Patients diagnosed with definite MS according to the modified McDonald criteria[21] by experienced neurologists, recruited from a local regional hospital in Madrid (Spain) between September 2013 and December 2014, were screened for eligibility criteria. The exclusion criteria included comorbid neurological diseases including herniated disk and other disorders of the spine, renal disease, cancer, diabetes mellitus, other psychiatric diseases and a Mini Mental State Examination score<25.[22] Written informed consent was obtained from all participants prior to their inclusion in the study. The study design was approved by the Ethics Committee of Hospital Universitario Fundación Alcorcón (HUFA 11/087) in Madrid (Spain). All procedures were conducted according to the Declaration of Helsinki

Patients were recruited during their routine neurological visits and were screened and explored during a stationary phase of the disease. Patients completed a demographic and clinical questionnaire including age, sex, weight, height, medication, and history of pain, if existed. All participants underwent a neurological examination and neurological impairment was rated with the Expanded Disability Status Scale (EDSS).[23]

Multiple Sclerosis Related Fatigue

MS-related fatigue was assessed with the Fatigue Impact Scale (FIS).[24] The FIS consists of a 40-items questionnaire including 3 subscales assessing the impact of self-perceived fatigue on cognitive functioning (10 items), physical functioning (10 items), and psychosocial functioning (20 items). Patients rate on a 5 points Liker scale if fatigue causes problems during the previous month (0: no problem; 4: extreme problem). The total score ranges from 0 to 84 points, where higher scores represent more fatigue. This questionnaire has exhibited good test-retest reliability and validity in people with MS.[25]

In this study, the validated Spanish version of the FIS was used.[26] We considered as main outcome the total FIS score.

Depression

Depression was assessed with the Beck Depression Inventory (BDI-II). It consists of 21-items assessing affective, cognitive and somatic symptoms of depression.[27] Patients choose from a group of sentences which best describe how they had been feeling in the preceding two weeks. The score ranges from 0 to 63 points where higher score suggests higher level of depressive symptoms.[28] This questionnaire has exhibited good internal consistency and good convergent and divergent validity in MS.[29]

Health-Related Quality of life

The Short-Form Health Survey 36 (SF-36) was used to assess health-related quality of life. This questionnaire assesses 8 domains including physical function, physical role, bodily pain, general health, vitality, social function, role-emotional, and mental health.[30] Each domain is standardized on scores ranging from 0 to 100points where higher scores represent better quality of life. The SF-36 has shown the ability to discriminate between subjects with health problems and healthy people.[31,32] In the current study, the validated Spanish version of the SF-36 questionnaire was used.[33]

Statistical analysis

Means, standard deviations, and confidence intervals were calculated to describe the sample. The Kolmogorov-Smirnov test revealed that all quantitative data exhibited a normal distribution. To determine the relationship between fatigue and the remaining variables, i.e., depression and health-related quality of life domains, different Pearson product-moment correlation coefficients were firstly assessed.

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] A path model is a diagram relating independent, intermediary (mediating), and dependent (final) variables.[35] In our hypothesized model, fatigue was the dependent variable, health-related quality of life domains were the independent variables and depression the intermediate, predictor, of fatigue. In a path analysis, single arrows indicate causation between intermediary and dependent variable. Further, arrows also connect the error terms with their respective intermediary variables. Double arrows indicate correlation between pairs of independent variables. The path coefficient is a standardized regression coefficient (beta) showing the direct effect of an independent variable (health-related quality of life domain) on the dependent (fatigue) variable. Indirect effects occur when the relationship between two variables (e.g. fatigue and mental health) is mediated by one or more variables (i.e., depression).

Previous conditions from data were assessed: linearity, additivity, interval level data, recursivity, low multicollinearity and adequate sample size.[36] Confirmation of the adequacy of the model was conducted within absolute fit indices.[37,38] AMOS provides several fit indices that are largely independent of the sample size: the goodness of fit index (GFI) and adjusted goodness of fin index (AGFI) whose value reference is at 90 to consider an acceptable model;[39] and the Comparative Fit Index (CFI), Normed Fit Index (NFI) and Tucker-Lewis Index (TLI) which are also adequate if their values are over 0.90.[40] Finally, within parsimony adjustment indices, the error of the Root Mean Square Approximation (RMSEA) whose values<0.08 or less are good.[41] Missing data were treated with maximum likelihood imputation. Missing data were removed to the

first recollected sample of participants, and just the sample was composed by the final subjects satisfying all inclusion criteria (n=108).

Results

One hundred and twenty (n=120) consecutive subjects with MS were screened for eligibility criteria. Finally, one hundred and eight (n=108, 90%), 54% women, mean age: 44±8 years; height: 170±9 cm; weight: 71±15 kg satisfied all the eligibility criteria, agreed to participate, and signed the informed consent. The reasons for exclusion were as follows: previous surgery (n=6), pregnancy (n=2), and older than 65 years old (n=4). Demographic and clinical data of the total sample are listed in **Table 1**.

Correlation Analysis

Table 2 shows the Pearson's correlation coefficients between variables included in the path model showing significant association with fatigue. Fatigue was significantly negative associated (higher score) with bodily pain (r=-0.48, P<0.01), physical function (r=-0.31, P<0.01) and mental health (r=-0.42, P<0.01), and also significantly positive associated with depression (r=0.47, P<0.01): the higher the self-perceived fatigue, the worse physical function, the worse mental health, the higher bodily pain, or the higher depressive symptom. Depression was also negatively associated with bodily pain (r=-0.40, P<0.01) and mental health (r=-0.61, P<0.01): the worse mental health or higher presence of bodily pain, the higher the level of depression.

Path analysis

The hypothesized model fit of the data was excellent with Goodness of Fit Index (GFI): 0.98; Adjusted Goodness of Fit Index (AGFI): 0.91; Comparative Fit Index (CFI): 0.98; Tucker-Lewis Index: 0.94; Normed Fit Index: 0.97. Further, Root Mean

Square Error of Approximation (RMSEA) was 0.08. **Figure 1** displays the parameter estimates (standardized solution).

According to the direct effects, a significant path was noted from mental health (*B*=-.53, P<0.01) to depression. Likewise, significant paths were also indicated between physical function (*B*=-.23, P<0.01), bodily pain (*B*=-.36, P<0.01) and depression (B= .29, P<0.01) on fatigue. The direct effect from bodily pain on depression did not reach the significance (*B*=-.15, P=0.07). Furthermore, significant indirect effects in the path analysis model from bodily pain to fatigue, exerted through depression (*B*=-.04, P<0.01) and from mental health to fatigue, exerted through depression (*B*=-.16 P<0.01) were observed. Overall, the amount of fatigue explained by all predictors in the model was R^2 = 0.37. All standard errors were between .035 and .070 with a confidence level of 95%.

Discussion

The present study demonstrated that depression mediates the relationship between some health-related quality of life domains, such as mental health and bodily pain, and fatigue in individuals with MS. These results support the assumption that depression is directly related with fatigue and that can indirectly mediate the effects of health-related quality of life in MS.

Our findings have shown, firstly, and in accordance with prior literature[9,10 14-17] that depression is a psychological factor directly associated with fatigue in people with MS. However, previous studies did not investigate the potential indirect effects of depression on the association between other variables. Our 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 depressive levels mediate the contribution of quality of life to related-fatigue. The relevance of depression was

further supported by the fact depression have both direct and indirect effects on self-perceived fatigue in our sample of subjects with MS, that is, depression has a direct influence on fatigue, but also other indirect influence on other outcomes. This finding is quite interesting if we consider that depression symptoms of our sample of people with MS was small since scores reflected minimal or mild signs of depression.[27] It would be probable that higher levels of depression may reveal other relationships.

The association between mental health and fatigue in MS is not also new since some studies have reported that fatigue contributes to mental fatigue, worse emotional well-being, and worse cognitive performance.[42,43] The novelty of the current study was that the effect of mental health on fatigue was indirectly mediated by depression. This is an expected finding, since depression has been found to contribute to worse cognitive performance.[13] It would be reasonable that MS patients suffering fatigue experience worse cognitive function, which may in turn provoke depressive symptoms, and hence increasing the self-perceived fatigue. Bidirectional reinforcement between mental health and depression can create a vicious cycle by promoting self-perceived fatigue in people with MS.

Another health-related quality of life domain which was directly associated with fatigue was bodily pain. This seems to be expected since the presence of pain can also contribute to fatigue.[44] Nevertheless, similarly than mental health, the effect of pain on fatigue was indirectly mediated by depression. It can be hypothesized that pain induces depression and that the latest will promote a worse fatigue self-perception. In fact, this hypothesis has been supported by a study, which used a similar analysis that our study, where higher pain levels were associated with fatigue, which in turn were associated with higher depressive symptoms.[45] Current and previous findings suggest that proper

management of depressive symptoms would be a key element in the treatment of pain in individuals with MS; although further studies are needed.

The path model also identified that physical function was associated with self-perceived fatigue in our sample of individuals with MS. In this case, the association of physical function and fatigue was not mediated by depression, supporting a direct effect between these variables. These findings agree with the results by Turpin et al who found that MS patients with greater fatigue and disability exhibited poorer physical activity.[46] Again, it is expected that subjects reporting greater fatigue have lower physical activity. Nevertheless, this association could influence on other psychological outcomes included in our path, since fatigue may contribute to depression by reducing physical function as the result of lack of energy.[47] These associations support a complex interaction between physical outcomes, depressive symptoms, and fatigue.

Uncertainty over biological mechanisms withstanding in these interactions, the current results have important clinical implications. Our results indicate that depression, that is, an emotional status, plays a relevant role in the relationship between fatigue and health-related quality of life in people with MS. Therefore, current results suggest that proper management of depression can be effective for improving self-perceived fatigue in people with MS by acting on mental health and bodily pain. In such scenario, proper management of fatigue by indirectly treating depressive symptoms would lead increase of physical activity in these individuals. This hypothesis is supported by a recent review reporting that psychological treatment produced improvement in both psychological and physiological outcomes in patients with MS.[48] Nevertheless; future randomized clinical trials are needed to confirm this hypothesis.

There are a number of limitations that should be recognized. First, we used a cross-sectional design; therefore, cause and effect relationships between the variables cannot be inferred. Second, the sample was composed of patients with MS recruited from different urban hospitals. Therefore, extrapolation of the current results to more diverse populations should be conducted with caution. 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. 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. 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. Finally, other potential variables, such as anxiety or sleep disturbances, which could give a broader vision of the biopsychosocial model approach were not included. This study would benefit from longitudinal data to further determine the impact of proper management of depressive symptoms on the identified associations over time in patients with MS.

Conclusions

This study found that depression mediated the relationship between mental health and bodily pain, but not the association of physical activity, and fatigue in people with MS. These results support the assumption that depression is directly related with fatigue and that can indirectly mediate the effects of health-related quality of life in MS. Future longitudinal studies will help to determine the clinical implications of these findings.

Author contributions

All authors contributed to the study concept and design. JJFM and CFdlP did the main statistical analysis and interpretation of data. CFdlP and MCM contributed to draft the report. CFdlP obtained funding. MGC and ENP provided administrative, technical, and material support. ENP and MPHT supervised the study. All authors revised the text for intellectual content and have read and approved the final version of the manuscript.

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Legend of Figure

Figure 1: Path analyses relating mental health, bodily pain and physical function with fatigue with the intermediate effect of depression. Standardized direct path coefficients are presented. In this model mental health predicts depression, while the independent variable (fatigue) is predicted by depression and also directly by physical activity. The straight arrows represent regression paths for presumed causal relationships, which the curved double-headed arrows represent assumed correlations among the variables.

TABLE 1: Demographics and specific disease clinical data for the total sample (n = 108)*

Gender (male / female) n (%)	49 (45%) / 59 (55%)
Age (years)	44 ± 8 (42 - 45)
Height (cm)	170 ± 9 (168-172)
Weight (kg)	71.5 ± 15 (68-75)
Disease course n, (%) Relapsing remitting Secondary progressive Primary progressive	 80 (74%) 19 (18%) 8 (8%)
Disease duration (years)	12.5 ± 8.0 (11.0-14.2)
EDDS (0-10)	3.4 ± 1.7 (3.1-3.8)
FIS (total score, 0-84)	38.7 ± 19.2 (34.9-42.5)
Physical Function (SF-36, 0-100)	55.5 ± 27.8 (49.9-60.9)
Physical role (SF-36, 0-100)	49.5 ± 40.7 (41.4-57.6)
Bodily pain (SF-36, 0-100)	66.2 ± 23.5 (62.5-70.8)
General health (SF-36, 0-100)	44.8 ± 21.1 (40.6-49.1)
Vitality (SF-36, 0-100)	44.9 ± 19.8 (40.9-48.8)
Social function (SF-36, 0-100)	71.2 ± 24.2 (66.4-76.0)
Emotional role (SF-36, 0-100)	78.3 ± 35.9 (71.2-85.4)
Mental health (SF-36, 0-100)	68.6 ± 16.4 (65.4-71.9)
BDI - II (0-63)	10.2 ± 6.7 (8.8-11.5)

FIS: Fatigue Impact Scale; EDSS: Expanded Disability Status Scale; BDI - II: Beck Depression Inventory

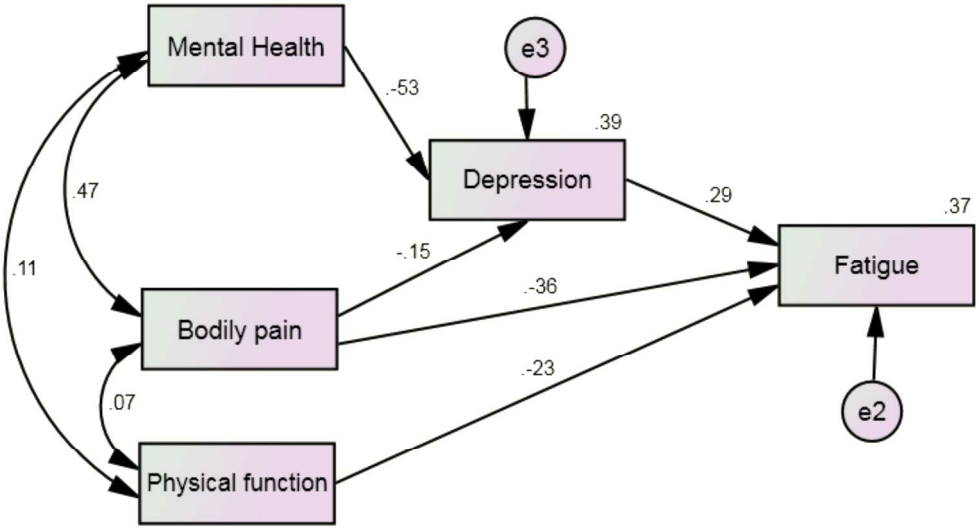
*Data are mean ± SD (95% confidence interval).

TABLE 2: Pearson-Product Moment Correlation Matrix for the Study Variables Included in the Path Model

	Mean	SD	95%CI	Kurtosis	Skewness	1	2	3	4
1. Fatigue (FIS, 0-84)	38.7	19.2	34.9 - 42.5	-.48	.22				
2. Bodily pain (0-100)	66.2	23.5	62.5 - 70.8	-.46	-.28	-.488**			
3. Physical function (0-100)	55.5	27.8	49.9 - 60.9	-1.20	.00	-.308**	.072		
4. Mental Health (0-100)	68.6	16.4	65.4 - 71.9	-.70	-.15	-.424**	.468**	.106	
5. Depression (0-63)	10.2	6.7	8.8 - 11.5	.33	.72	.475**	-.403**	-.184	-.606**

SD: Standard deviation; 95%CI: 95% confidence interval

[1] Skewness standard error = .23; [2] Kurtosis standard error = .46: ** P<.01; *P<.05 (two tailed)



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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any pre-specified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study size	10	Explain how the study size was arrived at	13
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	7-8
		(*c*) Explain how missing data were addressed	7-8
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	7-8
		(*e*) Describe any sensitivity analyses	7-8

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9, table 1
		(b) Indicate number of participants with missing data for each variable of interest	
Outcome data	15*	Report numbers of outcome events or summary measures	9-10, table 2, Fig. 1
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-10, table 2, Fig. 1
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	N/A

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Is the Association between Health -Related Quality of Life and Fatigue Mediated by Depression in Patients with Multiple Sclerosis? A Spanish Cross Sectional Study

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Is the Association between Health -Related Quality of Life and Fatigue Mediated by Depression in Patients with Multiple Sclerosis? A Spanish Cross Sectional Study

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Keywords: multiple sclerosis, depression, fatigue, quality of life.

Abstract

Objectives: To determine the mediating effects of depression on health-related quality of life and fatigue in individuals with multiple sclerosis (MS). **Design:** A cross-sectional study. **Setting:** Tertiary urban hospital. **Participants:** One hundred and eight patients (54% women) with MS participated in this study. **Outcome measures**: Demographic and clinical data (weight, height, medication, and neurological impairment), fatigue (Fatigue Impact Scale-FIS), depression (Beck Depression Inventory-BDI/II) and health-related quality of life (Short-Form Health Survey 36 - SF36) were collected. **Results**: Fatigue was significantly associated with bodily pain, physical function, mental health and depression. Depression was associated with bodily pain and mental health. The path analysis found direct effect from physical function, bodily pain and depression to fatigue (all, $P<0.01$). The path model analysis revealed that depression exerted a mediator effect from bodily pain to fatigue (B=-0.04, $P<0.01$) and from mental health to fatigue (B=-0.16 $P<0.01$). The amount of fatigue explained by all predictors in the path model was 37%. **Conclusions**: This study found that depression mediates the relationship between some health-related quality of life domains and fatigue in people with MS. Future longitudinal studies focusing on proper management of depressive symptoms in individuals with MS will help to determine the clinical implications of these findings.

Keywords: multiple sclerosis, depression, fatigue, quality of life.

Strengths and limitations of this study

- The main strength of this study was the inclusion of a homogeneous sample of individuals with multiple sclerosis and the use of specific statistical analyses.
- Since this was a cross-sectional study, cause and effect relationships between the associated variables cannot be inferred. In addition, the sample was composed of patients recruited from urban hospitals, not from the general population.
- The level of depression in our sample of individuals with multiple sclerosis was lower than expected. We do not known if the presence of higher symptoms of depression can lead to further associations or effects.
- We used a general, but not disease-specific questionnaire for assessing health-related quality of life. It is possible that the use of a disease-specific quality of life questionnaire would lead to other potential associations.

Conflict of Interest

The authors declare no conflicts of interest with the content of this article.

Funding

No funds were received for the study.

Patient consent

Obtained

Ethics approval

This study was approved by the local ethical research committee of the Hospital Universitario Fundación Alcorcón, Madrid, Spain

Is the Association between Health -Related Quality of Life and Fatigue Mediated by Depression in Patients with Multiple Sclerosis? A Spanish Cross Sectional Study

Introduction

Multiple sclerosis (MS) is a chronic demyelizing disease of the central nervous system and includes a variety of symptoms, which interferes with daily activities, social, and working life, disturbs emotional well-being and reduce quality of life. It has been reported a worldwide annual incidence of 5.2 per 100,000 persons and an prevalence of 112 cases per 100,000 habitants.[1] In Spain, the prevalence of MS has been found to be 125 cases per 100,000 habitants;[2] however, recent studies have observed an increased prevalence in the previous decade.[3,4]

Among all symptoms experienced by people with MS, fatigue is considered one of the most disabling.[5] The prevalence of fatigue in MS ranges from between 53% to 80%.[6] Fatigue is a risk indicator for conversion from moderate-severe disability to relapsing-remitting MS.[7] In fact, fatigue is influenced by several aspects such as psychological status, social relationship, personal beliefs, as well as personal interaction with the environment.[8] Among all potential relationships, depression and health-related quality of life exhibit the greatest impact on fatigue in people with MS.[9,10]

Depression is the most prevalent comorbid condition reported by subjects with MS.[11,12] It has been recently reported that the presence of depression is an important determinant of cognitive performance[13] and quality of life[14] in individuals with MS. In fact, the relationship between related-fatigue and depression is bidirectional: fatigue can promote depression, but depression may also contribute to worsening self-perceived fatigue. However, the results from current literature are sometimes conflicting. Bakshi

et al observed that fatigue was associated with depression, but independently of disability.[15] Similarly, a recent study found that both fatigue and sleep disturbances contribute to the development of depression.[16] Other authors have investigated the role of depression on fatigue. Kroencke et al found that depressed mood was a significant predictor of fatigue accounting for approximately 23% of its variance.[17] Nevertheless; others have reported that depression is not directly related to fatigue.[18]

Since depression and fatigue can be related by multiple interactions, additional studies including other variables such as health-related quality of life are needed. In fact, fatigue and depression can also influence self-perceived quality of life. Tanriverdi et al observed that fatigue and depression strongly influence the quality of life in MS.[19] Recent studies have reported that depression and fatigue, as well as related-disability and physical co-morbidities, are associated with health-related quality of life in people with MS.[9,10,20] Future studies investigating the association between depression, health-related quality of life and fatigue in MS are necessary. In fact, a better understanding of the possible interaction between these multidimensional aspects associated with fatigue can potentially assist clinicians in determining better therapeutic programs for individuals with MS. Therefore, the aim of the current study was to further determine the mediating effects of depression on the association between health-related quality of life and fatigue in individuals with MS. 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.

Methods

Patients diagnosed with definite MS according to the modified McDonald criteria[21] by an experienced neurologist recruited from a local regional hospital in Madrid (Spain) between September 2013 and December 2014, were screened for eligibility criteria. The exclusion criteria included comorbid neurological diseases including herniated disk and other disorders of the spine, renal disease, cancer, diabetes mellitus, other psychiatric diseases and a Mini Mental State Examination score<25.[22] Written informed consent was obtained from all participants prior to their inclusion in the study. The study design was approved by the Ethics Committee of Hospital Universitario Fundación Alcorcón (HUFA 11/087) in Madrid (Spain). All procedures were conducted according to the Declaration of Helsinki

Patients were recruited during their routine neurological visits and were screened and explored during a stationary phase of the disease. Patients completed a demographic and clinical questionnaire including age, sex, weight, height, medication, and history of pain. Subjects underwent a neurological examination and their neurological impairment was rated with the Expanded Disability Status Scale (EDSS).[23]

Multiple Sclerosis Related Fatigue

MS-related fatigue was assessed with the Fatigue Impact Scale (FIS).[24] The FIS consists of a 40-items questionnaire including 3 subscales assessing the impact of self-perceived fatigue on cognitive functioning (10 items), physical functioning (10 items), and psychosocial functioning (20 items). Patients rate on a 5 point Likert scale if fatigue caused problems during the previous month (0: no problem; 4: extreme problem). The total score ranges from 0 to 84 points, where higher scores represent more fatigue. This questionnaire has exhibited good test-retest reliability and validity in people with MS.[25] In this study, the validated Spanish version of the FIS was used as the main outcome.[26]

Depression

Depression was assessed with the Beck Depression Inventory (BDI-II). It consists of 21-items assessing affective, cognitive, and somatic symptoms of depression.[27] Patients choose from a group of sentences which best describe how they had been feeling in the preceding two weeks. The score ranges from 0 to 63 points where higher score suggests higher level of depressive symptoms.[28] This questionnaire has exhibited good internal consistency and good convergent and divergent validity in individuals with MS.[29]

Health-Related Quality of life

The Short-Form Health Survey 36 (SF-36) was used to assess health-related quality of life. This questionnaire assesses 8 domains including physical function, physical role, bodily pain, general health, vitality, social function, role-emotional, and mental health.[30] Each domain is standardized on scores ranging from 0 to 100 points where higher scores represent better quality of life. The SF-36 has shown the ability to discriminate between subjects with health problems and asymptomatic individuals.[31,32] In the current study, the validated Spanish version of the SF-36 questionnaire was used.[33]

Statistical analysis

Means, standard deviations, and confidence intervals were calculated to describe the sample. The Kolmogorov-Smirnov test revealed that all quantitative data exhibited a normal distribution. To determine the relationship between fatigue and the remaining variables, i.e., depression and health-related quality of life domains, different Pearson product-moment correlation coefficients were firstly assessed.

Secondly, a path model with maximum likelihood estimation was conducted to evaluate the effects of depression between the variables significantly associated with

fatigue using AMOS computer program.[34] A path model is defined as a diagram relating independent (exposure), intermediary (mediating) and dependent (outcome) variables.[35] In our hypothesized model, fatigue was the dependent variable, health-related quality of life domains were the independent variables and depression the intermediate, mediating, of fatigue. In a path analysis, single arrows indicate causation between intermediary and dependent variable. Further, arrows also connect the error terms with their respective intermediary variables. Double arrows indicate correlation between pairs of independent variables. The path coefficient is a standardized regression coefficient (beta) showing the direct effect of an independent variable (health-related quality of life domain) on the dependent (fatigue) variable. Indirect effects occur when the relationship between two variables (e.g. fatigue and mental health) is mediated by one or more variables (i.e., depression).

Previous conditions from data were assessed: linearity, additivity, interval level data, recursivity, low multicollinearity and adequate sample size.[36] Confirmation of the adequacy of the model was conducted within absolute fit indices.[37,38] AMOS provides several fit indices that are largely independent of the sample size: the goodness of fit index (GFI) and adjusted goodness of fin index (AGFI) whose value reference is at 90 to consider an acceptable model;[39] and the Comparative Fit Index (CFI), Normed Fit Index (NFI) and Tucker-Lewis Index (TLI) which are also adequate if their values are over 0.90.[40] Finally, within parsimony adjustment indices, the error of the Root Mean Square Approximation (RMSEA) whose values<0.08 or less are good.[41] Missing data were removed to the first recollected sample of participants, and just the sample was composed by the final subjects satisfying all inclusion criteria (n=108).

Results

One hundred and twenty (n=120) consecutive subjects with MS were screened for eligibility criteria. Finally, one hundred and eight (n=108, 90%), 54% women, mean age: 44±8 years; height: 170±9 cm; weight: 71±15 kg satisfied all the eligibility criteria, agreed to participate, and signed the informed consent. The reasons for exclusion were as follows: previous surgery (n=6), pregnancy (n=2), and older than 65 years old (n=4). Demographic and clinical data of the total sample are listed in **Table 1**.

Correlation Analysis

Table 2 shows the Pearson's correlation coefficients between variables included in the path model showing significant association with fatigue. Fatigue was significantly negative associated (higher score) with bodily pain (r=-0.48, P<0.01), physical function (r=-0.31, P<0.01) and mental health (r=-0.42, P<0.01), and also significantly positive associated with depression (r=0.47, P<0.01): the higher the self-perceived fatigue, the worse physical function, the worse mental health, the higher bodily pain, or the higher depressive symptom. Depression was also negatively associated with bodily pain (r=-0.40, P<0.01) and mental health (r=-0.61, P<0.01): the worse mental health or higher presence of bodily pain, the higher the level of depression.

Path analysis

The hypothesized model fit of the data was excellent with Goodness of Fit Index (GFI): 0.98; Adjusted Goodness of Fit Index (AGFI): 0.91; Comparative Fit Index (CFI): 0.98; Tucker-Lewis Index: 0.94; Normed Fit Index: 0.97. Further, Root Mean Square Error of Approximation (RMSEA) was 0.08. **Figure 1** displays the parameter estimates (standardized solution).

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 R^2 0.37.

Discussion

The present study demonstrated that depression mediates the relationship between some health-related quality of life domains, such as mental health and bodily pain, and fatigue in individuals with MS. These results support the assumption that depression is related to fatigue and that can mediate the effects of health-related quality of life in MS.

Our findings have shown, firstly, and in accordance with prior literature[9,10 14-17] that depression is a psychological factor directly associated with fatigue in people with MS. However, previous studies have not investigated the mediating effects of depression on the association with other variables. The current study showed that depression mediated the association between some health-related quality of life domains, such as bodily pain and mental health, with fatigue, suggesting that depressive levels mediate the contribution of quality of life to related-fatigue. The relevance of depression was further supported by the fact that depression also showed an effect on self-perceived fatigue in our sample of subjects with MS. This means that depression has an influence on fatigue, but also other mediating influences in other outcomes. This finding is quite interesting if we consider that depression symptoms of our sample of people with MS was small

since scores reflected minimal or mild signs of depression.[27] It would is plausible that higher levels of depression may reveal stronger relationships.

The association between mental health and fatigue in MS is not new since some studies have reported that fatigue contributes to mental fatigue, worse emotional well-being, and worse cognitive performance.[42,43] The novelty of the current study was that the effect of mental health on fatigue was mediated by depression. This is an expected finding, since depression contributes to worse cognitive performance.[13] It would be reasonable to consider that individuals with MS suffering fatigue experience worse cognitive function, which may in turn provoke depressive symptoms, and therefore, increase the self-perceived fatigue. Bidirectional reinforcement between mental health and depression can create a vicious cycle by promoting self-perceived fatigue in people with MS.

Another health-related quality of life domain which was directly associated with fatigue was bodily pain. This was expected since the presence of pain also contributes to fatigue.[44] Nevertheless, similar to mental health, the effect of bodily pain on fatigue was mediated by depression. It can be hypothesized that pain induces depression and that pain will promote a worse fatigue self-perception. This hypothesis is also supported by another study which used a similar analysis that in our study, where higher pain levels were associated with fatigue, which in turn were associated with higher depression.[45] Current and previous findings suggest that proper management of depressive symptoms would be a key element in the treatment of pain in individuals with MS; although further studies are needed.

The path model also identified that physical function was associated with self-perceived fatigue in our sample of individuals with MS. In this case, the association of

physical function and fatigue was not mediated by depression, supporting a direct effect between these variables. These findings are similar to the results by Turpin et al who found that patients with MS with greater fatigue and disability exhibited poorer physical activity.[46] Again, it is expected that individuals reporting greater fatigue have lower physical activity. It is possible that this association could influence other psychological outcomes included in our path analysis, since fatigue may contribute to depression by reducing physical function as the result of lack of energy.[47] These associations support a complex interaction between physical outcomes, depressive symptoms, and fatigue.

Uncertainty over biological mechanisms accounting for these interactions, the current results have important clinical implications. Our results indicate that depression, that is, an emotional status not directly caused by the condition, plays a relevant role in the relationship between fatigue and health-related quality of life in people with MS. Therefore, our results suggest that proper management of depression can be effective for improving self-perceived fatigue in people with MS by impacting mental health and bodily pain. It is possible that management of fatigue by treating depressive symptoms would lead to an increase of physical activity in these individuals. This hypothesis is supported by a recent review reporting that proper psychological management produced improvements in both psychological and physiological outcomes in patients with MS.[48] However; future randomized clinical trials are needed to confirm this hypothesis.

There are a number of limitations that should be recognized. First, we used a cross-sectional design; therefore, cause and effect relationships between the variables cannot be inferred. Second, the sample was composed of patients with MS recruited from different urban hospitals. Therefore, extrapolation of the current results to more diverse populations should be conducted with caution. Additionally, 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. 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. 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. Finally, other potential cofounder variables, such as sleep disturbances or anxiety, which could give a broader vision of the biopsychosocial model approach were not included. This study would benefit from longitudinal data to further determine the impact of proper management of depressive symptoms on the identified associations over time in patients with MS.

Conclusions

This study found that depression mediated the relationship between mental health and bodily pain, but not the association of physical activity, and fatigue in people with MS. These results support the assumption that depression is directly related with fatigue

and that can mediate the effects of health-related quality of life in individuals with MS. Future longitudinal studies will help to determine the clinical implications of these findings.

Author contributions

All authors contributed to the study concept and design. Juan J. Fernández-Muñoz and César Fernández-de-las-Peñas did the main statistical analysis and interpretation of data. César Fernández-de-las-Peñas, Margarita Cigarán-Méndez and Paula Parás-Bravo contributed to draft the report. Margarita Cigarán-Méndez, Esperanza Navarro-Pardo and Paula Parás-Bravo provided administrative, technical, and material support. Esperanza Navarro-Pardo and Marta Pérez-de-Heredia-Torres supervised the study. All authors revised the text for intellectual content and have read and approved the final version of the manuscript.

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Legend of Figure

Figure 1: Path analyses relating mental health, bodily pain and physical function with fatigue with the intermediate effect of depression. Standardized direct path coefficients are presented. In this model mental health predicts depression, while the independent variable (fatigue) is predicted by depression and also directly by physical activity. The straight arrows represent regression paths for presumed causal relationships, which the curved double-headed arrows represent assumed correlations among the variables.

TABLE 1: Demographics and specific disease clinical data for the total sample (n = 108)*

Gender (male / female) n (%)	49 (45%) / 59 (55%)
Age (years)	44 ± 8 (42 - 45)
Height (cm)	170 ± 9 (168-172)
Weight (kg)	71.5 ± 15 (68-75)
Disease course n, (%) Relapsing remitting Secondary progressive Primary progressive	 80 (74%) 19 (18%) 8 (8%)
Disease duration (years)	12.5 ± 8.0 (11.0-14.2)
EDDS (0-10)	3.4 ± 1.7 (3.1-3.8)
FIS (total score, 0-84)	38.7 ± 19.2 (34.9-42.5)
Physical Function (SF-36, 0-100)	55.5 ± 27.8 (49.9-60.9)
Physical role (SF-36, 0-100)	49.5 ± 40.7 (41.4-57.6)
Bodily pain (SF-36, 0-100)	66.2 ± 23.5 (62.5-70.8)
General health (SF-36, 0-100)	44.8 ± 21.1 (40.6-49.1)
Vitality (SF-36, 0-100)	44.9 ± 19.8 (40.9-48.8)
Social function (SF-36, 0-100)	71.2 ± 24.2 (66.4-76.0)
Emotional role (SF-36, 0-100)	78.3 ± 35.9 (71.2-85.4)
Mental health (SF-36, 0-100)	68.6 ± 16.4 (65.4-71.9)
BDI - II (0-63)	10.2 ± 6.7 (8.8-11.5)

FIS: Fatigue Impact Scale; EDSS: Expanded Disability Status Scale; BDI - II: Beck Depression Inventory

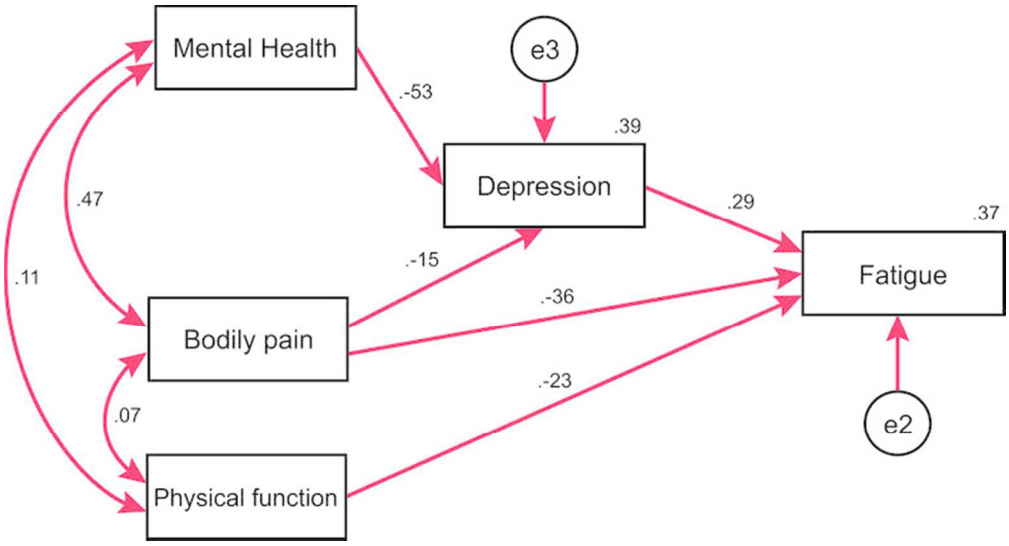
*Data are mean ± SD (95% confidence interval).

TABLE 2: Pearson-Product Moment Correlation Matrix for the Study Variables Included in the Path Model

	Mean	SD	95%CI	Kurtosis	Skewness	1	2	3	4
1. Fatigue (FIS, 0-84)	38.7	19.2	34.9 - 42.5	-.48	.22				
2. Bodily pain (0-100)	66.2	23.5	62.5 - 70.8	-.46	-.28	-.488**			
3. Physical function (0-100)	55.5	27.8	49.9 - 60.9	-1.20	.00	-.308**	.072		
4. Mental Health (0-100)	68.6	16.4	65.4 - 71.9	-.70	-.15	-.424**	.468**	.106	
5. Depression (0-63)	10.2	6.7	8.8 - 11.5	.33	.72	.475**	-.403**	-.184	-.606**

SD: Standard deviation; 95%CI: 95% confidence interval

[1] Skewness standard error = .23; [2] Kurtosis standard error = .46: ** P<.01; *P<.05 (two tailed)



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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any pre-specified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study size	10	Explain how the study size was arrived at	13
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	7-8
		(*c*) Explain how missing data were addressed	7-8
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	7-8
		(*e*) Describe any sensitivity analyses	7-8

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9, table 1
		(b) Indicate number of participants with missing data for each variable of interest	
Outcome data	15*	Report numbers of outcome events or summary measures	9-10, table 2, Fig. 1
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-10, table 2, Fig. 1
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	N/A

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.