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ANXIETY AND DEPRESSION INFLUENCE THE RELATION BETWEEN DISABILITY STATUS AND QUALITY OF LIFE IN MULTIPLE SCLEROSIS

Abstract

Disability status, depression and anxiety are important determinants of quality of life (QoL) in patients with multiple sclerosis (MS). We investigated whether anxiety and depression influence the relation between disability status and QoL in our cohort of recently diagnosed patients. Disability status (EDSS), anxiety and depression (HADS), and QoL (SF-36) were prospectively obtained in 101 MS patients. The relation between EDSS and SF-36 scales was examined using regression analyses, without and with adjustment for anxiety and depression. Interaction effects were investigated by comparing the relation between EDSS and QoL in patients with high and low anxiety and depression. In the unadjusted analyses, EDSS was significantly related to all SF-36 physical and mental health scales. After adjustment for anxiety and depression, EDSS was significantly related only to the SF-36 physical functioning, role-physical functioning and bodily pain scales. The relation between EDSS and these SF-36 scales was consistently higher in patients with more symptoms of anxiety or depression, suggesting that anxiety and depression strengthened the association of EDSS with these SF-36 physical health scales. After adjustment for anxiety and depression, EDSS was not significantly related to the SF-36 mental health scales and the general health scale. This finding is compatible with the hypothesis that anxiety and depression are intermediate factors in the association of EDSS with these SF-36 scales. Screening for symptoms of anxiety and depression is recommended in studies that use QoL as an outcome measure of treatment or intervention efficacy.

Introduction

A large number of studies have demonstrated that patients with multiple sclerosis (MS) have poorer quality of life (QoL) than persons from the general population.^[1-6] The disease has negative effects on both the physical and mental health dimensions of QoL.^[1-5] This reduction of QoL in patients with MS is for a large part explained by the severity of their neurological symptoms. As expected, patients with more physical limitations generally report poorer QoL on the physical health dimensions than those with fewer limitations.^[1-10] In addition, several studies have demonstrated a negative effect of disability status also on mental health,^[1-3] but this was not confirmed by others.^[4-10]

In MS, only two studies have investigated the association of depression and anxiety with health-related QoL. These studies showed that MS patients with more symptoms of depression or anxiety reported poorer QoL.^[9,11] Moreover, depression was an important predictor of both the physical and mental health dimensions of QoL, independent of clinically-assessed disability status.^[11] In these studies, the relation between depression and QoL was stronger than the association between clinical disability, as measured by the Expanded Disability Status Scale (EDSS), and QoL. Further, patients with higher disability were found to be more anxious and depressed.^[10-14] These findings combined led to the hypothesis that higher disability is associated with higher levels of anxiety or depression in patients with MS, which in consequence may affect QoL. This hypothetical model, in which anxiety and depression are intermediate factors in the relationship between disability status (EDSS) and QoL, as measured by the SF-36, is depicted in Figure 1.

Intermediate factor



Moderating factor

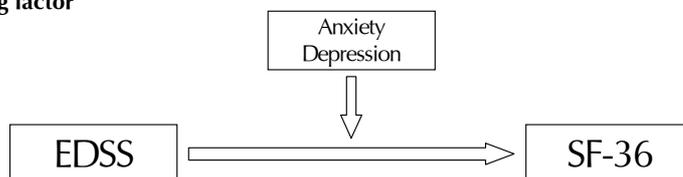


Figure 1 Schematic presentation of anxiety and depression as intermediate or moderating factors of the relation between disability status (EDSS) and quality of life (SF-36).

On the other hand, it can be argued that disability status may have a stronger impact on QoL when patients are anxious or depressed. In this alternative hypothesis, anxiety and depression moderate the relationship between disability status and QoL (Figure1). As QoL is increasingly recommended as an outcome measure in clinical trials and intervention studies,^[1,3,4,8,9,15] it is important to understand the role of factors that may strengthen the impact of physical limitations on QoL. In our cohort of recently diagnosed patients with MS, we investigated whether anxiety and depression alter the relationship between disability status and health-related QoL.

Methods

Participants and procedures

Patients were recruited through the Departments of Neurology of the Erasmus MC (Rotterdam), three hospitals within the region of this academic hospital, and the VU Medical Center (Amsterdam) in the period of March 1999 – December 2000. Patients were eligible if they were diagnosed with definite or probable MS based on the criteria of Poser^[16] within two years before study entry, were between 18 and 55 years old and had signed informed consent. Diagnoses were verified by senior neurologists of the academic hospitals. Patients with serious comorbidity or with insufficient understanding of the Dutch language were excluded. Of the 120 patients who met the criteria, 101 agreed to participate in the study. Patients who declined participation mentioned the emotional burden (n=3) or a lack of interest (n=3). Nine patients declined without additional comments and four never responded to our reminders. Patients underwent a neurological examination and filled out questionnaires. The study protocol was approved by the medical ethical committees of the participating hospitals.

Measurements

Functional limitations were assessed by trained physicians of the Erasmus MC and VU Medical Center following a standardized research protocol. Functional limitations were rated on the Expanded Disability Status Scale (EDSS). The EDSS ranges from 0.0 (no disability) to 10.0 (death due to MS).^[17] None of the patients were hospitalized at the time of data collection. Assessments of the EDSS were postponed when patients experienced a relapse at the scheduled examination.

Health-related QoL was assessed using the SF-36.^[18] The SF-36 is a commonly used and well-validated instrument comprising four physical health (physical functioning, role-physical functioning, bodily pain and general health) and four mental health scales (vitality, social functioning, role-emotional functioning and

mental health). In the SF-36, role-physical functioning refers to the interference of physical limitations with daily activities and work and role-emotional functioning refers to the interference of emotional problems on activities of daily life. The general health scale assesses the overall evaluation of the patient's health status. For each SF-36 scale, the items are summed and transformed into scores between 0 (poor health) and 100 (optimal health). Patients returned their questionnaires at the neurological examinations where they were asked to fill in missing values, if any. Therefore, the percentage of missing values at individual scales was low (< 3%). In this population, internal consistency reliability of the SF-36 scales was high^[19] with Coefficient α ranging from 0.74 to 0.94.

Anxiety and depression were assessed by the two 7-item scales of the Hospital Anxiety and Depression Scale (HADS).^[20,21] The HADS is a validated self-report screening scale developed for use in medical settings that indicates the presence of anxious or depressed states. The anxiety and depression scales range from 0-21 with high scores reflecting more symptoms of anxiety or depression. A total HADS score is obtained by summation of the anxiety and depression scores. Scores between 8 and 10 are considered clinically borderline and 11 or higher are considered clinically definite levels of anxiety and depression.^[20] In this study, internal consistency reliability for the HADS was high: Coefficient α was 0.83 for the anxiety and 0.81 for the depression scale. Depression and anxiety were strongly correlated ($r = 0.66$, $p < 0.001$).

Statistical analysis

Mean scores of the SF-36 and median score of EDSS were compared between patients with high and low levels of anxiety and depression. These groups were defined by the median score of the total HADS. Differences between patients with lower (total HADS < 8) and higher (HADS \geq 8) anxiety and depression were tested using t-test (SF-36) and Mann-Whitney U test (EDSS).

Next, we performed a series of regression analyses to investigate the role of EDSS, anxiety and depression as well as their interaction in relation to QoL (SF-36). 'Unadjusted' coefficients were calculated by separate regression analyses of EDSS, anxiety and depression with each SF-36 scale, including only age and sex in the model. Adjusted coefficients were obtained by simultaneous analysis of EDSS, anxiety and depression. In these analyses, anxiety and depression were included as continuous variables. Then, two strategies were followed to determine whether anxiety and depression alter the relationship between EDSS and QoL. First, we examined whether anxiety and depression were an intermediate step in the relation between EDSS and QoL. This was evaluated by comparing the unadjusted

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and adjusted regression coefficients of EDSS. When regression coefficients for EDSS are no longer significant after adjustment, anxiety or depression are likely intermediate factors in the relationship between disability status and QoL. Second, we examined whether depression and anxiety modify the relationship of EDSS and QoL. For this purpose, we evaluated interaction effects by comparing the strength of association between EDSS and SF-36 in patients with high and low levels of anxiety and depression. These groups were defined by median split of the total HADS scores. Further, differences in the strength of the associations were tested for significance by adding interaction effects in the models specified above. P-values of 0.05 and lower were considered statistically significant.

Results

The mean age of the patients was 37.5 years (SD 9.5) and 70% were women. Ninety percent of the patients were diagnosed with definite MS and 10% with probable MS. The mean time since diagnosis was 7.8 months (median 5.1, SD 6.5) and the mean time since first symptoms was 3.7 years (median 2.1, SD 4.6). EDSS scores ranged from 0.0 to 7.0 (median 2.5). The majority of the patients (75%)

Table 1 Comparison of quality of life, depression, anxiety and EDSS between patients with low and high levels of anxiety and depression

	Total (n = 98)	Anxiety and depression		p
		Low (n = 42)	High (n = 56)	
Quality of life (SF-36)				
<i>Physical health</i>				
Physical functioning	68.8 (25.9)	80.6 (18.2)	59.6 (27.3)	< 0.001
Role-physical functioning	49.2 (41.3)	69.1 (35.7)	34.4 (39.2)	< 0.001
Bodily pain	75.4 (23.0)	84.4 (19.4)	68.7 (23.3)	< 0.001
General health	49.1 (19.4)	56.1 (16.6)	43.9 (19.8)	0.002
<i>Mental health</i>				
Vitality	52.5 (18.2)	60.2 (15.4)	46.6 (18.0)	< 0.001
Social functioning	77.2 (23.3)	86.9 (18.3)	69.9 (24.1)	< 0.001
Role-emotional functioning	73.0 (35.9)	86.9 (25.4)	62.5 (39.2)	< 0.001
Mental health	72.7 (16.2)	81.5 (11.4)	66.1 (16.2)	< 0.001
Depression (HADS)	3.7 (3.2)	1.2 (0.8)	5.6 (3.1)	-†
Anxiety (HADS)	6.6 (4.1)	3.4 (1.5)	8.8 (3.9)	-†
EDSS (median)	2.5	2.5	3.0	0.002

Values are means (SD) unless otherwise indicated. P-values are based on t-test or Mann-Whitney U (EDSS). High and low anxiety and depression are defined by a median split of the total HADS score (see Methods). † Not relevant.

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were still employed. Ten patients were on interferon treatment and one patient was treated for depression. Table 1 presents mean scores of QoL, depression and anxiety. QoL was significantly poorer among patients who reported more symptoms of anxiety or depression. These patients also had significantly higher EDSS scores than patients with low anxiety and depression scores (median 2.5 versus 2.0, $p = 0.002$). Thirty-four percent of the patients had clinically relevant levels of anxiety (scores ≥ 8) and 10% of depression. SF-36 QoL, anxiety, depression and EDSS did not differ between patients recruited through the three different hospitals ($p > 0.20$). Patients who used interferon treatment had similar anxiety, depression and SF-36 scores compared to patients who did not use medication, except that they reported poorer role-physical functioning (mean 15.0 versus 53.1, $p < 0.001$).

Table 2 shows the relation of EDSS, anxiety and depression with QoL as assessed by the physical health scales of the SF-36. The negative coefficients indicate that a higher EDSS and more symptoms of depression and anxiety were associated with poorer QoL. In the unadjusted analyses, EDSS, depression and anxiety were significantly correlated to all four SF-36 physical health scales ($p < 0.01$). When including EDSS, anxiety and depression simultaneously in the model, EDSS remained significantly related to physical functioning ($\beta = -0.64$, $p < 0.001$), role-physical functioning ($\beta = -0.24$, $p = 0.03$) and bodily pain ($\beta = -0.33$, $p = 0.002$), but was no longer associated with general health ($\beta = -0.09$, $p = 0.40$). Depression was the only significant determinant of general health, and was further associated with role physical functioning and bodily pain.

EDSS, depression and anxiety were also significantly associated with each of the SF-36 mental health scales in the unadjusted analyses (Table 3). When including all three predictors simultaneously in the model, EDSS was not

Table 2 Relationship between EDSS, depression, anxiety and SF-36 physical health scales

	SF-36 Physical health							
	Physical functioning		Role-physical functioning		Bodily pain		General health	
	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
EDSS	-0.70***	-0.64***	-0.43***	-0.24*	-0.46***	-0.33**	-0.26**	-0.09
Depression	-0.45***	-0.11	-0.53***	-0.38**	-0.43***	-0.21*	-0.41***	-0.24*
Anxiety	-0.31***	-0.05	-0.35***	-0.05	-0.31***	-0.09	-0.35***	-0.17

Values are standardized regression coefficients (β). In the 'unadjusted' analyses, each variable was entered separately, with adjustment for age and sex only. In the 'adjusted' analyses, EDSS, depression, anxiety, age and sex were entered simultaneously. Negative β 's indicate that higher EDSS and more symptoms of depression or anxiety are related to poorer QoL or more (bodily) pain. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table 3 Relationship between EDSS, depression, anxiety and SF-36 mental health scales

	SF-36 mental health							
	Vitality		Social functioning		Role-emotional functioning		Mental health	
	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
EDSS	-0.34***	-0.14	-0.37***	-0.13	-0.32**	-0.14	-0.37***	-0.09
Depression	-0.51***	-0.37**	-0.57***	-0.39**	-0.45***	-0.15	-0.64***	-0.41***
Anxiety	-0.37***	-0.12	-0.43***	-0.18	-0.43***	-0.32**	-0.53***	-0.28**

Values are standardized regression coefficients (β). In the 'unadjusted' analyses, each variable was entered separately, with adjustment for age and sex only. In the adjusted analyses, EDSS, depression, anxiety, age and sex were entered simultaneously. Negative β 's indicate that higher EDSS and more symptoms of depression or anxiety are related to poorer QoL. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

significantly associated to the mental health dimensions of QoL (see adjusted analysis in Table 3). This finding suggests that the relation between EDSS and the SF-36 mental health scales, observed in the unadjusted analyses, was for a large part explained by the relation of EDSS with anxiety and/or depression. In the adjusted analyses, depression remained significantly associated to three SF-36 mental health scales (vitality, social functioning and mental health), while anxiety remained significantly associated to two scales (role emotional functioning and mental health).

Although the association between EDSS and SF-36 physical health scales was independent of anxiety and depression, these factors may still modify the relationship between EDSS and these SF-36 scales. Therefore, we compared the relationship of EDSS and SF-36 between patients with high and low levels of anxiety and depression. Figure 2 shows that the relationship between EDSS and SF-36 physical functioning, role-physical functioning and bodily pain was stronger in patients with higher scores of anxiety or depression. Moreover, the relation of EDSS with SF-36 role-physical functioning and bodily pain was significant only in patients with high total HADS scores ($p < 0.001$), but was not significant in those with lower levels of anxiety and depression. This suggests that more feelings of anxiety and depression strengthen the association between disability status and these SF-36 physical health scales. When testing for the statistical significance of the interaction effects only the relation between EDSS and the SF-36 physical functioning scale differed significantly between patients with high and low total HADS scores (β for interaction term = -0.59, $p = 0.05$). The standardized regression coefficients for the interaction terms for SF-36 role-physical functioning (β interaction = -0.43, $p = 0.32$) and bodily pain (β interaction = -0.65, $p = 0.13$)

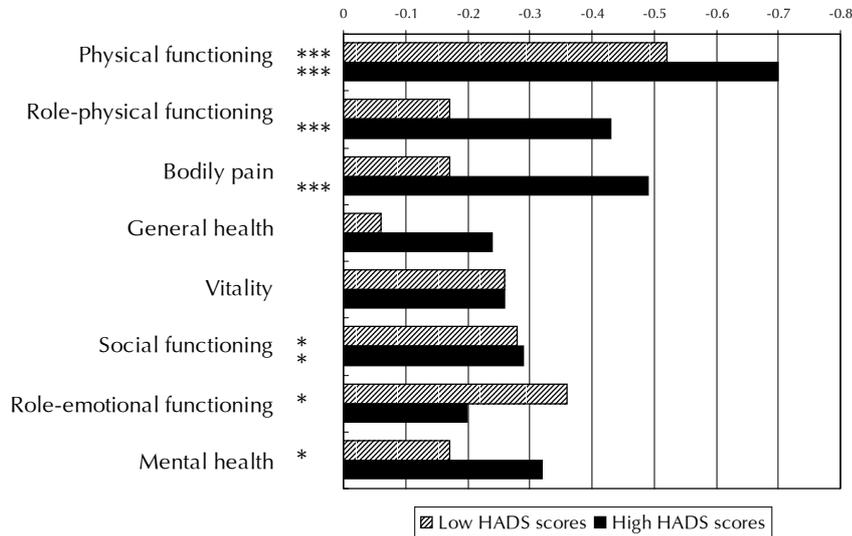


Figure 2. The relation between EDSS and SF-36 scores in groups with low and high levels of anxiety and depression

Values are standardized regression coefficients (β), adjusted for age and sex. High and low anxiety and depression are defined by median split of the total HADS scores (see Methods).

scale were not statistically significant. Further, as patients with high levels of anxiety or depression also had higher EDSS (Table 1), it is important to rule out that a difference between these two groups could be explained by a non-linear relationship of EDSS with the SF-36. Examination of the residuals scatterplots of EDSS with each of the SF-scales did not show evidence for a non-linear relationship (data not shown). This means that the regression coefficients of the high and low anxiety and depression groups would have been equal when there was no effect modification.

Discussion

In this cohort of patients with a recent diagnosis of MS, we found that disability status (EDSS), depression and anxiety were significantly associated with all SF-36 scales. Yet, after adjustment for anxiety and depression, we found that EDSS was only significantly related to the SF-36 physical functioning, role-physical functioning and bodily pain scales. The association of EDSS with these SF-36 scales was higher among patients who reported more symptoms of anxiety or depression. EDSS was not significantly associated with the mental health scales after adjustment for anxiety and depression.

Before interpreting the results, three methodological issues need to be discussed. The first point concerns the overlap in the measurement of several study variables. In our study, there was a high correlation between EDSS and the SF-36 physical functioning scale ($r = -0.73$). This means that EDSS explained much (54%) but not all of the variance of the scale suggesting that other determinants were involved. An important difference between the instruments is that the EDSS aims to assess the objective clinical status, whereas the SF-36 is a subjective evaluation of physical functioning by the patient. The latter is also determined by other factors such as illness intrusiveness^[10] and mood^[9,11]. A similar point concerns the overlap between the assessment of anxiety and depression and the SF-36 mental health scale. This SF-36 scale comprises questions that may reflect anxious and depressed mood. In line with previous findings,^[22] we found that the correlation of the SF-36 mental health scale with depression ($r = -0.60$) and anxiety ($r = -0.57$) was substantial. But again, anxiety and depression did not entirely explain the variance in this SF-36 mental health score (42%), suggesting that other factors played a role.

The second point concerns our study of interaction effects between EDSS and total HADS scores. We only found evidence for a significant interaction effect for the SF-36 physical functioning scale. Although the standardized regression coefficients (β) of the other interaction effects were comparable and were higher than the coefficients of the main effects included in the model, they were not statistically significant. This suggests that the study may have been too small to demonstrate significant interaction effects. This is likely because large studies are needed to examine interaction effects with sufficient statistical power.^[23] However, due to the small sample size, we can also not exclude a false positive interaction effect in SF-36 physical functioning. Our findings on the moderating effect of anxiety and depression remain to be replicated in future studies.

A third methodological issue is the cross-sectional design of this study, which limits the interpretation of relationships in terms of causality. Together with theoretical considerations and findings of previous studies, cross-sectional studies can only point to causal pathways, but not prove them. In previous studies, disability status has generally been modeled as a predictor of emotional well-being^[10-14] and QoL.^[1-10] Also, anxiety and depression have been analyzed as determinants of QoL,^[9,11] rather than vice versa. The view that anxiety and depression depend on disability status and determine QoL has led us to examine whether anxiety and depression mediate or moderate the relationship between disability status and QoL (see Figure 2).

Our study differs in two aspects from those previously conducted on health-related QoL in patients with MS. First, we have studied the interrelation between

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disability status, anxiety and depression as well as their joint and independent effects on QoL. Second, we have only included patients who were diagnosed with MS no longer than two years before study entry. These patients have relatively mild disability and will still be coping with the diagnosis of this chronic unpredictable disease. In this cohort, we found that patients with more physical limitations reported poorer QoL on all SF-36 scales, including those assessing mental health. These findings are in line with several previous studies,^[1-3] but in contrast with studies that only found a significant relation of EDSS with the physical dimensions of QoL and not with mental health dimensions.^[4-6,8,9]

The two important findings of this study result from the simultaneous analysis of EDSS, anxiety and depression. The first finding is that the associations of EDSS with the SF-36 mental health scales and the general health scale were not significant after adjustment for anxiety and depression. This is compatible with the hypothesis that anxiety and depression are intermediate factors in the relation between EDSS and these SF-36 scales. That is, higher levels of disability lead to increased feelings of anxiety and depression, which subsequently lower the self-reported quality of mental health. An important question, still to be answered, is whether anxiety and depression actually lower QoL or bias the evaluation of QoL in that depressed patients perceived themselves as more disabled.

The second important finding is that our study suggests that anxiety and depression modify the negative effect of disability status on three out of four physical health scales of the SF-36. The relationship of EDSS with physical functioning, role-physical functioning and bodily pain was stronger in patients with more symptoms of anxiety or depression, albeit that the interaction effects reached statistical significance for only one scale. Although findings remain to be confirmed, our study suggests that in patients with more symptoms of anxiety and depression, physical limitations may have a greater impact on the quality of physical health as assessed by the SF-36. A possible explanation is that anxiety and depression impede coping with physical limitations and therefore result in a diminished QoL on these scales.

In this study, we did not consider the role of fatigue. As several studies have demonstrated significant associations of fatigue with EDSS, depression and QoL in MS,^[9,24-26] fatigue could represent another intermediate factor in the relationship between disability status and QoL. In our patients, we assessed the frequency of fatigue symptoms on a four-point scale (often, frequently, seldom, never). Although the scale was not validated, we explored a possible confounding role by repeating the analyses presented in Tables 2 and 3 including fatigue in the model. There were no major changes in the association of EDSS, anxiety and depression with

QoL, except that the strength of the relationship between depression and SF-36 vitality was markedly lower ($B = 0.24$, $p = 0.05$). Fatigue significantly added to the prediction of SF-36 role-physical functioning and general health scores, but not in the other scales. These findings suggest that fatigue does not explain the relationship between EDSS, anxiety and depression on the one hand, and QoL on the other.

In conclusion, we found that disability status as measured by the EDSS is an important determinant of QoL in patients with a recent diagnosis of MS. Our data were compatible with the hypothesis that anxiety and depression are intermediate factors in the relation of EDSS with the SF-36 mental health scales and the general health scale, and may moderate the relation between EDSS and the SF-36 physical health scales. Improvement in QoL in therapeutic studies may depend on the patient's level of anxiety and depression. It is therefore important to assess symptoms of anxiety and depression when studying QoL as an outcome measure in clinical trials or other intervention studies.

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