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Clinical trial

Depression, fatigue and disability are independently associated with quality of life in patients with multiple Sclerosis: Results of a cross-sectional study

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ABSTRACT

Background: Quality of life (QoL) is significantly impaired in patients with Multiple Sclerosis (MS). As the expanded disability status scale (EDSS) inadequately reflects the impact of clinical symptoms on QoL, the present study aimed to identify factors associated with reduced QoL in MS patients.
Design: Single-center cross-sectional study in 260 MS patients.
Methods: QoL was assessed by the Multiple Sclerosis International QoL Questionnaire (MusiQoL), depression by the Center for Epidemiological Studies Depression Scale (CES-D scale), and fatigue by the Fatigue Scale for motor function and cognition (FSMC).
Results: 79.6% patients were female and 21.4% male. The mean age was 44.5 ± 11.2 years and the median EDSS 3.0 (range 0.0–8.5). 35.8% had depression and 56.9% moderate to severe fatigue. The mean MusiQoL index score was 73.9 ± 11.3. Using linear regression, depression, fatigue, family status, physical activity, and occupation were associated with QoL. EDSS was only associated with QoL in patients with an EDSS 0.5.0.
Conclusions: Depression, fatigue, family status, physical activity, and occupational status were closely associated with QoL in MS patients. Potential measures to improve QoL include assessment and treatment of depression, physical exercise, and maintaining patients employed in accordance with their physical and mental disabilities.

1. Background

Multiple sclerosis (MS) is a chronic autoimmune disorder of the central nervous system with potentially severe disabling consequences. About 2.3 million individuals are affected by MS worldwide (Livingston et al., 2016). MS is the most common cause of physical disability in adults of working age. First symptoms generally occur at the age of 20 to 40 years, when individuals usually try to establish their professional careers or start a family (Milo and Kahana, 2010). In MS, quality of life (QoL) is impaired by various factors (Miller and Dishon, 2006). Beyond physical disability, people with MS suffer from fatigue, bladder and sexual dysfunction with subsequent impact on their professional and private lives (Krupp et al., 1988; Zorzon et al., 2001). A recent Europe-wide survey has demonstrated that very early in the course disease a substantial number of people affected by MS are unable to maintain or resume employment even in the absence of significant physical disability underpinning the major impact fatigue may have on occupational status irrespective of physical disability (Kobelt et al., 2017; Flachenecker et al., 2017).

While endpoints in clinical trials traditionally focus on physical disability as assessed by the Expanded Disability Status Scale (EDSS) and magnetic resonance imaging (MRI) criteria (T1- and T2 lesions, contrast enhancement, and brain atrophy), patient surveys have demonstrated that fatigue exerts a greater impact on QoL than the extent of physical disability might predict a priori (Benito-León et al., 2003). Therefore, health-related quality of life (HRQoL) has been used more frequently as a study endpoint in recent years (Nortvedt and Riise, 2003). However, HRQoL assessment has been mostly restricted to

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Abbreviations: MS, Multiple Sclerosis; EDSS, Expanded Disability Status Scale; QoL, Quality of life; HRQoL, Health related quality of life; SF-36, 36-Item short form survey; MuSIQoL, Multiple Sclerosis International QoL Questionnaire; RRMS, Relapsing-remitting Multiple Sclerosis; PPMS, Primary Progressive Multiple Sclerosis; SPMS, Secondary progressive MS; AMG, Medicinal Products Act; BfArM, Federal Institute for Drugs and Medical Devices; PEI, Paul Ehrlich Institute; CES-D scale, Center for Epidemiological Studies Depression Scale; FSMC, Fatigue Scale for motor function and cognition; ADL, Activity of daily living; PWB, Psychological well-being; SPT, Symptoms; RFr, Relationship with friends; RFa, Relationship with the family; SHCS, Satisfaction with health care; SSL, Sentimental and sexual life; COP, Coping; REJ, Rejection

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the usage of the SF-36 and other HRQoL instruments not covering all aspects of QoL relevant for people with MS (Fisk et al., 2005). Given the lack of an MS-specific patient questionnaire, the Multiple Sclerosis International QoL questionnaire (MusiQoL) was developed by an independent scientific steering committee in conjunction with MS patients, neurologists and health economists (Simeoni et al., 2008). This validated 31-item questionnaire covers the dimensions: activity of daily living, psychological well-being, symptoms, relationship with friends and the family, relationship with the health care system, emotional and sexual life, coping, and rejection.

This cross-sectional study was conducted to analyze factors contributing to QoL in people with MS. The identification of these factors may provide therapeutic clues how to modify and improve QoL in people with MS.

2. Methods

This cross-sectional retrospective study was conducted at a single MS outpatient center in Germany (Neurologische Gemeinschaftspraxis Bonn) between April 2011 and December 2012. Due to the retrospective nature of the study, formal approval of the ethics committee was waived in accordance to current guidelines of the ethics committee of Ärztekammer Nordrhein. Adults (≥ 18 years) with relapsing-remitting (RRMS) and secondary progressive MS (SPMS) were included. No diagnostic or therapeutic measures exceeding the predefined clinical assessments were required, and treatment routine was not altered. All patients gave written informed consent prior to participation.

2.1. Participants

Patients fulfilling the diagnostic criteria of MS according to the revised McDonald criteria (Polman et al., 2011) were eligible for the study. Participants were recruited from the MS outpatient Center Neurologische Gemeinschaftspraxis Bonn. In order to obtain a representative real-world sample, no restrictions in EDSS score, treatment and disease duration were applied.

2.2. Study end points

Patient demographics, disease duration, clinical course of MS, EDSS, current MS treatment, and co-medication were documented by the treating neurologist by standardized questionnaires. Patient reported outcomes included QoL assessed by MuSIQoL, depression assessed by the Center for Epidemiological Studies Depression Scale (CES-D scale), and fatigue assessed by the Fatigue Scale for motor function and cognition (FSMC).

2.3. Evaluation of patient questionnaires

2.3.1. MuSIQoL

The MuSIQoL was applied using the validated (Flachenecker et al., 2011) German versions 5.2 and 3.5. Since the only difference between version 5.2 and 3.5 applies to the order of the questions and since the number of questions as well as their content are identical, both versions were pooled as no difference in the outcome was to be expected. This questionnaire comprises 31 items addressing nine dimensions: activity of daily living (ADL, eight items); psychological well-being (PWB, four items); symptoms (SPT, three items); relationship with friends (RFr, four items); relationship with the family (RFa, three items); satisfaction with health care (RHCS, three items); sentimental and sexual life (SSL, two items); coping (COP, two items) and rejection (REJ, two items). The negatively worded item scores were reversed so that higher scores indicated higher level of health related QoL. For each individual, the score of each dimension was obtained by computing the mean of the item scores of the dimension. If less than half of the items were missing, the mean of the non-missing items was substituted for the missing items. If half of the items or more were missing, the entire dimension was set to missing. All dimension scores were linearly transformed to a 0–100 scale. A global index score was computed as the mean of the following dimension scores (Simeoni et al., 2008).

2.3.2. CES-D scale

The validated German version of the CES-D scale (Hautzinger and Bailer, 1993) comprises 20 questions, each scored between 0 and 3 points. The CES-D score is calculated as the total sum of all points. A CES-D score ≥16 indicates a depression that requires treatment.

2.3.3. FSMC

The validated FSMC (Penner et al., 2009) comprises 20 statements concerning daily issues associated with fatigue. Ten statements are allotted to the subscale for cognition and the remaining ten statements are allotted to the subscale of motor function. Each statement is evaluated by the patients on a 5-point Likert scale (1 = strongly disagree, 2 = disagree, 3 = neither agree nor disagree, 4 = agree, 5 = strongly agree). This results in a maximum score of 50 per subscale, respectively a total score of 100. Cut-off values have been determined from a healthy sample to differentiate normal findings from pathological fatigue: Total FSMC, ≥43 mild, ≥53 moderate, ≥63 severe fatigue; cognitive subscale, ≥22 mild, ≥28 moderate, ≥34 severe cognitive fatigue; motor function subscale, ≥22 mild, ≥27 moderate, ≥32 severe motor fatigue.

2.4. Statistical analysis

Descriptive statistical analysis of all collected data was performed using the SPSS (IBM Deutschland GmbH, Ehningen, Germany) for Windows program package (Version 22.0). The Kolmogorov-Smirnov-Test was used to test for normal distribution. For continuous variables, statistic parameters including arithmetic mean, standard deviation and range were calculated. Frequency distributions for discrete variables were provided as percentage in relation to the total sample. Spearman correlation was applied to evaluate correlations between quality of life, disability status, depression, and fatigue. To identify associations, multivariate linear regression was applied using quality of life as dependent variable and clinical course, smoker status, BMI, physical activity, family status, occupation, EDSS score, presence of depression, and presence of fatigue as independent variables. Missing data were not imputed. All tests were two-sided, and significance was declared at the 0.05 level. EDSS stratified regression analyses were performed post-hoc.

3. Results

3.1. Patients and baseline characteristics

830 patients were screened for eligibility. In total 260 patients in whom all questionnaires (MuSIQoL, CES-D, FSMC) were available, were finally enrolled into this cross-sectional study and included in the analysis. The majority of patients had RRMS (66.9%). The median EDSS was 3.0 (range 0.0–8.5) and the median duration of disease was 8.2 years (range 0–40.8). The majority of patients (79.6%) were female. Baseline characteristics are summarized in Table 1. A total of 56.5% of patients were in employment, 31.2% worked full time and 10.4% worked physically. About one third (31.2%) received rehabilitation measures, among which physiotherapy was most common (25.0%). 54 Patients (20.8%) applied relaxation measures on a regular basis, predominantly yoga (4.6%), Qi Gong (3.1%) and autogenic training (2.7%).

189/260 (72.3%) of patients received immunomodulatory or immunosuppressive and 110/260 (42.3%) symptomatic medical treatment (Table 2).

3.2. Patient reported outcomes (MusiQoL, CES-D, FSMC)

The MusiQoL index score was evaluable for 202/260 (77.7%)

Table 1
Baseline demographics.

Parameter	Total (n = 260)	RRMS (n = 174)	SPMS (n = 64)
Gender, n (%)			
Female	207 (79.6%)	139 (79.9%)	51 (79.7%)
Male	53 (20.4%)	35 (20.1%)	13 (20.3%)
Age (years)			
Mean ± SD	44.5 ± 11.1	40.8 ± 9.7	51.7 ± 9.6
Median (Range)	44 (17–77)	42.0 (17–77)	51.5 (26–73)
BMI, n (%)			
$< 20\,\mathrm{kg/m^2}$	32 (12.3%)	19 (10.9%)	11 (17.2%)
$20\text{–}25\,\mathrm{kg/m^2}$	112 (43.1%)	75 (43.1%)	29 (45.3%)
$25\text{–}30\,\mathrm{kg/m^2}$	53 (20.4%)	34 (19.5%)	15 (23.4%)
$> 30\,\mathrm{kg/m^2}$	43 (16.5%)	32 (18.4%)	5 (7.8%)
Unknown	20 (7.7%)	14 (8.0%)	4 (6.3%)
Family status, n (%)			
Single	68 (26.2%)	41 (23.6%)	22 (34.4%)
Married/Partnership	188 (72.3%)	130 (74.7%)	42 (65.6%)
Unknown	4 (1.5%)	3 (1.7%)	0 (0.0%)
Occupation, n (%)			
Working	147 (56.5%)	119 (68.4%)	18 (28.1%)
Full time	81 (21.2%)	70 (40.2%)	6 (9.4%)
Half-time	61 (23.5%)	46 (26.4%)	11 (17.2%)
Desk job	92 (35.4%)	76 (43.7%)	10 (15.6%)
Physically demanding work	27 (10.4%)	20 (11.5%)	6 (9.4%)
Permanenty unable to work	55 (21.2%)	21 (12.1%)	28 (43.8%)
Retired	22 (8.5%)	6 (3.4%)	11 (17.2%)
Housewife/-husband	18 (6.9%)	13 (7.5%)	5 (7.8%)
Seeking work	11 (4.2%)	9 (5.2%)	1 (1.6%)
Unknown	7 (2.7%)	6 (3.4%)	1 (1.6%)
Smoker, n (%)	69 (26.5%)	50 (28.7%)	17 (26.6%)
Physical activities, n (%)			
Never	55 (21.2%)	30 (17.2%)	14 (21.9%)
Occasionally	85 (32.7%)	61 (35.1%)	20 (31.3%)
Regularly	113 (43.5%)	78 (44.8%)	28 (43.8%)
Unknown	7 (2.7%)	5 (2.9%)	2 (3.1%)
Rehabilitation measures, n (%)	81 (31.2%)	50 (28.7%)	24 (37.5%)
Physiotherapy	65 (25.0%)		
Occupational Therapy	4 (1.5%)		
Others	9 (3.5%)		
Regular relaxation measures, n (%)	54 (20.8%)	29 (16.7%)	20 (31.3%)
Yoga	12 (4.6%)		
Qi Gong	8 (3.1%)		
Autogenic Training	7 (2.7%)		
Others	24 (9.2%)		
Duration of disease (years)			
Mean ± SD	10.6 ± 8.7	7.7 ± 6.0	17.7 ± 10.3
Median (Range)	8.2 (0–40.8)	6.3 (0.2–29.5)	17.5 (0.0–40.8)
Clinical course, n (%)			
Relapse-remitting MS	174 (66.9%)	174 (100.0%)	64 (100.0%)
Primary progressive MS	13 (5.0%)		
Secondary progressive MS	64 (26.6%)		
Unknown	9 (3.5%)		
EDSS			
Mean ± SD	3.3 ± 1.9	2.4 ± 1.3	5.0 ± 1.5
Median (Range)	3.0 (0.0–8.5)	2.0 (0.0–6.5)	5.0 (2.5–8.5)

patients. With regard to each single dimensions, there were missing values for ADL (n = 5), PWS (n = 5), SPT (n = 1), RFr (n = 17), RFa (n = 12), SSL (n = 21), COP (n = 33), REJECT (n = 35) and RHCS (n = 1).The mean index score was 73.9 ± 11.3. The CES-D was evaluable for 249/260 patients (95.8%) 93/249 patients (37.3%) fulfilled the diagnostic criteria of depression as assessed by the CES-D. Among the 93 patients with a diagnosis of depression, only 16 patients were treated with antidepressants. The FSMC was evaluable in 254/260 patients (97.7%). 29/254 (11.4%) had mild, 33/254 (13.0%) moderate and 115/254 (45.3%) severe fatigue.

Table 2
Current treatment modalities.

Therapy, n (%)	Total (n = 260)	RRMS (n = 174)	SPMS (n = 64)
Immunomodulators and Immunosuppressants	188 (72.3%)	155 (89.1%)	27 (42.2%)
Recombinant Interferon beta	77 (29.6%)	69 (39.7%)	6 (9.4%)
Glatiramer acetate	48 (18.5%)	45 (25.9%)	2 (3.1%)
Natalizumab	32 (12.3%)	28 (16.1%)	4 (6.3%)
Mitoxantrone	16 (6.2%)	3 (1.7%)	12 (18.8%)
Fingolimod	13 (5.0%)	12 (6.9%)	1 (1.6%)
Azathioprine	5 (1.9%)	3 (1.7%)	1 (1.6%)
Rituximab	2 (0.8%)	1 (0.6%)	1 (1.6%)
Symptomatic therapy	110 (42.3%)	52 (29.9%)	42 (65.6%)
Anti-neuropathic drugs	44 (16.9%)		
Muscle relaxants	35 (13.5%)		
Psychiatric medications	29 (11.2%)		
Antiepileptic drugs	20 (7.7%)		
Analgesics/NSAIDs	15 (5.8%)		
Others	29 (11.2%)		

Multiple answers were possible.

3.3. EDSS by subgroup

As expected, patients with SPMS had statistically significantly higher disability than patients with RRMS (5.0 ± 1.5 vs. 2.4 ± 1.3; $p < 0.001$). Employed patients had a lesser degree of disability when compared to patients who were retired or permanently unable to work (2.4 ± 1.4 vs. 43 ± 1.9; $p < 0.001$). Singles had higher EDSS score than patients living in a partnership (3.6 ± 2.0 vs. 3.1 ± 1.8; $p = 0.048$). Smoking status, BMI and physical activity had no impact on the EDSS.

3.4. Quality of life

There was a statistically significant negative correlation ($r = 0.408$, $p < 0.001$) between EDSS score and QoL (Fig. 1). The statistically significant negative correlation between EDSS score and QoL was reproduced in all subgroups, except for patients with SPMS and non-employed patients. QoL was statistically significantly higher in patients with RRMS when compared to those with SPMS ($p < 0.001$), in those who were physically active versus those who were inactive ($p = 0.004$), in patients living in a partnership versus those living as singles ($p = 0.019$), and in those being employed versus those who were not working ($p < 0.001$). Smoking, BMI, and current medical MS treatment had no impact on QoL.

3.5. Depression

There was a statistically significant positive correlation ($r = 0.269$, $p < 0.001$) between the EDSS and the CES-D score. The statistically significant positive correlation between the EDSS and the CES-D score was confirmed for all subgroups except for patients with SPMS, smokers, and non-employed patients. The CES-D score was also negatively correlated with QoL ($r = -0.707$, $p < 0.001$), i.e. patients without depression had a lower EDSS score and higher QoL (**Fig. 2A**), whilst patients with depression had lower QoL and a higher EDSS score (**Fig. 2B**). Depression was statistically significantly more frequent in patients with SPMS as compared to those with RRMS ($p = 0.014$), in patients exercising irregularly or not at all as opposed to those who were physically active ($p = 0.020$), and in employed patients as compared to non-employed or retired patients ($p < 0.001$). Smoking status, BMI, family status, and the current medical MS treatment had no impact on the occurrence of depression.

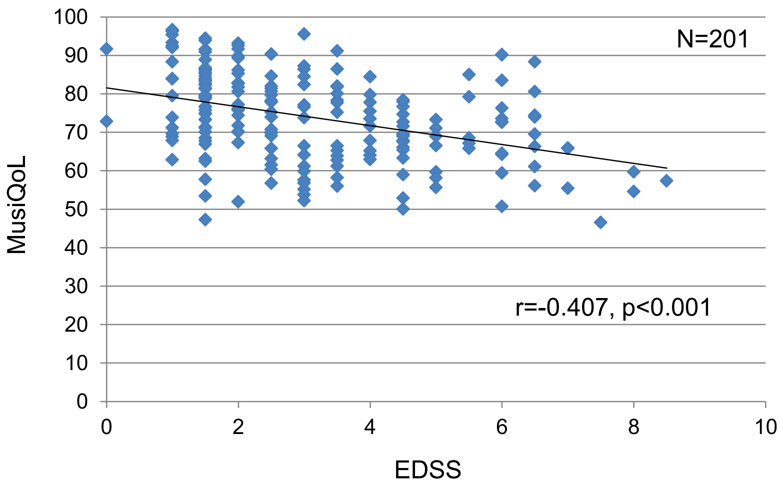

Fig. 1. EDSS scores are negatively correlated ($r = 0.408, p < 0.001$) with QoL; $n = 201$ refers to the number of patients for whom both the MusiQoL index score and the EDSS score were available. Expanded Disability Status Scale (EDSS); Quality of life (QoL).

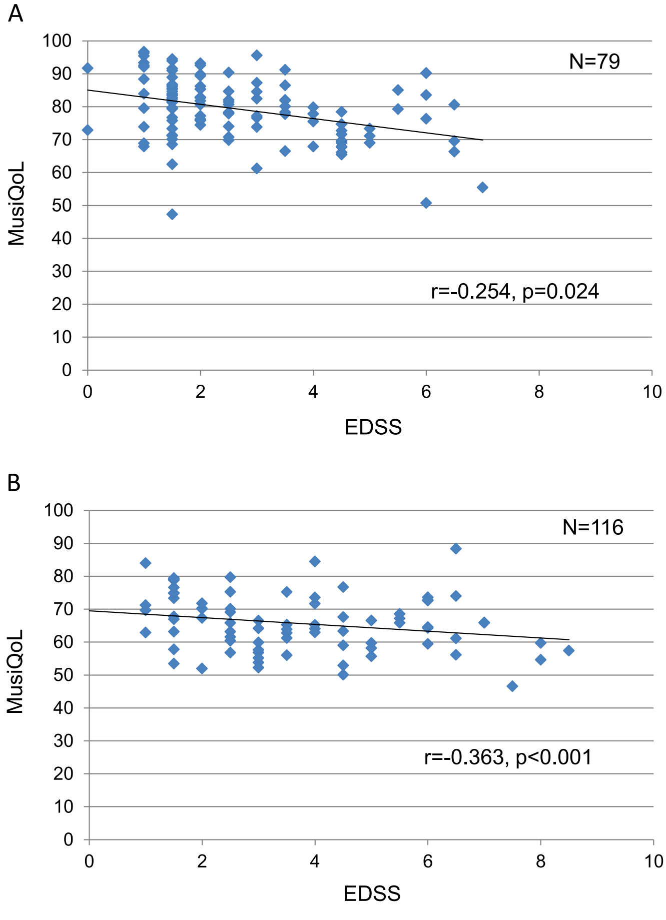

Fig. 2. (A): Patients without depression (CES-$D < 16$) have lower EDSS scores and higher QoL as assessed by MusiQoL; $n = 79$ refers to the number of patients for whom both the MusiQoL index score and the EDSS score were available and who did not have depression according to the CES-D scale. Center for Epidemiological Studies Depression Scale (CES-D scale); Expanded Disability Status Scale (EDSS); Quality of life (QoL); Multiple Sclerosis International QoL Questionnaire (MuSIQoL) **(B):**Patients with depression (CES-$D \geq 16$) have higher EDSS scores and lower QoL assessed by MusiQoL; $n = 116$ refers to the number of patients for whom both the MusiQoL index score and the EDSS score were available and who had depression according to the CES-D scale. Center for Epidemiological Studies Depression Scale (CES-D scale); Expanded Disability Status Scale (EDSS); Quality of life (QoL); Multiple Sclerosis International QoL Questionnaire (MuSIQoL).

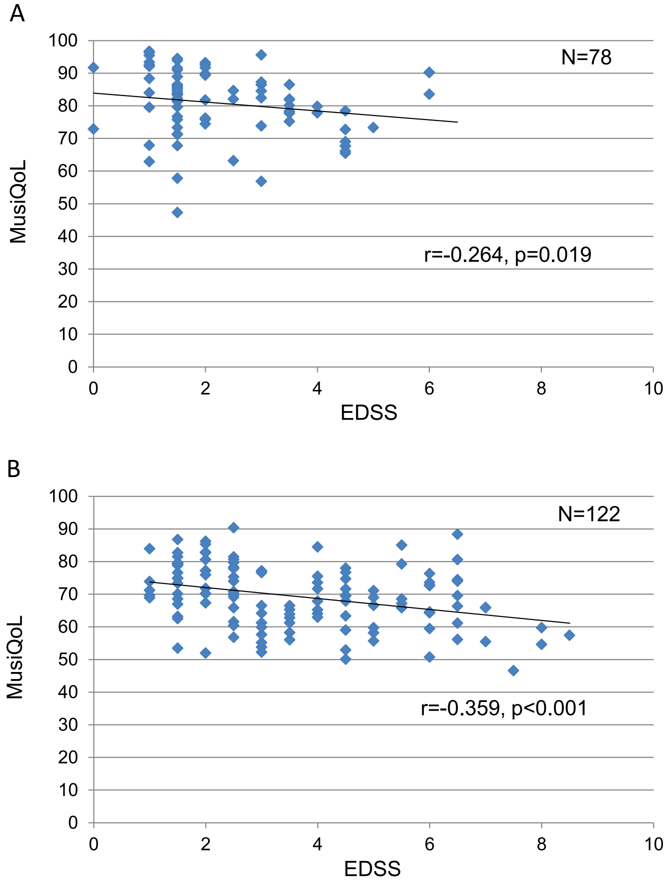

Fig. 3. (A): Patients without fatigue (FSMC < 43) have lower EDSS scores and higher QoL as assessed by MusiQoL; $n = 78$ (Fig. 3A) refers to the number of patients for whom both the MusiQoL index score and the EDSS score were available and who did not have fatigue according to the FSMC. Fatigue Scale for motor function and cognition (FSMC); Expanded Disability Status Scale (EDSS); Quality of life (QoL); Multiple Sclerosis International QoL Questionnaire (MuSIQoL) **(B):** Patients with fatigue (FSMC ≥ 43) have higher EDSS scores and lower QoL as assessed by MusiQoL Fatigue Scale for motor function and cognition (FSMC); $n = 122$ refers to the number of patients for whom both the MusiQoL index score and the EDSS score were available and who had fatigue according to the FSMC. Expanded Disability Status Scale (EDSS); Quality of life (QoL); Multiple Sclerosis International QoL Questionnaire (MuSIQoL).

3.6. Fatigue

Fatigue was positively correlated with EDSS ($r = 0.405, p < 0.001$) and negatively correlated with QoL ($r = 0.568$, $p < 0.001$), i.e. patients without fatigue had a lower EDSS score and higher QoL (Fig. 3A), whereas patients with fatigue had lower QoL and a higher EDSS score (Fig. 3B). Fatigue was statistically significantly more pronounced in patients with SPMS as compared to those with RRMS ($p < 0.001$) and in non-employed as opposed to employed patients ($p < 0.001$). Of note, patients with BMI > 25 kg/m2 exhibited statistically significantly more severe fatigue when compared to patients with BMI < 25 kg/m2 ($p = 0.030$). However, this difference was solely attributable to motor fatigue ($p = 0.026$), so that there was no impact of BMI on cognitive fatigue ($p = 0.071$). Conversely, smoking affected cognitive fatigue ($p = 0.050$) but not motor fatigue ($p = 0.337$). Physical activity, family status, and current medical MS treatment did not affect fatigue.

3.7. Associations with QoL

Using linear regression, the presence of depression was most strongly associated with reduced QoL. Other associations with less pronounced statistical significance were fatigue, family status, physical activity, and the occupational status (Fig. 4A). The clinical course of disease, smoking status, BMI, and the EDSS were not associated with QoL. The association of the EDSS with QoL increased considerably when linear regression was performed in a subgroup of patients with an EDSS score ≤5.0 (Fig. 4B). Linear regression analysis using a restricted number of variables (MusiQoL being the dependent variable and depression, fatigue and EDSS score the independent variables) demonstrated that all three independent variables including the EDSS were of associated with QoL (Fig. 4C). The association of the EDSS with QoL decreased when the occupational status was added as an independent variable (Fig. 4D).

4. Discussion

This cross-sectional study investigated factors affecting QoL in people with MS under real-life conditions. For this purpose clinical data from 260 patients obtained from the database of a single Neurological MS outpatient center in Germany were analyzed including patient reported outcomes such as QoL, fatigue and depression. Patient demographics were comparable to those in other MS studies (Jelinek et al., 2016; Jones et al., 2016).

4.1. EDSS

As expected, the EDSS was negatively correlated with QoL in this patient population. However, subgroup analysis revealed that this correlation held only true for patients with RRMS, but not for those with SPMS. In line with this finding, EDSS was only associated with QoL in patients with an EDSS score ≤5.0, but not in those with an EDSS score > 5.0, i.e. the majority of patients with SPMS. There is broad consensus that the EDSS does not adequately reflect patients' perceptions and the impact of their symptoms (Hemmett et al., 2004). Our data confirm this observation especially in patients with more advanced disease. This inconsistency may be explained by the different impact that disability progression exerts on individual patients. For example, patients with less advanced disability might perceive the impact of progressive motor or coordinative deficits on QoL as more serious than patients with an already more pronounced disability, i.e. with EDSS scores > 5.0 or SPMS. Comparable results were demonstrated in a German survey that assessed QoL by the Multiple Sclerosis Quality of Life (MSQOL) – 54 questionnaire. In this study MS patients were allocated to three subgroups according to different stages of disability. QoL was comparable in patients with EDSS steps 4.5–6.5 and EDSS ≥7 when compared to those with EDSS ≤4 and EDSS steps 4.5–6.5, indicating a non-linear relationship between disability and QoL in MS patients (Twork et al., 2010). Similarly, the difference in HRQoL between patients who used a walking aid and wheelchair-bound patients was smaller than that between patients walking unaided and those patients using a walking aid (Vickrey et al., 1995). Finally, it was demonstrated that reduced QoL as assessed by the SF-36 was negatively correlated with the EDSS but mainly in the subdomain physical functioning which is best explained by the fact that the EDSS score heavily depends on mobility, whereas the negative correlation of QoL in other subdomains of the SF-36 were rather dependent on the presence of depression (Patti et al., 2003).

4.2. Depression

In line with this finding, the present study demonstrates that QoL in MS patients is in particular negatively correlated with depression and fatigue. With depression being known to be common in MS patients (Marrie et al., 2009) and national guidelines recommending early screening (Deutsche Gesellschaft für Neurologie 2012), depression was formally assessed in this study via standardized questionnaires (Oken et al., 2004). Nonetheless, the data presented here reveal a striking discrepancy between patients being treated with antidepressants and those fulfilling the criteria of depression according to the CES-D indicating that depression was both underdiagnosed and undertreated. In line with this interpretation, depression had been documented as a relevant comorbidity in only 13.5% of patients. However, since the present study only recorded medical treatment of depression while no information was obtained on non-medical treatment such as psychotherapy, the number of depressed patients left untreated might be less. A recent survey reported that 65% of people with MS and concomitant depression were treated with antidepressants (Raissi et al., 2015). Conversely, only a minority of patients received antidepressants in the MS population presented here. Although not systematically investigated, patients' refusal to be treated with antidepressants may be an important issue as previously shown (Sollom and Kneebone, 2007). On the other hand, subtle symptoms of depression may remain unnoticed by either patient or neurologist. Therefore, inadequate treatment of depression is of utmost clinical importance since – according to the results presented here and in accordance with previous reports (Göksel Karatepe et al., 2011; Mohr et al., 1997) – depression has been most strongly negatively associated with QoL in people with MS (D'Alisa et al., 2006). Furthermore, depression is known to reduce adherence to disease-modifying treatment (Mohr et al., 1997) and to increase the risk of suicide (Feinstein, 2002). Therefore, applying standard questionnaires such as the CES-D to detect depression should be used as a clinical routine in people with MS in order to reveal this important co-morbidity as early as possible and to offer adequate treatments for the affected individuals. Depression has previously been linked to treatment with recombinant interferon beta (The IFNB Multiple Sclerosis Study Group 1993). However, in line with a recent database analysis (Mirsky et al., 2016), the results presented here reveal no association between treatment with recombinant interferon beta and the prevalence of depression when compared to other disease-modifying drugs.

4.3. Fatigue

The percentage of patients affected by fatigue in the present cohort was within the range of 50–90% commonly reported in people with MS (Colosimo et al., 1995; Fisk et al., 1994). In accordance with published data, fatigue was strongly associated with reduced QoL (Garg et al., 2016), and there was a strong correlation between fatigue and disability. Linear regression analysis demonstrated that fatigue and depression were independently associated with QoL in people with MS.

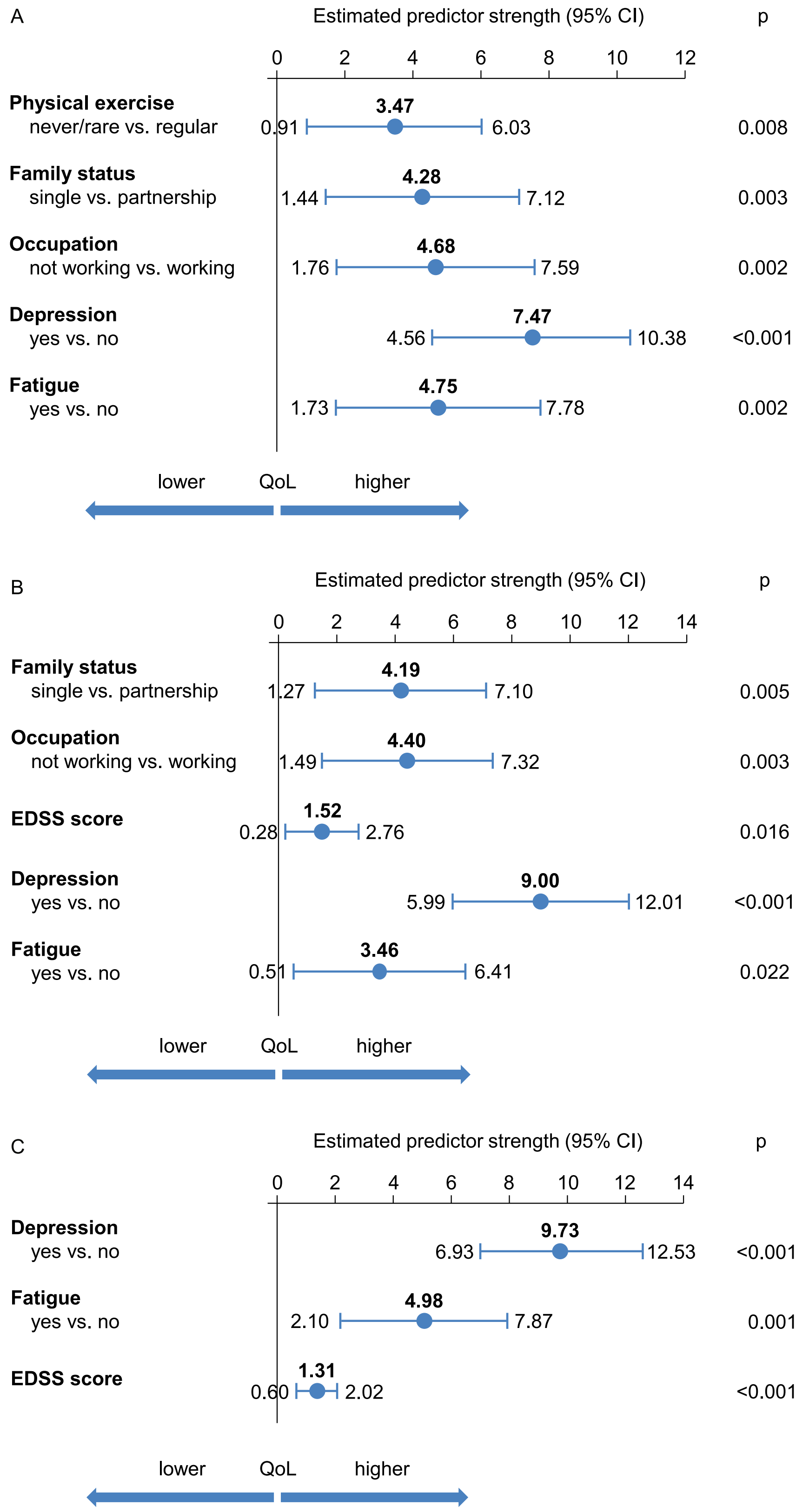

Fig. 4. **(A):**Using linear regression, depression is most strongly associated with reduced QoL. Fatigue, family status, physical activity, and the occupational status are also associated with reduced QoL, albeit to a lesser extent. Quality of life (QoL) **(B):**Linear regression in a subgroup of patients with an EDSS score ≤5.0 reveals an association of the EDSS with QoL. Expanded Disability Status Scale (EDSS); Quality of life (QoL) **(C):**Linear regression analysis using a restricted number of variables (MusiQoL being the dependent variable and depression, fatigue and EDSS score the independent variables) reveals that all three independent variables including the EDSS were are associated with QoL. Multiple Sclerosis International QoL Questionnaire (MuSIQoL); Quality of life (QoL) **(D):** The association of the EDSS with QoL decreases when the occupational status is added as an independent variable. Quality of life (QoL).

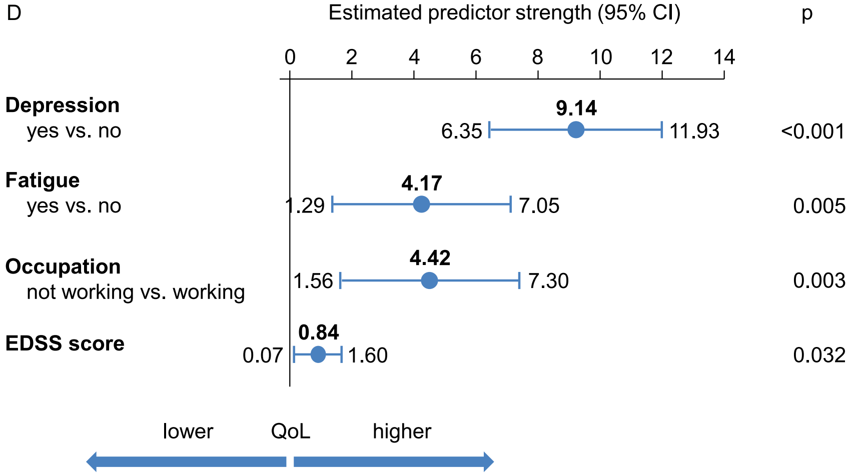

Fig. 4. (*continued*)

4.4. Occupational status

Modifiable lifestyle factors also exert a considerable impact on QoL. For example, singles had lower QoL when compared to patients living in a relationship. As a possible explanation singles may tend to withdraw from social life representing a potential predictor of depression (Feinstein, 2002). Disease progression is associated with increased levels of unemployment (Simmons et al., 2010). Of note, the data presented here indicate that employed patients (half or full-time) had higher QoL compared to non-employed or retired patients. This somewhat surprising finding might indicate that finding solutions to adapt the occupational status of an individual patient according to his physical and mental capacity may help to maintain QoL. However, since almost all patients with an EDSS score ≥5.5 were unemployed or retired, the predictive value of the occupational status with regard to QoL remains restricted to a subgroup of patients with mild to moderate disability.

The results of the study presented here suggest that patients participating in regular physical exercise had higher QoL than patients who were less active or preferred a sedentary life-style. While MS patients have been traditionally discouraged from physical exercise (Sutherland and Andersen, 2001), more recent studies have shown that endurance and resistance training may improve fatigue, gait parameters and QoL (Oken et al., 2004; White and Dressendorfer, 2004; Dalgas et al., 2008; Schmidt and Wonneberger, 2014; Wonneberger and Schmidt, 2015; Dalgas et al., 2010; Rasova et al., 2006; Mostert and Kesselring, 2002; Petajan et al., 1996). Based on these studies, recommendations for physical exercise in people with MS have been published (Dalgas et al., 2009; Latimer-Cheung et al., 2013).

4.5. Limitations of the study

This study is limited by its observational cross-sectional design which allows the identification of associations, but excludes the conclusion of causal relationships. The strength of this study is represented by the use of validated questionnaires for the assessment of patient reported outcomes, in particular the use of an MS-specific questionnaire for the assessment of QoL, which reflects the perspectives of people with MS more accurately than generic tools such as SF-36 or the EQ-5D. The MusiQoL has been validated internationally (Simeoni et al., 2008) as well as for German MS patients (Flachenecker et al., 2011). It has become a widely accepted instrument easily applicable in clinical practice. Although patients with more advanced disease may suffer from more advanced cognitive impairment affecting adequate self-assessment, a cross-sectional study demonstrated that there was no difference between patients with cognitive impairment and non-impaired patients using the MusiQoL (K Baumstarck et al., 2012; K Baumstarck et al., 2012). Conducting a cross-sectional study in a single center may cause selection bias but alleviates consistent data acquisition. The study cohort investigated comprises people with MS with a broad range of disability (EDSS score 0.0 to 8.5). Patient demographics correspond to those seen in other studies conducted in MS patients suggesting that a representative sample of MS patients was analyzed.

5. Conclusions

The data of this cross-sectional study confirm that depression, fatigue, family status, physical activity, and occupation are closely associated with QoL in people with MS. Of note, QoL in more advanced stages of disease (i.e. EDSS score > 5.0) was not associated with disability. Therefore, apart from treatments targeting disability progression, early diagnosis and consequent treatment of depression, regular physical exercise, and maintaining patients employed in accordance with their physical and mental disabilities, may be of critical importance to improve QoL in MS patients.

Declaration of Competing Interest

Competing interests: P. Jöstingmeyer was contracted by Neurologische Gemeinschaftspraxis Bonn (Dr. S. Schmidt) for data analysis and medical writing services. S. Schmidt received speaker's honoraria from and served on advisory boards for Bayer Vital, Teva, Roche, Merck Serono, Novartis, Biogen, Genzyme.

Authors' contributions

PJ performed the statistical analysis and contributed to the interpretation of the data. She was a major contributor in writing the manuscript. SSCH was responsible for data collection, patient ascertainment, interpretation of the data as well as the preparation of the manuscript. Both authors read and approved the final manuscript.

We hereby declare that the manuscripts has not been published previously in print or electronic format and is not under consideration by another publication or electronic medium.

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