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Preference-based Health status in a German outpatient cohort with multiple sclerosis

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Abstract

Background: To prospectively determine health status and health utility and its predictors in patients with multiple sclerosis (MS).

Methods: A total of 144 MS patients (mean age: 41.0 ± 11.3y) with different subtypes (patterns of progression) and severities of MS were recruited in an outpatient university clinic in Germany. Patients completed a questionnaire at baseline (n = 144), 6 months (n = 65) and 12 months (n = 55). Health utilities were assessed using the EuroQol instrument (EQ-5D, EQ VAS). Health status was assessed by several scales (Expanded Disability Severity Scale (EDSS), Modified Fatigue Impact Scale (M-FIS), Functional Assessment of MS (FAMS), Beck Depression Inventory (BDI-II) and Multiple Sclerosis Functional Composite (MSFC)). Additionally, demographic and socioeconomic parameters were assessed. Multivariate linear and logistic regressions were applied to reveal independent predictors of health status.

Results: Health status is substantially diminished in MS patients and the EQ VAS was considerably lower than that of the general German population. No significant change in health-status parameters was observed over a 12-months period. Multivariate analyses revealed M-FIS, BDI-II, MSFC, and EDSS to be significant predictors of reduced health status. Socioeconomic and socio-demographic parameters such as working status, family status, number of household inhabitants, age, and gender did not prove significant in multivariate analyses.

Conclusion: MS considerably impairs patients' health status. Guidelines aiming to improve self-reported health status should include treatment options for depression and fatigue. Physicians should be aware of depression and fatigue as co-morbidities. Future studies should consider the minimal clinical difference when health status is a primary outcome.

Keywords: Health status, FAMS, EuroQol, Multiple sclerosis, Germany, Depression, Fatigue, Quality of life

Introduction

Multiple sclerosis (MS) is a demyelinating autoimmune disease and a common cause of severe neurological disability in young adults in the Western world, presenting with diverse and often unpredictable symptoms and an uncertain course of progression. According to recent estimates, 1.3 million patients suffer from MS worldwide with 0.08-0.13% of the German population being affected [1-3].

The subtypes are defined by their pattern of progression; approximately 10-20% of MS patients suffer from primary progressive disease (PPMS), which has a slightly later onset compared to the other subtypes. The long-term prognosis remains generally poor; 15 years after diagnosis, over

80% of patients have functional and/or cognitive limitations and 50-60% require assistance to walk.

Health status (HS) in MS has been intensively studied in the past two decades and approximately 20 disease-specific health-status measures have been developed [4]. Predictors of health status reveal that physical and psychological symptoms are interrelated and that both are important. Depression is one of the strongest psychiatric predictors of poor health, as well as cognitive impairment and fatigue (for a review see e.g. [5]).

Psychological and behavioural symptoms have long been disregarded and undertreated in patients with MS [6]. The burden of living with MS affects physical and mental health and has negative effects on work life [7]. Neuropsychiatric symptoms such as fatigue present early in the course of disease, and specific cognitive impairments can

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be observed in more than half of patients in the early stages [8,9]. Even in patients with short (less than 2 years) disease durations, discrete impairment of cognitive function may be observed in up to 60% of patients upon neuropsychological testing [10]. Symptoms of depression also present early in the course of disease and affect cognitive performance. Within a year of diagnosis, 48% of patients and 46% of their relatives show clinically relevant anxiety, depression or distress [11,12].

Therapies that are newly available or undergoing clinical trials may place an economic strain on health-care systems. Therefore, one important aspect in the appraisal of new treatments is the effectiveness at improving health status.

The aim of this study was to systematically explore factors associated with MS and their contribution to decreases in patient-reported health status. To address this question, we used a longitudinal study design in which patients were repeatedly questioned over a 12-month period. We used the EuroQoL (EQ-5D) instrument and its Visual Analogue Scale (EQ VAS) [13] as well as the disease-specific Functional Assessment of MS (FAMS) [14] to quantify preference-based measures.

Patients and methods

Patient selection

Patients were recruited in the Department of Neurology, Philipps-University Marburg from October to December 2007 for baseline assessments. A convenience sample was recruited from 186 patients admitted to the Department of Neurology during that time. 77.4% of these patients participated. Patients were included if they fulfilled the McDonald diagnostic criteria for MS [15,16]. The case report form (CRF) consisted of two parts: one to be completed by the examining physician and one to be completed by the patient. Patients could complete their part of the CRF during their hospital stay or return it later by mail. Patients were assessed three times: at baseline ($n = 144$) and at follow-up assessments after 6 ($n = 65$) and 12 months ($n = 55$). The local ethics committee of Philipps-University Marburg approved this study and all patients gave written consent prior to participation.

Measurements

The questionnaire consisted of an evaluation of the socio-demographic, clinical, and health status of patients suffering from MS. In addition, health-care resource utilisation for MS and indirect costs were examined.

In the patients' part of the CRF, health status was first evaluated by an MS-specific measure: the Functional Assessment of MS (FAMS) which consists of four subscales covering mobility ("I have trouble walking"), symptoms ("I have pain"), emotional well-being ("I am able to enjoy

life"), and general contentment ("I have accepted my illness") with seven items each and scores ranging from 0 (poor QoL) to 28 (high QoL), as well as a thinking-and-fatigue subscale ("I feel tired") that contains 8 items and is scored from 0 to 36. The FAMS sum score has a maximum score of 172 [14].

Second, health status was measured by the generic EuroQoL instrument. Applicable to a wide range of health conditions and treatments, EQ-5D generates a health profile, but is also capable of expressing health status as a single index value (utility value). Thus, it can be used for clinical and economical evaluations of health care. The questionnaire consists of five questions representing five different dimensions ("Mobility", "Self-Care", "Usual Activities", "Pain/Discomfort", and "Anxiety/Depression"). An index score can be derived by time-trade-off methods based on a recent European study [13]. The second part of the EuroQoL instrument consists of a visual analogue scale (EQ VAS) on which respondents rate their subjective health status on a scale from 0 (poorest) to 100 (best imaginable) [13].

The impact of fatigue was assessed using the Modified Fatigue Impact Scale (M-FIS) [17]. The scale consists of 21 items, with 10 items related to mental fatigue and 11 items related to physical and social fatigue. The scoring ranges between 0 and 82, with higher scores reflecting greater impact. In the literature, a cut-off value of 38 has been used to distinguish fatigued from non-fatigued patients [18,19].

In addition, depression was assessed using the Beck Depression Inventory (BDI-II), a 21-item scale used to measure self-reported severity of depression. According to common conventions, the BDI sum score was categorised into five groups: no (0–8 points), minimal (9–13 points), mild (14–19 points), moderate (20–28 points), and severe (>28 points) depressive symptoms [20,21].

The second part of the CRF was to be completed by the examining physician and concerned the pattern of progression (MS subtype), comorbidities, neuropsychiatric symptoms, and the assessment of disease severity by the Expanded Disability Status Scale (EDSS) [22] and the MS Functional Composite (MSFC) [23].

The EDSS is an MS-specific scale consisting of a neurological assessment quantifying disability in eight functional systems (e.g., sensory functions, cerebellar functions). The assessment of these functional systems yields a sum score ranging from 0 (no neurological impairment) to 10 (death due to MS) [24].

The MS Functional Composite (MSFC) comprises quantitative functional measures of three key clinical dimensions of MS: leg function/ambulation, arm/hand function, and cognitive function. Scores on component measures are converted to standard scores (z-scores), which are averaged to yield a single MSFC score [25].

Statistical analysis

Results are presented as means \pm SD and median or percentages as appropriate. Groups were compared by the appropriate parametric and nonparametric tests (*t*-test, Mann–Whitney-U test, Kruskal-Wallis test). The baseline investigation and the follow-up investigations were compared using repeated-measures analysis of variance. Missing values were handled by pairwise deletion. The potential changes in the five EQ-5D domains were analysed using univariate repeated-measurement tests. Variables were screened for impact on health status using the Spearman rank correlation ($p = 0.10$). From the variables that proved significant in bivariate analyses, reasonable variables were chosen for multiple linear regression with EQ VAS, EQ-5D index score, and FAMS sum score as dependent variables. We used a stepwise forward mode to include independent predictors with a significance level of $\alpha = 0.05$. Uni- and multivariate logistic regression analyses were applied to test for significant predictors of single dimensions of the EQ-5D index. The variables for the five dimensions were dichotomised into “having problems” or “having no problems” (e.g., “no problems with daily activities” was represented as 0, “some problems” or “severe problems with daily activities” was represented as 1). Statistical analyses were performed with the SPSS 19.0 software package (IBM Inc., Armonk, NY.).

Results

Clinical and socio-demographic characteristics

A total of 144 MS patients were evaluated in this study: 99 women (68.3%) and 45 men (31.7%). At the 6-month follow-up, 65 patients remained in the study; at the 12-month follow-up, 55 patients remained. Furthermore,

7 patients did not complete the demographic questionnaire at baseline and were therefore excluded from further analyses. The patients’ demographic and clinical data are presented in Table 1.

Most of the patients lived with partners (76.1%); 45% had a secondary school education (or higher); and 38% stated that their career advancement was impaired by MS. In addition, 37% claimed that due to the disease, they earned less than their unaffected colleagues.

Health status

At baseline, the distribution of patients among the different subtypes of MS was as follows: 66.8% relapsing-remitting multiple sclerosis (RRMS), 27% secondary progressive multiple sclerosis (SPMS), and 6.2% primary progressive multiple sclerosis (PPMS). Within the 12-months observation period, the median EDSS score increased from 3.50 (range 0 to 8.5) to 4.00 (range 0 to 9.00) with 60.3% of patients progressing to higher EDSS stages. The mean total MSFC z-score improved minimally, from -0.100 (SD: 0.741) to 0.199 (SD: 0.682) during the 12-month observation period (Table 2). SPMS and PPMS patients were older and had worse disability scores (EDSS and MSFC, Table 1) than RRMS patients at baseline.

The PPMS group was the most impaired group by fatigue and depression. Clinically relevant depressive symptoms, as measured by BDI-II, were very common in the study population (Table 2). In all, 61 patients (41.5%) had depressive symptoms (BDI sum score >13 pts); 12 (8.2%) thereof had severe depressive symptoms at baseline. Depressive symptoms were significantly positively correlated with Expanded Disability Status (Jonckheere-Terpstra $J = 5163$, $z = 284.7$, $r = 23.7$, $p =$

Table 1 Demographic and clinical data of the study sample at baseline (n = 137)

Variable	RRMS % (n)	SPMS % (n)	PPMS % (n)	Total % n
Females % (n)	67.7 (63)	29.1 (27)	3.2 (3)	100 (93)
Males % (n)	65.9 (29)	25.0 (11)	9.1 (4)	100 (44)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age (years)	36.4 (9.7)	50.4 (8.9)	50.5 (10.4)	41.1 (11.3)
Disease duration (years)	5.3 (5.1)	13.6 (8.1)	8.3 (11.7)	7.3 (7.2)
MSFC Z-composite score	0.100 (0.632)	-0.670 (0.654)	-0.882 (1.128)	-0.121 (0.750)
M-FIS sum score	33.2 (20.4)	44.1 (13.7)	40.6 (15.2)	36.4 (18.6)
FAMS sum score	120.3 (33.2)	101.7 (26.3)	98.1 (27.6)	113.3 (32.4)
EQ-5D index score	0.83 (0.18)	0.64 (2.78)	0.64 (0.26)	0.77 (0.23)
EQ VAS	68.4 (18.2)	50.6 (18.4)	44.8 (20.1)	62.0 (20.5)
BDI sum score	14.7 (10.2)	14.5 (8.6)	16.2 (11.2)	14.7 (10.4)
EDSS score	2.6 (1.5)	5.4 (1.5)	5.9 (1.2)	3.5 (2.0)

MSFC: Multiple Sclerosis Functional Composite, M-FIS: Modified Fatigue Impact Scale, FAMS: Functional Assessment in Multiple Sclerosis, EQ-5D: EuroQoL, EQ VAS: Visual Analogue Scale, BDI: Beck Depression Inventory II, EDSS: Extended Disability Symptom Scale; SD: standard deviation.

Table 2 Clinical characteristics of patients with multiple sclerosis included in this study and results of EDSS, EQ-5D, FAMS, MSFC, M-FIS, and BDI-II at baseline, 6 months and 12 months follow-up investigation

Variable	Baseline	6 months	Δ Baseline – 6 M	12 months	Δ Baseline – 12 M
	Median (range)	Median (range)	p-value	Median (range)	p-value
	Mean ± SD	Mean ± SD	p-value	Mean ± SD	p-value
EDSS (N = 55)	3.50 (0–8.5)	3.25 (0–8.0)	n.s.	4.0 (0–9.0)	<0.001
EuroQol					
EQ-5D Index Score (N = 56)	0.79 ±0.20	0.79 ±0.19	n.s.	0.78 ±0.23	n.s.
EQ VAS (N = 51)	59.84 ±20.0	61.82 ±18.7	n.s.	61.37 ±18.4	n.s.
FAMS (N = 56)					
Sum Score	113.7 ±32.3	115.1 ± 31.6	n.s.	110.3 ± 31.6	n.s.
Mobility	16.7 ±7.1	16.4 ± 7.0	n.s.	15.7 ± 7.1	n.s.
Symptoms	20.1 ±5.6	20.3 ± 5.3	n.s.	20.1 ± 5.2	n.s.
Emotional Well-being	19.3 ±6.2	19.8 ± 6.0	n.s.	18.9 ± 6.1	n.s.
General Contentment	17.2 ±6.6	17.5 ± 6.2	n.s.	16.8 ± 5.9	n.s.
Thinking and Fatigue	21.0 ±9.1	21.4 ± 9.2	n.s.	19.3 ± 9.6	n.s.
Family/ Social Well-being	19.5 ±6.5	19.7 ± 6.5	n.s.	19.5 ± 5.4	n.s.
MSFC (Z-composite) (N = 55)	- 0.162 ±0.764	-0.155 ± 0.763	n.s.	- 0.120 ±0.985	n.s.
M-FIS Sum Score (N = 52)	37.9 ±18.1	37.4 ±21.4	n.s.	36.1 ±20.6	n.s.
BDI Sum Score (N = 55)	14.4 ±9.8	14.8 ±10.0	n.s.	14.6 ±8.9	n.s.
	% (n)	% (n)		% (n)	
Normal (0–8 pts)	30.9 (17)	32.7 (18)		25.5 (14)	
Minimal (9–13 pts)	27.3 (15)	21.8 (12)		14.5 (8)	
Mild (14–19 pts)	20.0 (11)	23.7 (13)		21.8 (12)	
Medium (20–28 pts)	14.5 (8)	10.9 (6)		32.7 (18)	
Severe (29–63 pts)	7.3 (4)	10.9 (6)		5.5 (3)	

EDSS Extended Disability Symptom Scale, EQ-5D EuroQoL, EQ VAS Visual Analogue Scale, FAMS Functional Assessment in Multiple Sclerosis, MSFC Multiple Sclerosis Functional Composite, M-FIS Modified Fatigue Impact Scale, BDI-II Beck Depression Inventory.

Changes from baseline to either 6 months or 12 months did not reach statistical significance ($p > 0.10$, Pillai's Trace) except for EDSS at 12 months.

0.04). High BDI scores were also correlated with low MSFC z-scores indicating that disease severity is associated with depressive symptoms ($p = 0.032$, $r = -0.190$).

PASAT scores (below the 5th percentile) revealed 71 patients (49.3%) with cognitive impairment with no significant difference between genders. A total of 24 (16.7%) patients had pain syndromes, and 4.2% suffered from anxiety.

Fatigue was also a common symptom, reported by 63.2% ($n = 91$) of the patients. The mean score of the M-FIS at baseline was 36.5 (SD: 18.5).

Patient-reported health status was assessed by the MS-specific FAMS and the generic EuroQol instrument. The mean total score of the FAMS was 113 (SD: 34) at baseline. The FAMS sum score and all of its sub-scores except family/social well-being were significantly positively correlated with disease severity, as measured by MSFC.

At the 12-month follow-up, no significant change was observed in the FAMS sum score or in any of its subscales.

The EQ-5D index score was 0.77 (SD: 0.23) at baseline. The mean score on the EQ VAS was 62.0 (SD: 20). The EQ VAS of MS patients differed considerably from

that of the general population, as depicted in Figure 1. Neither measure showed any change after one year (Figure 2).

We also analysed negative effects on the dimensions measured by the EQ-5D questionnaire (Table 3, Figure 2). In each dimension, MS patients reported problems more frequently than the general population. Approximately 60% reported problems with mobility (vs. 16% in the general population); 20% had problems with self-care (vs. 3%); 65% had problems with usual activities (vs. 10%); 70% suffered from pain (vs. 28%); and 56% had problems with anxiety and/or depression. No significant difference between genders was observed, except in self-care: 23% of male MS patients had problems with self-care, whereas only 14% of female patients reported such problems. Furthermore, we used univariate and multivariate analyses to determine whether demographic data such as disease subtype, age, and/or gender predict reported impairments in the EQ-5D dimensions. RRMS, SPMS, and age were significant predictors of problems with mobility, self-care, and usual activities. RRMS and SPMS were also significant

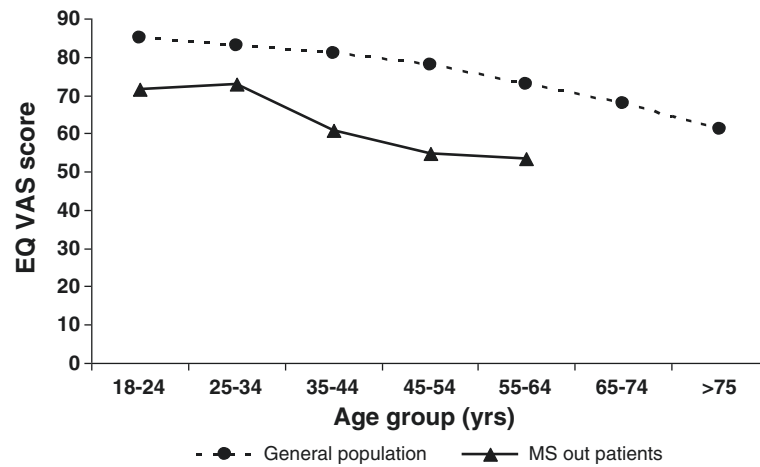


Figure 1 Mean EQ VAS score for age-grouped MS patients ranking their health status using the EQ VAS compared to a representative sample of the German general population [26].

predictors of problems with anxiety or depression, but none of the demographic variables predicted problems with the EQ-5D dimension “pain”. Gender was significantly correlated with problems in the dimension “usual activities”.

Next, the impact of clinical symptoms and socioeconomic variables on health status were analysed in multivariate regression analyses (Table 4). The regression models fit the data well to identify predictor of health status in terms of FAMS and EQ-5D. M-FIS, BDI-II, MSFC and EDSS were identified as significant predictors in multivariate analyses. Higher scores in M-FIS, BDI-II, and EDSS predicted lower scores in FAMS and EQ-5D while lower scores in MFSC predicted lower scores in FAMS

and EQ-5D. Socioeconomic and socio-demographic parameters such as working status, family status, number of household inhabitants, age, and gender did not prove significant in multivariate analyses.

Discussion

This prospective study evaluated the impact of MS on health status using the generic EuroQol instrument and the disease-specific measure FAMS. In line with previous studies, we have shown that MS substantially affects health status (Figure 1; for a review, see [5]).

Many health-status assessments have focused on MS patients, but our study aimed to address three particular

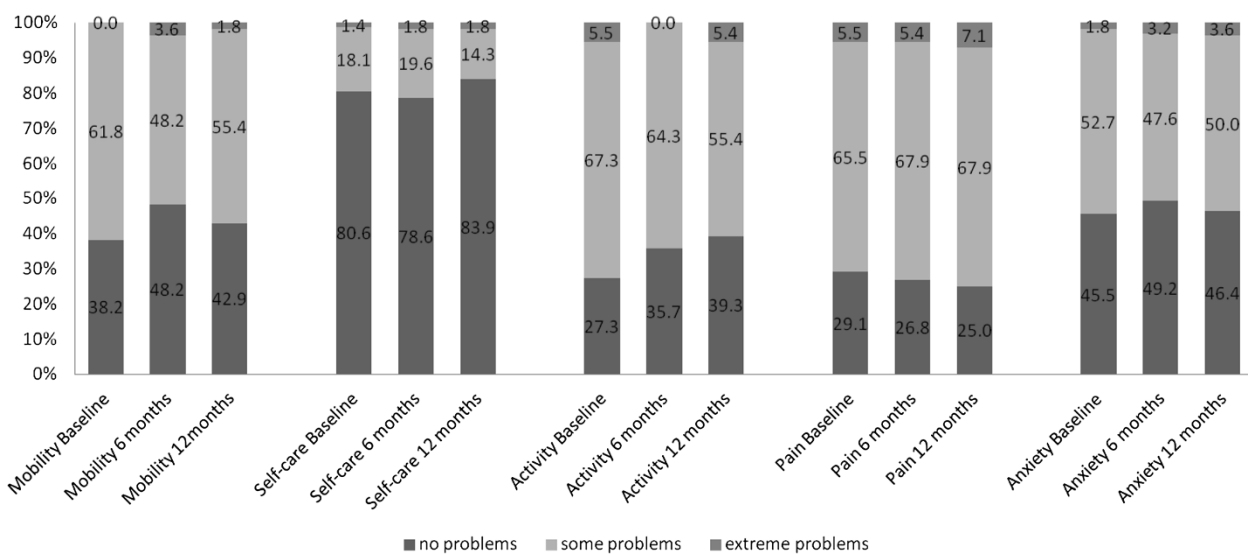


Figure 2 Quality of life parameters from baseline to month 6 and month 12 (subjective assessment of the EQ-5D domains at baseline and after 6 and 12 months (n = 55)). Changes from baseline to either 6 months or 12 months did not reach statistical significance ($p > 0.18$, Pillai's Trace).

Table 3 Percentage of age-grouped individuals with problems in the different EQ-5D dimensions

	Mobility			Self-care			Usual activities			Pain			Anxiety/depression		
	Tot.	M	F	Tot.	M	F	Tot.	M	F	Tot.	M	F	Tot.	M	F
Gen. Pop. ¹ [%]	15.9	14.9	16.8	2.8	2.2	3.4	9.9	8.9	10.7	27.6	24.9	30.0	4-3	3.6	4.9
MS ² [%]	60.4	55.6	62.6	19.4	22.2	18.2	65.3	62.2	66.7	69.4	62.2	72.7	56.3	44.4	61.6
	UV OR [CI]	MV OR [CI]		UV OR [CI]	MV OR [CI]		UV OR [CI]	MV OR [CI]		UV OR [CI]	MV OR [CI]		UV OR [CI]	MV OR [CI]	
RRMS ⁵	.077** [0.026;0.232]	n.s.		.07** [0.04;0.25]	n.s.		.10** [0.03;0.31]	n.s.		n.s.	n.s.		n.s.		17.92* [1.50;214.83]
SPMS	8.92** [2.96;26.87]	n.s.		8.14** [3.29;20.15]	n.s.		9.72** [2.82;33.57]	n.s.		n.s.	n.s.		n.s.		22.83* [1.94;269.30]
Age	1.11** [1.07;1.15]	n.s.		1.11** [1.06;1.16]	n.s.		1.10** [1.03;1.10]	n.s.		n.s.	n.s.		n.s.		n.s.
Gender	n.s.	n.s.		n.s.	n.s.		.82** [0.40;1.72]	n.s.		n.s.	n.s.		n.s.		n.s.
Disease Duration	1.16** [1.08;1.25]	n.s.		1.14** [1.07;1.21]	n.s.		1.13* [1.05;1.21]	n.s.		n.s.	n.s.		n.s.		n.s.
EDSS Score	3.19** [2.20;4.61]	2.86** [1.95;4.18]		4.01** [2.37;6.81]	4.10** [2.36;7.12]		1.94** [1.50;2.50]	1.61* [1.21;2.13]		n.s.	n.s.		n.s.		n.s.
MSFC z-score ⁵	.19** [0.09;0.37]	n.s.		.08** [0.03;0.23]	n.s.		.31** [0.17;0.58]	n.s.		n.s.	n.s.		n.s.		n.s.
BDI Score	n.s.	n.s.		n.s.	n.s.		1.10** [1.05;1.15]	n.s.		1.14** [1.07;1.21]	n.s.		1.19** [1.12;1.28]	1.13* [1.04;1.24]	
M-FIS Score	1.05** [1.03;1.08]	n.s.		1.04* [1.02;1.07]	n.s.		1.08** [1.05;1.10]	n.s.		1.08** [1.05;1.11]	1.08** [1.05;1.12]		1.06** [1.04;1.09]	n.s.	
FAMS Score ⁵	.97** [0.96;0.99]	n.s.		.98* [0.96;0.99]	n.s.		.96** [0.94;0.97]	.96** [0.95;0.98]		.96** [0.95;0.98]	n.s.		.96** [0.95;0.98]	.97* [0.95;0.99]	

^{1,2}Percentage of people having problems in the EQ-5D subdimensions: comparison between data concerning the general population [26] and the specific MS population in our study, ⁵protecting factors, **($p < .001$); * ($p < .05$), n.s. not significant ($p > .05$).

RRMS Relapsing-Remitting MS; SPMS Secondary Progressive MS; EDSS Extended Disability Symptom Scale, MSFC Multiple Sclerosis Functional Composite; BDI-II Beck Depression Inventory; M-FIS Modified Fatigue Impact Scale; FAMS Functional Assessment of Multiple Sclerosis; Gen. Pop.: General population; Tot.: Total; M: male; F: female.

Uni- and multivariate logistic regression analysis identifying predictors for each EQ-5D subdimension.

Table 4 Analysis of predictor variables for the FAMS score, EQ-5D index score and EQ VAS

	FAMS score			EQ-5D index score			EQ VAS		
	beta	95% CI for B	p-value	beta	95% CI for B	p-value	beta	95% CI for B	p-value
Constant		157.067;191.542	<0.001		0.851;1.291	<0.001		65.058;101.797	<0.001
M-FIS	-0.611	-1.289;-0.831	<0.001	-0,431	-0.008;-0.002	<0.001	-0.523	-0.809;-0.325	<0.001
BDI-II	-0.344	-1.579;-0.759	<0.001	-0,040	-0.006;0.004	n.s.	-0.094	-0.638;0.237	n.s.
MSFC (z-score)	0.104	0.480;8.680	<0.05	0,194	0.004;0.109	<0.05	0.268	3.002;11.666	0.001
EDSS	-0.209	-6.129;1.411	n.s.	-0.259	-0.063;-0.001	<0.05	-0.281	-5.617;-0.670	<0.05
Age	0.018	-0.251;0.360	n.s.	-0.044	-0.005;0.003	n.s.	0.035	-0.263;0.393	n.s.
Gender	-0.060	-10.103;1.625	n.s.	-0.030	-0.88;0.060	n.s.	-0.007	-6.478;5.888	n.s.
Working status	-0.021	-2.166;1.325	n.s.	-0.026	-0.026;0.019	n.s.	-0.032	-2.269;1.470	n.s.
Family status	0.020	-2.221;3.607	n.s.	-0.046	-0.048;0.026	n.s.	0.081	-1.312;4.813	n.s.
Number of household inhabitants	0.033	-0.167;0.394	n.s.	0.134	0.000;0.007	n.s.	0.101	-0.077;0.512	n.s.
		R ² = 0.840			R ² = 0.420			R ² = 0.581	

beta: Beta standardized linear coefficient, 95% CI: 95% confidence interval for unstandardized linear coefficients, R2: coefficient of determination. FAMS Functional Assessment in Multiple Sclerosis; EQ-5D EuroQoL, EQ VAS Visual Analogue Scale, M-FIS Modified Fatigue Impact Scale, BDI-II Beck Depression Inventory, MSFC: Multiple Sclerosis Functional Composite.

gaps. First, only few German studies have assessed patient preferences to derive QALY measures for economic evaluation [27,28]. Second, health-status assessments stratified by MS subtype are scarce; here, we provide insight into the health- status differences associated with the three different types of MS (RRMS, SPMS, PPMS) in a well-characterised patient population. Third and most importantly, we provide a detailed longitudinal analysis of patient-relevant outcomes in MS.

Concerning problems in the EQ-5D domains, we show considerable impairments in health status in our study population compared to the general German population. Our results, however, differ from those found in the study by Putzki et al., as our cohort reported more problems. In our study, approximately 60% of MS patients reported some or extreme problems with mobility (vs. 38% in the study by Putzki et al. [28]); 71% had problems

with usual activities (vs. 42%); 69% suffered from pain (vs. 50%); 56% reported problems with anxiety and depression (vs. 52%); and 17% had problems with self-care (vs. 9%). Although the patients in our study sample reported problems in the five dimensions more frequently, these problems were most likely less extreme, explaining the very similar mean index scores in the two studies.

Furthermore, the influence of psychological symptoms such as depression and fatigue on self-perceived health status was assessed. The multivariate linear and logistic regression demonstrated the importance of depression and fatigue to self-perceived health status. Previous studies also identified those variables as independent predictors of health-related quality of life [29,30]. Two studies have identified depression as the strongest determinant of impaired quality of life in patients with MS [31,32]. Recent studies relate symptoms of fatigue, major contributor to

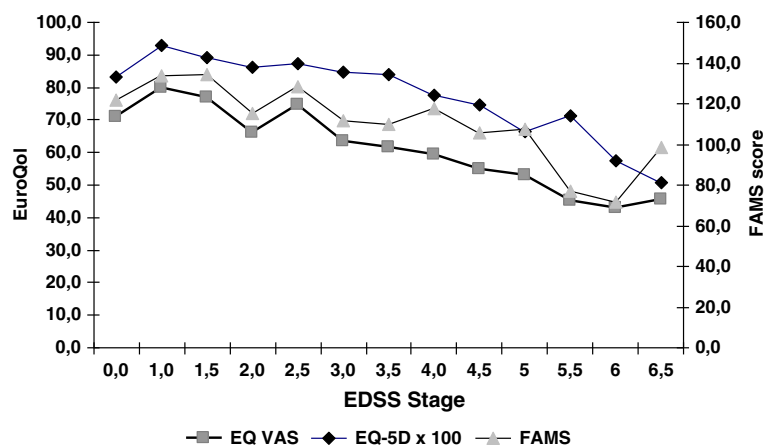


Figure 3 Mean health utility (EQ-5D, EQ VAS) and health status (FAMS) scores for MS patients by EDSS points.

the burden of disease, to sleep disorders [33-36], thus emphasising the necessity of considering non-disease-specific symptoms when treating patients with MS. Depression and fatigue are important facets of MS and must be considered not as secondary outcomes, but as an integral part of disease presentation and management.

We also confirm a strong correlation between health status and disability level (measured by EDSS), as shown in recent publications (for a review, see [5]) in Germany [27]. As illustrated in Figure 3, FAMS and health-utility measure EuroQol may not adequately distinguish among the different degrees of disease severity (i.e., the EDSS groups) and may therefore be inappropriate outcome measures for clinical and economic studies. Thus, we also applied the MSFC, which shows better scaling properties in combination with health-utility measures [37,38].

We could not demonstrate any change in health-status measurements over a 12 month observation period in our cohort, although the EDSS changed significantly during this time. Therefore, studies evaluating patient-reported outcomes using the EQ-5D and FAMS should encompass longer observation periods. Recently, a large German study (n = 674) compared EuroQoL health status before and 12 months following beta-interferon treatment and detected a difference of only 0.02 pts in the EQ-5D index score; this finding is significant but not clinically relevant [28]. The baseline value in that study (0.75) is similar to ours (0.77).

Our study has some limitations: First, the study is based on a convenience sample rather than an epidemiological survey, and only MS patients from a specialised university outpatient clinic were included. Therefore, generalisations should be made cautiously. The sample may be not representative of the German population of MS patients or MS patients of other geographic or ethnic origins. As patients were not evenly distributed across levels of care, more or less severely affected patients may bias the health-status results. Very few patients in our sample have disability levels higher than EDSS 6.5. Our results therefore apply only to patients in levels with less pronounced disabilities. Additionally, relapses may have a substantial influence on health status and self-reported quality of life in patients with MS [27,28]. We did not collect data on relapses and therefore cannot exclude the possibility that patient populations with different patterns of progression and relapse frequencies may show different results. Furthermore, quality of life is a multi-faceted phenomenon influenced by multiple other factors apart from those being measured in this study. For example, it was recently shown that certain patterns of visual impairment are specific to patients with MS [39,40] and considerably affect health-related quality of life [41]. Patients attach great importance to visual functioning, which should be taken into

account when assessing patients with MS [42]. It is of utmost importance to comprehensively assess factors being related to quality of life.

In conclusion, this study is in line with previous findings and confirms that MS has a substantial impact on the self-perceived health status of the patients. Depression and fatigue are major predictors of impaired health status and should be considered integral parts of MS in disease management. We observed no significant changes after 6 or 12 months of observation in any patient-reported outcome used in this study. Our data may help in estimating sample sizes for future clinical trials using patient-reported outcomes.

Conclusion

The quality of life and health status of patients with MS, as well as their correlation with clinical and socio-demographic outcomes, were comprehensively assessed in a longitudinal study over 12 months. In addition to an extensive and detailed clinical examination, a thorough evaluation of fatigue, depression, quality of life, and disease severity was included. MS considerably impairs patients' health status, with depression and fatigue contributing considerably to the burden of disease. Guidelines aiming to improve self-reported health status should include treatment options for depression and fatigue. Physicians should be aware of depression, fatigue and other non-disease-specific parameters as comorbidities. Future studies should consider the minimal clinical difference when health status is a primary outcome.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

JPR drafted the manuscript, participated in study design and conducted analysis. GW assessed the patients and participated data analysis. AJ assessed the patients and participated in data analysis. AL conducted data analysis and revised the manuscript. MBG planned study design, secured data quality and revised the manuscript. UOM revised the manuscript and data analysis. BT planned study design and revised the manuscript. RD planned study design, revised data analysis and the manuscript. All authors read and approved the final manuscript.

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