Acta Neurol Scand 2006: 114: 102–108 DOI: 10.1111/j.1600-0404.2006.00659.x

ACTA NEUROLOGICA
SCANDINAVICA

Association of factors influencing health-related quality of life in MS

Pfaffenberger N, Pfeiffer K-P, Deibl M, Höfer S, Günther V, Ulmer H. Association of factors influencing health-related quality of life in MS. Acta Neurol Scand 2006: 114: 102–108.

Objectives –As results regarding associative demographic and disease-specific factors on health-related quality of life (HRQoL) in patients with multiple sclerosis (MS) are partially inconsistent and contradictory, we reinvestigated this question on a large Austrian MS dataset. *Materials and methods* –Patients received a questionnaire covering demographic and disease-specific characteristics and the Nottingham health profile (NHP) for assessing HRQoL. In order to estimate the risk for suboptimal HRQoL, adjusted odds ratios were calculated from logistic regression models including gender, age, expanded disability status scale (EDSS), disease course, disease duration and walking ability as covariates. *Results* –The EDSS was the only factor contributing to both physical and mental dimensions ($P < 0.001$), whereas disease course, gender and age showed a significant effect on all physical, but not consistently on mental dimensions. *Conclusion* – The regression models fitting better for physical than for mental dimensions, clearly indicate a lack of explanation of demographic and disease-specific factors in these dimensions of HRQoL.

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Key words: demographic factors; disease course; disease duration; EDSS; health-related quality of life; multiple sclerosis; Nottingham health profile

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Accepted for publication March 17, 2006

Introduction

Multiple sclerosis (MS) is one of the most common causes of neurological disability in young- and middle-aged adults in Austria, producing diverse and often unpredictable symptoms together with uncertain disease progression (1–3). Suffering from MS is frequently associated with a decline in functioning and alteration of life roles. This can be particularly arduous for patients adapting to and coping with MS (4). While clinicians are mostly concerned about physical manifestations, the affected persons tend to identify role limitations, cognition and emotional problems as the most significant parameters regarding their health-related quality of life (HRQoL) (5). Research predominately demonstrates that overall well-being is not a simple manifestation and main determinant of physical disability and impairment (2). Kurtzke's expanded disability status scale (EDSS), which is the generally used outcome measure for assessing impairment disability, is heavily weighted towards mobility and does not capture the full impact and multidimensional effects of the disease (3, 6–7). In contrast, HRQoL, which not only focussed on physical functioning but also includes social and emotional well-being, attracted great attention to MS patients and the substantial consequences of their disease (8). Self-reported HRQoL gained great acceptance and has become one of the most important evaluation criteria and outcome in research and clinical practice as well as for the decision-making process in health policy over the recent years (2–3, 6, 9, 10).

A large number of studies evaluating HRQoL in this special population have already been carried out. The majority of the results correspondingly indicate that persons suffering from MS experience lower HRQoL in comparison with the healthy population and with the persons suffering from other chronic diseases (11–13). In contrast, results dealing with the association of demographic and disease-specific factors and HRQoL in MS patients are partially inconsistent and contradictory (9, 10, 13–16).

Because of this inconsistency, we reinvestigated the question of associative factors on HRQoL in

patients with MS on a large Austrian MS dataset. This was part of a larger study analysing the adjusted association of gender, age, EDSS score, disease course, disease duration and walking ability.

Materials and methods

This study was conducted between November 1998 and March 1999 under the auspices of the Austrian MS Society, an organization for patients that provides regional social and psychological services. Study details are reported in Baumhackl et al. (1).

Procedure

Data were collected by sending questionnaires to two sources.

Data set 1:

Neurologists based at 32 specialized MS clinics received questionnaires by post asking for demographic and MS-specific information of patients. Only patients with confirmed diagnosis based on the diagnostic criteria described by Poser et al. (17) were included.

With respect to the presented study, this data set was only used for harmonizing patients' self-assessment regarding disability status (disease course and EDSS) with the neurologists' assessment.

Data set 2:

A total of 2,600 patients received a self-assessment questionnaire from their doctor or via the Austrian MS Society per mail. Since data were also used for estimating the prevalence of MS in Austria, in addition to the posted questionnaires, 700 office-based physicians handed out questionnaires to their MS patients in order to reach full coverage of the MS patients. Validation of diagnosis was confirmed by asking for the diagnostic procedure that was used while specifying the following prevailing methods: visual evoked potential (VEP), magnetic resonance imaging (MRI) and lumbal puncture.

Both data sets were screened to identify patients who were both registered at MS clinics (data set 1), and returned a self-assessment questionnaire by mail (data set 2). In the overlap group consisting of 380 patients, the neurologist's assessment and the patient's self-assessment regarding the disease status, such as the degree of disability and the course of MS, were harmonized (1).

Patients and neurologists returned questionnaires free of charge to a data collection centre (Fessel-GfK, Institute for Market Research, Vienna, Austria), which guaranteed the privacy of all given information. All study participants signed a letter of agreement giving their informed consent.

Questionnaire design

The questionnaire completed by neurologists (data set 1) at specialized MS clinics comprised of 15 items including patient demographic and medical details, e.g. time and method of confirmed diagnosis (17), course of MS (18), degree of disability according to the EDSS (19) and others. For details, see Baumhackl et al. (1).

The questionnaire completed by patients (data set 2) comprised of 390 items covering general demography, disability, disease course and other disease-specific items as well as the Nottingham health profile (NHP, Part 1) for assessing HRQoL. The NHP by Hunt et al. (20) is a generic instrument containing 38 questions in six dimensions, measuring *energy*, *pain*, *emotional reactions*, *sleep*, *social isolation* and *mobility*. The number of items varies from three to nine per scale. All questions are health-related statements, which are scored dichotomously. Items are weighted and the dimension scores range from zero (no problems at all) to 100 (highest degree and presence of all problems within a dimension). Major advantages of the instrument are its efficiency, taking about 10 min to complete, and its proven reliability and validity (21). The internal consistency (Cronbach's Alpha) for the German version of the NHP ranges from 0.65 to 0.85 (21).

Self-assessment of disability was performed according to the EDSS score, and information about the disease courses by asking for relapses and disease progression, additionally visualized by schematic charts.

Study population

From a total of 2,600 questionnaires that were handed out, 2,414 (92.8%) were returned. Of these, 1.6% did not have the NHP filled out and therefore were excluded from further analyses. Furthermore, we eliminated all patients with unconfirmed MS: in 3.2% of the participants none of the prevailing methods regarding diagnosis (VEP, MRI, lumbal puncture) were used. Diagnosis was considered as confirmed for 2,299 study participants based on the use of three procedures in 50% and of two procedures in over 30% of the patients. MRI was used in 91.6%, lumbal puncture in 86.6% and VEP in 58.5% of the study population.

Statistical analyses

Subgroups of disease courses were summarized and attributed to the two main forms of relapsing–remitting (benign, relapsing–remitting) vs progressive (secondary progressive, progressive relapsing, primary progressive). Participants, who did not answer the item asking for the appropriate disease course, were considered as a third group.

For description, quantitative variables were characterized by means, standard deviations, medians, 25th and 75th percentiles, respectively, and categorical variables by absolute and relative frequencies.

With regard to the NHP, dimensions were dichotomized into two categories: 'optimal' (value = 0) vs 'suboptimal' (value > 0). This dichotomization was done in order to be able to perform multivariate analyses, as patient responses strongly deviated from normal distribution showing *u*-shaped patterns.

To evaluate associations of demographic and disease-specific factors and to estimate the risk for suboptimal HRQoL in each of the six dimensions, adjusted odds ratios were calculated from logistic regression models, including gender, age, EDSS score, disease courses, disease duration and walking ability, as covariates. Adjusted odds ratios and their 95% confidence intervals were given as measures of risk for suboptimal HRQoL.

The degree of explained variance through the regression models was given by Nagelkerkes *R*-square. Goodness-of-fit was assessed by the Hosmer–Lemeshow test. We considered $P \leq 0.001$ to be statistically highly significant, $P < 0.05$ to be statistically significant, and values between $P \geq 0.05$ and $P \leq 0.1$ were interpreted as tendency or trend. Because of missing values, the sample size was not steady over the entire analyses, including missing data up to 5.2%.

Results

Demographic (gender, age) and disease-specific characteristics (EDSS, disease course, disease duration and walking ability) of the study population are given in Table 1.

Two-thirds of the patients were females. Mean age of the responders was 46.5 ± 12.6 years and mean disease duration was 11.5 ± 9.5 years. Most of the participants suffered from progressive courses of MS (47.2%), whereas 22.1% did or could not name their appropriate disease course. With regard to the EDSS, 50% belonged to the group with a score up to 3.5. The majority of the respondents (82.5%) were able to walk.

Table 2 shows the characteristics of the population with regard to the dimensions of the NHP, energy, pain, emotional reaction, sleep, social isolation and mobility. As dimension scores strongly deviate from normal distribution, the 25th percentile, the median and the 75th percentile were given for description.

With respect to the total study population, the lowest HRQoL was found in the dimension energy, by far. In general, the dimensions pain, sleep and social isolation showed a markedly better profile than emotional reaction and mobility.

Table 3 shows the effects of the covariates gender, age, EDSS, disease course, disease

Table 1 Description of the study population

				Disease courses, N (%)			EDSS, N (%)			Walking ability, N (%)	
Factors	Total N (%)	Age M ± sd	Duration M ± sd	RR[1]	P[2]	NK[3]	0–3.5	4–6.5	7–10	Yes	No
Total	2299 (100)	46.5 ± 12.6	11.5 ± 9.5	695 (30.2)	1097 (47.7)	507 (22.1)	1230 (53.5)	546 (23.7)	456 (19.8)	1896 (82.5)	403 (17.5)
Gender											
Female	1636 (71.2)	46.1 ± 12.8	11.3 ± 9.5	540 (77.8)	707 (64.6)	389 (76.7)	935 (76.1)	361 (66.1)	296 (65.2)	1379 (72.8)	257 (63.9)
Male	660 (28.7)	47.5 ± 12.1	11.8 ± 9.7	154 (22.2)	388 (35.4)	118 (23.3)	294 (23.9)	185 (33.9)	158 (34.8)	515 (27.2)	145 (36.1)
Disease courses											
RR [1]	695 (30.2)	39.8 ± 10.4	8.0 ± 6.6				635 (51.6)	45 (8.2)	8 (1.8)	687 (36.2)	8 (2.0)
P[2]	1097 (47.2)	51.5 ± 11.5	14.5 ± 10.2				251 (20.4)	428 (78.4)	382 (83.8)	762 (40.2)	335 (83.1)
NK[3]	507 (22.1)	44.7 ± 12.8	10.0 ± 9.3				344 (28.0)	73 (13.4)	66 (14.5)	447 (23.6)	60 (14.9)
EDSS											
0–3.5	1230 (53.5)	41.0 ± 10.7	7.7 ± 6.8	635 (92.3)	251 (23.7)	344 (71.2)				1229 (66.0)	1 (0.3)
4–6.5	546 (23.7)	51.2 ± 11.3	13.3 ± 9.5	45 (6.5)	428 (40.3)	73 (15.1)				531 (28.5)	15 (4.1)
7–10	456 (19.8)	54.5 ± 11.4	18.9 ± 10.4	8 (1.2)	382 (36.0)	66 (13.7)				102 (5.5)	354 (95.7)
Walking ability											
Yes	1896 (82.5)	44.6 ± 12.0	9.9 ± 8.6	687 (98.8)	762 (69.5)	447 (88.2)	1229 (99.9)	531 (97.3)	102 (22.4)		
No	403 (17.5)	55.3 ± 11.6	18.9 ± 10.1	8 (1.2)	335 (30.5)	60 (11.8)	1 (0.1)	15 (2.7)	354 (77.6)		

[1] Relapsing-remitting, [2] Progredient, [3] Not known

Table 2 Description of the study population regarding the dimensions of the Nottingham health profile

		Gender		Age			Duration			Disease Courses			EDSS			Walking Ability	
Dimensions	Total	Female	Male	<31	>30–60	>60	<16	>15–30	>30	RR[1]	P[2]	NK[3]	0–3.5	4–6.5	7–10	Yes	No
Energy																	
25th Pct.	24.0	24.0	24.0	0	24.0	60.8	24.0	36.8	60.8	0	60.8	0	0	60.8	60.8	24.0	60.8
Median	63.2	63.2	60.8	38.0	63.2	100	60.8	63.2	76.0	39.2	100	60.8	39.2	100	100	60.8	100
75th Pct.	100	100	100	63.2	100	100	100	100	100	63.2	100	100	100	100	100	100	100
Pain																	
25th Pct.	0	0	0	0	0	9.8	0	0	5.8	0	0	0	0	0	10.0	0	10.5
Median	10.0	10	10	0	9.0	36.0	0	19.7	32.1	0	22.9	0	0	21.4	29.7	0	30.7
75th Pct.	36.0	36.0	35.9	0	33.8	45.8	29.8	46.5	67.4	11.2	50.7	27.7	14.8	55.8	59.8	27.0	63.2
Emotional Reaction																	
25th Pct.	7.2	7.1	7.2	0	7.2	43.5	7.1	7.1	9.8	0	10.5	0	0	10.5	10.5	0	10.5
Median	20.2	20.2	20.2	14.0	21.2	34.8	20.2	21.2	24.4	14.0	26.7	20.2	17.0	26.7	27.5	17.7	30.2
75th Pct.	43.1	43.2	42.1	34.8	9.8	45.8	41.4	45.8	45.7	34.1	50.6	41.4	36.4	47.2	55.5	41.4	57.1
Sleep																	
25th Pct.	0	0	0	0	0	12.6	0	0	12.6	0	0	0	0	0	0	0	0
Median	12.6	12.6	12.6	0	12.6	28.7	12.7	12.6	34.3	0	16.1	12.6	0	12.6	22.4	12.6	22.4
75th Pct.	37.8	37.8	38.5	16.1	37.8	60.2	34.9	50.4	61.5	28.7	50.4	34.9	34.3	38.5	51.0	34.9	55.9
Social Isolation																	
25th Pct.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Median	16.0	0	17.7	0	0	22.5	0	22.0	22.5	0	23.5	0	0	22.0	22.5	0	22.5
75th Pct.	38.0	35.3	38.4	22.5	35.3	41.9	22.5	41.9	41.9	22.0	41.9	22.5	22.0	41.9	44.5	22.5	44.5
Mobility																	
25th Pct.	9.3	0	10.8	0	10.8	54.5	0	33.2	46.2	0	34.7	0	0	44.0	78.7	0	88.5
Median	32.6	31.1	41.9	0	32.6	78.8	22.0	66.1	69.4	0	66.1	12.6	10.8	55.5	88.5	22.0	100
75th Pct.	67.2	67.0	78.0	11.2	66.6	100	54.6	88.5	90.7	22.0	88.5	54.5	22.0	67.2	100	46.2	100

[1]Relapsing-remitting, [2]Progredient, [3]Not known

duration and walking ability on the dimensions of the NHP, operationalized by the binary outcome optimal vs suboptimal HRQoL.

With regard to energy, the covariates gender, age, EDSS-score, disease course and walking ability showed a significant effect. Women, older patients, participants with a higher EDSS score, progressive disease courses and non-walkers were at a higher risk of experiencing energy loss. Similar patterns were observed for the dimensions, pain and mobility.

Emotional reactions were significantly influenced by EDSS score, disease course and disease duration. Although problems within this dimension rose with the EDSS score and progressive disease courses, they decreased with disease duration.

The EDSS score was the only significant factor for reduced social isolation; for sleep, patients' age and EDSS contributed significantly.

Lack of knowledge regarding the appropriate disease course did not show any effect, neither on physical nor on mental dimensions. This suggests that most of the patients who did not know about their disease course belong to the group with relapsing–remitting MS.

Although not visible in univariate statistics (Table 2), male gender decreased the risk for suboptimal HRQoL. This was caused by a strong interaction of disease course with gender.

The regression models explain between 9 and 65% of the variance in NHP outcomes (energy – 24%, pain – 28%, emotional reaction – 5%, sleep – 9%, social isolation – 14% and mobility – 65%), fitting better for physical than for mental dimensions.

Discussion

This study, based on a comprehensive cross-sectional survey covering information on nearly all Austrian MS patients at the time of the study, allows new insight into the joint relationship of socio-demographic and disease-specific characteristics with HRQol. Multivariate associations of gender, age, EDSS score, disease course, disease duration and walking ability on the six dimensions of the NHP were analysed.

The results indicate – corresponding to the majority of previous research – the EDSS score to be a predictive factor with respect to HRQoL (5, 9, 14). While some study groups found the EDSS to be strongly related mainly to physical but not to mental dimensions (13, 22), in our study, the EDSS proved to be a highly appropriate instrument for assessing both physical and mental NHP-measured

Table 3 Multivariate association of demographic and disease-specific factors on reduced HRQoL

	Dimensions of the NHP					
Factors	Energy	Pain	Emot. Reaction	Sleep	Social Isolation	Mobility
Gender (Female[4])						
Male						
Odds ratio	0.582	0.758	0.863	0.942	0.828	0.562
95% CI	0.447–0.758	0.611–0.940	0.690–1.079	0.773–1.149	0.678–1.011	0.401–0.788
p	**<0.001**	**0.012**	0.195	0.557	0.064	**0.001**
Age per year						
Odds ratio	1.020	1.044	1.005	1.025	0.999	1.044
95% CI	1.006–1.033	1.034–1.055	0.994–1.016	1.015–1.035	0.990–1.008	1.027–1.060
p	**0.004**	**<0.001**	0.354	**<0.001**	0.843	**<0.001**
EDSS per score						
Odds ratio	1.505	1.282	1.160	1.143	1.251	4.062
95% CI	1.367–1.658	1.203–1.366	1.082–1.243	1.077–1.214	1.179–1.327	3.368–4.897
p	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Course (RR[14])						
P[2]						
Odds ratio	2.135	1.492	1.419	1.045	1.286	2.134
95% CI	1.467–3.107	1.131–1.969	1.051–1.918	0.800–1.364	0.986–1.678	1.347–3.383
p	**<0.001**	**0.005**	**0.023**	0.746	0.064	**0.001**
NK[3]						
Odds ratio	1.002	1.122	1.175	1.137	0.982	0.898
95% CI	0.759–1.323	0.861–1.463	0.898–1.539	0.887–1.457	0.760–1.268	0.655–1.231
p	0.989	0.393	0.240	0.311	0.889	0.505
Duration per year						
Odds ratio	0.983	0.992	0.978	0.997	0.999	0.981
95% CI	0.965–1.001	0.979–1.005	0.965–0.992	0.985–1.009	0.987–1.011	0.958–1.004
p	0.063	0.222	**0.001**	0.648	0.878	0.111
Walking (Yes[4])						
No						
Odds ratio	2.933	1.088	1.153	0.996	0.877	
95% CI	1.555–5.532	0.746–1.585	0.773–1.718	0.710–1.397	0.630–1.220	n.a.[5]
p	**0.001**	0.663	0.485	0.980	0.435	

[1]Relapsing-remitting, [2]Progredient, [3]Not known

[4]Reference

[5]not applicable since there were no patients with walking inability and optimal *mobility*

HRQoL. Patients with higher EDSS scores were consistently at a higher risk for reduced HRQoL, strongest with regard to mobility.

A reason for the good agreement between the EDSS and HRQoL is probably that for this population, both measures assess a mixture of interconnected traits, the EDSS being basically an 'objective' and HRQoL a 'subjective' assessment. Another important reason for the EDSS being of strong influence on the NHP could lie in the interdependence of its dimensions.

Discrepancy with previous studies showing a less strong effect of the EDSS score can probably be attributed to the fact that in these studies, further covariates, such as fatigue, depression or anxiety were included (9, 13, 22–25). With respect to mental dimensions, other subjective factors might be more relevant than the objective traits we included as covariates.

In this respect, our results are somehow limited because neither mental disorders associated with MS, such as cognitive impairment (23), depression (9) and anxiety (25) nor fatigue (22) were assessed. Especially referring to mental dimensions, these factors may have a major effect on HRQoL, contributing to the so-called 'silent' disability of MS (8). Research dealing with this relationship demonstrated that cognitively disabled patients are at a higher risk of being unemployed and more probable to experience restrictions in social activities, household responsibilities and others than patients with similar levels of physical impairment (23). In the course of MS, psychiatric complications are expected frequently. In literature, a lifetime prevalence rate of 50% of depressive disorders is reported (24). Fruehwald et al. (9) found depression to be the most important predictor for HRQoL, assessed by the QoL index, considering the EDSS to be less influential. Janssens et al. investigated whether anxiety and depression influence the relation between disability status and HRQoL assessed by the short form-36 (SF-36). Although

in unadjusted regression analyses, the EDSS was significantly related to all physical and mental health scales, after the adjustment for anxiety and depression, it was not significantly related to the SF-36 mental health scales and the general health scales any more, supposing that anxiety and depression are intermediate factors in the association of EDSS and HRQoL (25). However, the assessment of these factors does not appear to be practical in many clinical situations, while the characteristics examined in our study are a routine part of clinical practice.

Among the EDSS, in our study, the characteristics disease course, age and gender also indicated a significant effect on all physical dimensions. Furthermore, disease course was significant regarding emotional reaction, showing a decrease in HRQoL with progressive disease courses. In contrast, Ford (15), using Leeds multiple sclerosis QoL scale (LMSQoL), pointed out that HRQoL did not differ across disease course groups. The study group of Pfennings (14) assessed whether the differences in HRQoL among MS patients are correlated with EDSS, time since diagnosis, disease progression and gender. Each of these variables proved to be related to at least one domain of SF-36. They showed that the longer the disease duration, the more severe and progressive the MS, the lower the patient's subjective HRQoL. In our study, disease duration was only statistically significant concerning emotional reaction, showing a higher risk for reduced HRQoL in patients with longer disease duration. Based on the QoL index, Fruehwald et al. (9) did not show any influence of disease duration. In contrast, Ford (15) reported on differences concerning disease duration, but pointed out that patients with longer disease duration were more likely to experience relatively good HRQoL. With respect to gender, Benito-Leon (16), using the functional assessment of multiple sclerosis (FAMS) QoL instrument, and Fruehwald (9) did not find any differences, but Pfennings (14) reported on women describing lower HRQoL in role-emotional functioning and mental health. Conforming to lower HRQoL in women (14), we also found female gender resulting in a higher risk of experiencing suboptimal HRQol, which was statistically significant in the case of physical dimensions.

With respect to age, Fruehwald (9) did not report on any effects, whereas in our study, age contributed significantly to all physical dimensions and sleep, showing reduced HRQoL with advanced age. Differing, Ford (15) found that older patients are more probable to experience high HRQoL.

While in our study, progressive disease courses showed a significant effect on suboptimal physical HRQoL and emotional reactions, Ford reported on no differences based on this factor.

Walking ability contributed only significantly with regard to energy, showing a higher risk for non-walker in experiencing energy loss.

Results of previous studies are to some extent contradictory. The lack of concordance probably emerges because of differences in research methods, the partly used univariate analyses and small sample sizes in many of these studies or patients' selection bias; drawbacks that we were largely able to avoid in our study.

The risk for low physical HRQoL with respect to the dimensions energy, pain and mobility can consistently be predicted by demographic factors (gender and age) and EDSS score and disease courses. With regard to mental dimensions, no marked patterns regarding these variables (with the exception of EDSS) could be found. The fact that the EDSS also significantly contributes to emotional reaction, sleep and social isolation, should not mask the fact that these dimensions are in general less predictable by the studied covariates. This suggests further that the discriminative validity of the NHP is higher for its physical dimensions. The weaker association between most of the covariates and mental dimensions of the NHP can probably be attributed to coping, which is known as an important mediator between chronic illness and psychological well-being (16). Mohr et al. (26) even suggested that coping becomes increasingly important to an MS patient's psychical well-being as the disease progresses.

A limitation to the study is that the EDSS values are based on the patient's self-assessment, whereas the instrument actually requires a neurologist's classification. However, the correctness of the disease-specific information provided in data set 2 was confirmed by the analysis of the overlap group. The total of 380 patients appearing in both data sets were compared with regard to disability and course of the disease as rated by neurologists (data set 1) and by patient's self-assessment (data set 2). There was a significant correlation between the ratings of disability grade and individual EDSS values. A comparison between the two data sets with respect to the course of the disease also showed a significant correlation.

Recapitulating, our results clearly indicate the EDSS to be a highly appropriate instrument, revealing a direct effect on HRQoL. To our knowledge, this is the first study multivariately evaluating the clinically important EDSS score in a very large unselected sample. Since MS is a very

complex disease with lots of potentially predictive parameters, we consider this information to be essential for the interpretation of HRQoL domains and consequently for decision-making with regard to rehabilitative care and other supporting measures. Nevertheless, we consider further studies as necessary in order to evaluate the effect of associative factors on HRQoL, including additional covariates, such as cognitive impairment, depression, anxiety and fatigue.

Acknowledgements

We acknowledge all participating Austrian MS patients for completing questionnaires and all physicians for assisting. Particular thanks go to Prof Ganzinger, who initiated the study and was responsible for fund raising. The main sponsor was Schering Wien GesmbH. This study was further supported by the Austrian MS Society that was responsible for developing and sending out the questionnaires to its members.

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