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Preference-Based Assessments

Association between Disability, Cognition, Fatigue, EQ-5D-3L Domains, and Utilities Estimated with Different Western European Value Sets in Patients with Multiple Sclerosis

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ABSTRACT

Objectives: To assess the association between fatigue, cognition, domains of the EuroQol five-dimensional questionnaire (EQ-5D-3L), disability, and utilities estimated with several Western European value sets in patients with multiple sclerosis (MS). **Methods:** Data from a multinational, cross-sectional, observational study of patients with MS (N = 16,808) conducted in 16 European countries were used. Health-related quality of life data were collected through the EQ-5D-3L, and fatigue and cognitive difficulties were self-assessed on a 10-point visual analogue scale. Associations were assessed using Pearson correlation and multivariate regression model. **Results:** Symptoms of fatigue and cognitive difficulties were present in 90% and 70% of patients at all levels of disability, respectively, and thus only weakly correlated to disability. Problems in the EQ-5D-3L domains were common even at mild disability levels. Mobility, usual activities, and pain issues were experienced by 80% to 90% of patients with moderate and high levels of disability. Mobility, usual activities, and self-care were strongly correlated to disability. Disability, MS type, fatigue, and cognition were associated with utility in regression models, although the coefficients of fatigue and cognition were small. **Conclusions:** The strong relationship of disability with utility was confirmed. Despite this, fatigue and cognitive difficulties were associated with utility estimated with different European value sets.

Keywords: cognition, disability, EQ-5D-3L, fatigue, multiple sclerosis, utility values.

Introduction

Multiple sclerosis (MS) is a chronic neurological disorder that can lead to symptoms such as spasticity, movement disorders, fatigue, bladder and bowel dysfunction, pain, depression, visual disorders, and dysphagia [1]. The disease course is variable and highly individual, ranging from mild and benign with little associated disability to chronic and progressive with rapidly accumulating disability [2–5]. Disability is normally assessed using the Expanded Disability Status Scale (EDSS), which focuses on ambulation [6].

Health-related quality of life (HRQOL) in patients with MS has been reported to be impaired compared with that in the general population [7–11]. Work, fatigue, sports, social life, relationships, walking, cognition, balance, housework, and mood have been identified as important domains of quality of life in MS [12]. In particular, cognitive difficulties and fatigue are among the most common MS symptoms, estimated to occur in 43% to 70% [13] and 75% to 90% [14] of patients, respectively, across all levels of disability.

Neither fatigue nor cognitive difficulties are incorporated as domains in the generic EuroQol five-dimensional questionnaire (EQ-5D), which has been the most frequently used measure to derive utilities in patients with MS. Utility is a summary measure of health status ranging between 0 and 1 that is used in economic evaluations to calculate quality-adjusted life-years (QALYs). In economic models evaluating treatments for MS, the disease course is modeled to progress as the severity of disability increases using the EDSS. Utilities have been shown in previous studies to decrease with rising EDSS scores [15,16], although some inconsistencies have been observed [17].

Conflicts of interest: At the time of the study, J. Eriksson, M. Gannedahl, and J. Berg were employed at Mapi, a research company acting as a consultant to pharmaceutical companies. G. Kobelt has received consulting fees from Almirall, Bayer, Biogen, Merck Serono, Novartis, Oxford PharmaGenesis, Sanofi Genzyme, and Teva.

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In a health policy context, the health economic consequences of MS are highly linked to progression of disability [18]. Generic instruments used to derive utility values may not capture the full spectrum of HRQOL in MS [12,19]. Although some work has been done to develop MS-specific utility measures [20], these are not in widespread use in health technology assessments, where authorities, such as the National Institute for Health and Care Excellence, express a preference for the use of generic instruments [21].

Fatigue and cognition are some of the most important drivers of HRQOL [22] that have an impact not only on the patient but also on the society as a whole [23], but these are neither specifically captured by the EDSS nor covered by the EQ-5D. Therefore, it is important to ensure that the effects of these symptoms are reflected fully in the methods by which the clinical, humanistic, and societal burden of MS are evaluated.

Economic evaluations throughout Europe have typically been conducted using utilities derived from the EQ-5D instrument using the UK value set [24] despite evidence questioning the transferability of utilities between countries [25]. Thus far, the implications of different value sets, in particular the influence on utilities for different levels of disability, have received limited attention in MS. In addition to determining which three-level EQ-5D (EQ-5D-3L) domains are most important in patients with MS, it is of relevance to explore whether the most influential domains vary by country value set to understand how this could have an impact on country differences in utilities.

Using data from the largest cross-sectional study in patients with MS [18], we study the relationship of disability, fatigue, cognitive difficulties to EQ-5D domains, and utility valued with several different Western European value sets. Second, we describe the most impacted EQ-5D domains in our sample and relate this to influential domains within utility country value sets.

Methods

This study was a multinational, prevalence-based, cross-sectional, observational study of patients with MS conducted in the following 16 European countries: Austria, Belgium, the Czech Republic, Denmark, France, Germany, Hungary, Italy, the Netherlands, Poland, Portugal, Russia, Spain, Sweden, Switzerland, and the United Kingdom. The study was endorsed by the European Multiple Sclerosis Platform and carried out in collaboration with national MS patient organizations. All information on resource consumption, disease characteristics, HRQOL, and prevalent symptoms was collected directly from patients who were invited to participate by these organizations either through an online survey or via surveys mailed directly to the patients. The study design, methods, and data collected have been described in detail elsewhere [18].

The EQ-5D-3L

HRQOL was assessed with the EQ-5D-3L instrument, a validated, generic instrument [26]. The EQ-5D-3L measures five dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) within three levels of severity (no, some, and extreme problems). Health status may be quantified in terms of utility values anchored on a scale between 1 (full health) and 0 (death). All possible combinations of the EQ-5D-3L health dimensions and severity levels represent health states that may be valued by assigning preference weights. Preference weights for the EQ-5D-3L health states have been obtained in several countries using the time trade-off or the visual analogue scale (VAS) methodology. Health states may be valued directly by individuals experiencing the specific health state (experience-based valuation) or by valuation of hypothetical health states.

Utilities

Utilities were estimated with time trade-off value sets from the following Western European countries with patients enrolled in our study: the United Kingdom [24], Sweden [27], Denmark [28], France [29], the Netherlands [25,30], Spain [25,31], Italy [32], and Portugal [33]. The German value set was not included because only significant coefficients were included in the regression model with which this value set was developed [34]. There are several methodological differences in the valuation studies that may influence utility values, in addition to potential cultural differences in the ranking of the individual domains [25,35]. These methodological differences include, for example, the valuation method, inclusion of the N3 (any level 3 problems) variable, number of health states valued, mode of survey administration, number of participants in the valuation process, and the population surveyed (i.e., general population or patients).

Fatigue and Cognitive Difficulties

Fatigue and cognitive difficulties were self-assessed on a 10-point VAS (0 = no problems; 10 = severe problems).

Analysis

First, we checked the occurrence of problems in the EQ-5D-3L domains, fatigue, and cognition, and how these varied across EDSS levels. Second, pairwise associations of the EQ-5D-3L domains, utility, fatigue, and cognition to EDSS were investigated with Pearson correlation coefficients. Pairwise correlations between EQ-5D-3L domains, utility with fatigue and cognition, were also assessed. In the next step, we ran multiple linear regression models on utility using the UK, Swedish, and French value sets to explore the relationship between utility, EDSS, fatigue, and cognition while controlling for confounding factors. These value sets were selected because they provided diverging utilities in terms of range across the EDSS.

Predictors of utility were analyzed using ordinary least squares regression. The model included the following covariates: age, EDSS, MS type, living arrangements, employment status, cognition, fatigue, disease modifying treatment, walking/spasticity/pain treatments, depression treatments, and country. These covariates were included on the basis of previous research and correlation with utility. Significant variables were retained in the model using a stepwise model approach ($P < 0.05$).

Relapses were not included in the regression models because the information provided by the patients was not considered clinically reliable and had extensive missing data (19.7%). Furthermore, disease duration was excluded because of issues of collinearity with EDSS and age.

We then aimed to understand how the most impacted EQ-5D-3L domains in our sample relate to the most influential domains in country value sets. Using the most frequent health states for different disability levels in our sample, we aimed to illustrate the influential domains in each country value set. Utilities started to diverge in our sample within EDSS level 4 and above; therefore, the most common health states at each level were investigated in terms of the most influential domains within each value set. Domains within each value set and health state were ranked using the regression coefficient from the most influential (largest utility decrement) to the least influential (lowest utility decrement). The health states are defined by the combinations of the EQ-5D-3L responses; for example, extreme problems in the mobility, self-care, usual activities, pain/discomfort, and anxiety/depression domains are denoted as health state 33333.

Table 1 – Demographic and disease characteristics.

Characteristic	All patients (N = 16,808)	Mild EDSS 0-3 (n = 7,309)	Moderate EDSS 4–6.5 (n = 5,831)	Severe EDSS 7–9 (n = 3,255)	P value*
Age (y), mean ± SD					
Current	51.1 ± 12.3	45.3 ± 11.3	53.6 ± 10.8	58.0 ± 10.6	<0.0001
At diagnosis	36.5 ± 11.0	34.4 ± 10.1	38.2 ± 11.2	38.1 ± 10.7	<0.0001
At first symptoms	30.6 ± 10.2	29.6 ± 9.5	31.5 ± 10.6	31.3 ± 10.7	<0.0001
MS type, n (%)					
RRMS	8,148 (48.5)	81.0%	0.0%	7.5%	NA
SPMS	4,280 (25.5)	33.1%	43.9%	21.4%	
PPMS	3,133 (18.6)	6.0%	52.8%	39.2%	
Sex, female, n (%)	12,318 (73.3)	78.2%	72.8%	63.4%	<0.0001
Employment status, n (%)					
Employed (in workforce)	7,029 (41.8)	65.3%	31.2%	10.3%	NA
Not employed (in workforce)	6,771 (40.3)	27.8%	49.4%	51.7%	
Retired	2,908 (17.3)	6.6%	19.1%	37.0%	
Living situation, n (%)					
Alone	3,353 (20.0)	18.2%	22.1%	19.5%	NA
With family/friends	13,074 (77.8)	80.9%	76.6%	74.5%	
Nursing home	189 (1.1)	0.1%	0.4%	4.6%	
DMT treatment, n (%)	9,490 (56.5)	73.0%	54.4%	24.3%	<0.0001
Treatment for walking problems, n (%)	4,491 (26.7)	10.6%	36.0%	46.1%	<0.0001
Treatment for depression, n (%)	2,326 (13.8)	10.1%	16.6%	16.5%	<0.0001
Relapses in last 3 mo, n (%)†	2,248 (16.7)	14.8%	20.2%	14.6%	<0.0001
Fatigue VAS, mean ± SD	5.6 ± 2.5	4.9 ± 2.6	6.0 ± 2.2	6.1 ± 2.4	<0.0001
Cognitive difficulties VAS, mean ± SD	4.8 ± 2.2	4.3 ± 2.1	4.9 ± 2.1	5.4 ± 2.3	<0.0001

Note. P values for differences between means were calculated with a one-way ANOVA; P values for differences between proportions were calculated with a χ^2 test.

ANOVA, analysis of variance; DMT, disease modifying treatment; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; NA, not applicable/available; PPMS, primary progressive MS; RRMS, relapsing remitting MS; SPMS, secondary progressive MS; VAS, visual analogue scale.

[*] Difference between disability (EDSS) groups.

[†] Excluding patients who were unsure as to whether they had a relapse.

Results

The analysis included 16,808 patients with MS from 16 countries. Demographic characteristics, disease characteristics, and mean VAS values for fatigue and cognition are presented in Table 1. Further details on the patient sample have been presented elsewhere [18].

Health Status and Utility

Problems in the EQ-5D-3L domains were common and generally increased with increasing disability (Fig. 1). In particular, using a benchmark of, for example, general English population [36], problems were considerably more common even in the mild disability group for all EQ-5D-3L domains except self-care. Pain/discomfort was the most problematic domain in mild disability. Mobility, usual activities, and pain/discomfort were the most problematic domains in the moderate group. In the severe disability group, usual activities, mobility, and self-care, followed closely by pain/discomfort, were the most problematic domains. Fatigue was an issue in more than 90% of patients across all disability groups, and cognitive difficulties were reported by about 70% of patients.

Mean utilities and range varied depending on the country value set (see the Appendix in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.08.002). All value sets followed the same trend of declining utility with rising disability (Fig. 2; also see the Appendix in Supplemental Materials). In absolute terms, utilities were similar in the lowest disability range but differed substantially in the more severe disability range, starting at the

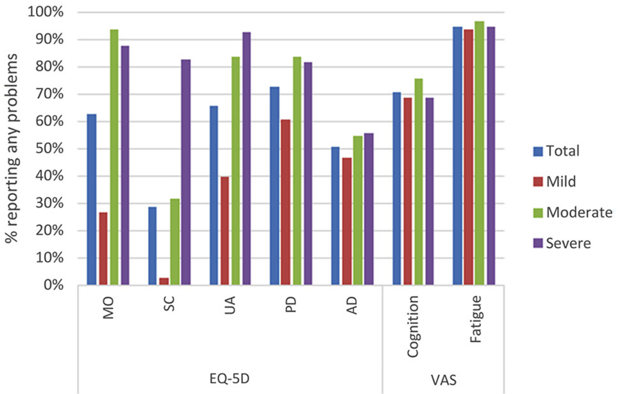

Fig. 1 – Proportion of patients with any problems in the EQ-5D-3L domains, cognition, and fatigue, overall and by disability groups. *Note.* Presence of problems defined as "some problems" or "extreme problems" in the EQ-5D-3L; cognitive difficulties and fatigue reported as VAS ≥ 1. Mild = EDSS 0–3; Moderate = EDSS 4–6.5; Severe = 7–9. Reference values for problems in the EQ-5D-3L domains in the general England population are MO = 17.5%, SC = 5.5%, UA = 16.0%, PD = 33.5%, and AD = 20.1% [36]. Domains: MO, mobility; SC, self-care; UA, usual activities; PD, pain/discomfort; AD, anxiety/depression; EDSS, Expanded Disability Status Scale; EQ-5D-3L, three-level EuroQol five-dimensional questionnaire; VAS, visual analogue scale.

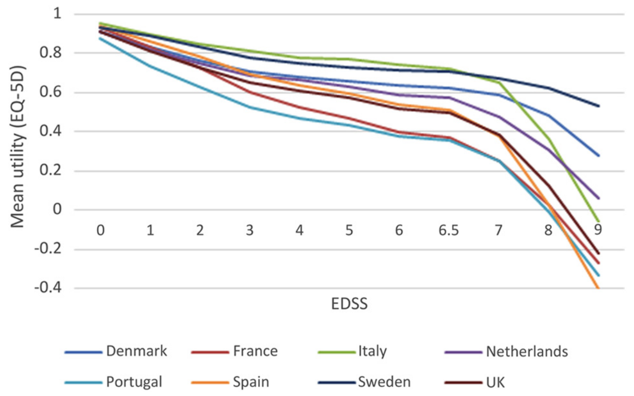

Fig. 2 – Mean utility per disability level using different EQ-5D-3L value sets in Europe (n = 15,694). EQ-5D-3L, three-level EuroQol five-dimensional questionnaire.

moderate disability levels. Utilities estimated with the UK value set were lower than those estimated with other country value sets except for the French and Portuguese. At the most severe disability levels, the lowest utilities were estimated with the Portuguese, French, UK and Spanish value sets. The Swedish value set, the only experience-based value set used in this analysis, gave the highest utilities in the most severe disability range, which is expected and likely because of the different methodology used in eliciting utilities [37].

Correlation between Fatigue, Cognition, EQ-5D-3L Domains, Disability, and Utility

There was a strong correlation of the EQ-5D-3L domains mobility, self-care, and usual activities to disability (Table 2). Pain/discomfort had a moderate correlation, whereas anxiety/depression was weakly correlated to disability. Fatigue and cognition were weakly correlated to disability. Utility was strongly correlated to disability.

Usual activities, pain/discomfort, and anxiety/depression were moderately correlated to fatigue, and usual activities and anxiety/depression were moderately correlated to cognition. Utility was moderately correlated to both fatigue and cognition.

Multivariate Analysis on Utility

Disability was the main driver of utilities (Table 3). In comparison with the reference group of relapsing remitting MS, primary progressive MS had a larger disutility than secondary progressive MS. Fatigue and cognition had a significant independent effect on utility. Fatigue had a larger impact than cognition; both of these were, however, lower than the threshold for clinical relevance for the UK value set (0.074 [38]). There was a significant and marked impact of other disease symptoms, measured by proxies such as receiving treatment with depression and walking/spasticity/pain medicines.

Table 2 – Pearson correlation coefficients.

Domain/value set	EDSS	Fatigue	Cognition
Fatigue	0.26	–	0.48
Cognition	0.17	–	–
Mobility	0.77	0.26	0.17
Self-care	0.67	0.23	0.16
Usual activities	0.64	0.39	0.32
Pain/discomfort	0.37	0.37	0.27
Anxiety/depression	0.13	0.33	0.30
Utility (UK value set)	−0.69	−0.45	−0.34
Utility (Swedish value set)	−0.71	−0.46	−0.36
Utility (French value set)	−0.77	−0.44	−0.33

Note. All correlation coefficients with $P < 0.001$.
EDSS, Expanded Disability Status Scale.

The range of utilities varies with the value set (see the Appendix in Supplemental Materials), and hence the magnitude of the coefficients varies between the regression models. In particular, the coefficients for EDSS were much smaller for the Swedish value set than for the UK and French value sets, which is a reflection of the smaller value range in the Swedish value set. The significance of predictors of utility and direction was similar between the value sets, with the exception of living situation and disease modifying treatment, which were significant using only the French value set.

Value Set Analysis

The most influential EQ-5D-3L domains within each value set for the most frequent health states at EDSS level 4 and above were examined. Table 4 presents the most frequent health states within each EDSS level in our sample with its corresponding utility values and ranked domains: 21222 (EDSS 4 [24% of all health states within this EDSS level], 5 [25%], and 6 [16%]); 22222 (EDSS 6.5 [18%] and 7 [19%]); and 33322 (EDSS 8 [9%] and 9 [22%]). These three health states represented in total 20% of all health states reported by the patients. Health state 21222 was the most frequently reported health state in the overall sample (11%). Health state 22222 represents some problems in all the five domains, whereas health state 33322 represents extreme problems in the mobility, self-care, and usual activities domains and some problems in the pain/discomfort and anxiety/depression domains.

A comparison of the country value sets shows that the importance of domains varies by value set for these health states. For example, for health states 21222 and 22222, the usual activities domain is the most influential domain in the Swedish value set, whereas for the UK value set this is the least influential domain. Similarly, pain/discomfort is an influential domain across all value sets but less so for the Swedish and French value sets. Anxiety/depression is the most influential domain in the Danish and Dutch value sets, but this domain is not the most problematic domain at moderate EDSS levels in our sample of patients with MS (see Fig. 1). For the more severe health state 33322, there was less variation between value sets in terms of the order of influence of the domains, with mobility being the most influential domain across all value sets, and the Swedish and Danish value sets having a diverting order of domains compared with the rest of the value sets. The anxiety/depression domain is the second most influential domain in the Danish value set, but is not the most problematic domain in our sample of patients with MS at severe EDSS levels (see Fig. 1).

The Spanish, French, Portuguese, and UK value sets gave the lowest utilities for these three health states that were the most common in our sample. Notably, health state 33322 was rated as worse than death with the UK, French, Italian, Portuguese, and Spanish value sets, but not with the Swedish, Danish, and Dutch value sets (although the Swedish value set is the only one to not produce negative values).

Discussion

In this article we studied the association of fatigue, cognitive difficulties, EQ-5D-3L domains, disability, and utility estimated

Table 3 – Predictors of utility, final main effects OLS model.

Variable	UK value set		Swedish value set		French value set	
	Coefficient (95% CI)	P value	Coefficient (95% CI)	P value	Coefficient (95% CI)	P value
Intercept	1.024 (1.007 to 1.042)	<0.0001	0.988 (0.978 to 0.998)	<0.0001	1.085 (1.067 to 1.103)	<0.0001
Age	NS		0.0003 (0.0001 to 0.0005)	0.0004	NS	
MS type (reference category: RRMS)						
SPMS	−0.01 (−0.022 to 0.001)	0.069	−0.007 (−0.012 to −0.003)	0.0009	−0.019 (−0.029 to −0.008)	0.0004
PPMS	−0.034 (−0.045 to −0.022	<0.0001	−0.013 (−0.017 to −0.008)	<0.0001	−0.037 (−0.048 to −0.026)	<0.0001
Employment (reference category: employed)						
Not employed (in workforce)	−0.033 (−0.041 to −0.024)	<0.0001	−0.012 (−0.015 to −0.008)	<0.0001	−0.03 (−0.037 to −0.022)	<0.0001
Retired	−0.022 (−0.033 to −0.01)	0.0002	−0.008 (−0.013 to −0.002)	0.005	−0.014 (−0.024 to −0.003)	0.011
Living situation (reference category: alone)						
With family, friend	NS		NS		−0.011 (−0.018 to −0.003)	0.008
Nursing home	NS		NS		−0.024 (−0.058 to 0.009)	0.1572
EDSS (reference category: EDSS 0)						
EDSS 1	−0.05 (−0.066 to −0.034)	<0.0001	−0.025 (−0.031 to −0.019)	<0.0001	−0.053 (−0.067 to −0.038)	<0.0001
EDSS 2	−0.09 (−0.106 to −0.074)	<0.0001	−0.057 (−0.064 to −0.051)	<0.0001	−0.112 (−0.127 to −0.098)	<0.0001
EDSS 3	−0.132 (−0.15 to −0.114)	<0.0001	−0.101 (−0.108 to −0.094)	<0.0001	−0.206 (−0.223 to −0.19)	<0.0001
EDSS 4	−0.169 (−0.187 to −0.15)	<0.0001	−0.129 (−0.137 to −0.122)	<0.0001	−0.277 (−0.294 to −0.26)	<0.0001
EDSS 5	−0.195 (−0.214 to −0.177)	<0.0001	−0.144 (−0.151 to −0.137)	<0.0001	−0.319 (−0.336 to −0.302)	<0.0001
EDSS 6	−0.236 (−0.256 to −0.216)	<0.0001	−0.158 (−0.166 to −0.15)	<0.0001	−0.376 (−0.394 to −0.358)	<0.0001
EDSS 6.5	−0.266 (−0.288 to −0.244)	<0.0001	−0.168 (−0.176 to −0.159)	<0.0001	−0.418 (−0.438 to −0.398)	<0.0001
EDSS 7	−0.358 (−0.379 to −0.338)	<0.0001	−0.193 (−0.201 to −0.184)	<0.0001	−0.51 (−0.529 to −0.492)	<0.0001
EDSS 8	−0.626 (−0.647 to −0.605)	<0.0001	−0.246 (−0.254 to −0.238)	<0.0001	−0.749 (−0.768 to −0.729)	<0.0001
EDSS 9	−0.886 (−0.924 to −0.848)	<0.0001	−0.302 (−0.317 to −0.287)	<0.0001	−0.947 (−0.982 to −0.913)	<0.0001
Fatigue (VAS 0–10)	−0.024 (−0.026 to −0.023)	<0.0001	−0.011 (−0.012 to −0.01)	<0.0001	−0.024 (−0.025 to −0.022)	<0.0001
Cognition (VAS 0–10)	−0.014 (−0.016 to −0.013)	<0.0001	−0.007 (−0.007 to −0.006)	<0.0001	−0.015 (−0.016 to −0.014)	<0.0001
Treated with DMT (yes vs. no)	NS		NS		0.008 (0.001 to 0.015)	0.0343
Treated for walking problems, spasticity, or pain (yes vs. no)	−0.045 (−0.054 to −0.037)	<0.0001	−0.014 (−0.017 to −0.011)	<0.0001	−0.041 (−0.048 to −0.033)	<0.0001
Treated for depression (yes vs. no)	−0.047 (−0.058 to −0.037)	<0.0001	−0.025 (−0.029 to −0.021)	<0.0001	−0.043 (−0.052 to −0.033)	<0.0001

Note. Country was included in the regression models as a covariate (results not shown).
CI, confidence interval; DMT, disease modifying treatment; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; NS, not significant; PPMS, primary progressive MS; RRMS, relapsing remitting MS; SPMS, secondary progressive MS; OLS, ordinary least squares; VAS, visual analogue scale.

with different Western European value sets. We used data from the largest study of MS of its kind; this large sample of patients enables more precise estimates of utility, in particular for the higher disability levels.

First, our analysis demonstrates the strong relationship of disability with utility, which confirms findings in several other studies [17,39–45]. Similar to other studies, the utility decrements between EDSS levels flatten at the moderate part of the scale, that is, between 4 and 6, compared with the lower and most severe EDSS levels. This is primarily related to issues with the EDSS scale such as difficulties distinguishing the severity levels in the mid-range scale [46]. Disability was strongly correlated to the EQ-5D-3L domains of mobility, self-care, and usual activities but weakly correlated to the pain/discomfort and anxiety/depression domains. This is in line with a study on a German MS sample that also found no association between disability and these two domains [43]. Issues in pain/discomfort and anxiety/depression were common in our sample, even so at the milder disability levels, suggesting that these are complementary and important disease symptoms not captured by the EDSS.

Second, fatigue and cognitive difficulties were highly common symptoms in our sample, with frequencies comparable with other studies [13,14]. Fatigue and cognitive difficulties had only a weak bivariate correlation to disability. The association between fatigue [14,47–51], cognition [52,53], and EDSS has been reported previously to be ambiguous. The EQ-5D-3L domains of usual activities, pain/discomfort, and anxiety/depression were moderately correlated to fatigue and cognition, suggesting that even though the EQ-5D-3L does not directly measure fatigue and cognition, these HRQOL aspects are to some extent captured by their correlation to the EQ-5D-3L domains.

Type of MS was self-reported by patients and the distribution found in this study was not representative of epidemiological data [54] but similar to other studies with similar methodology [17,40].

Table 4 – Comparison of coefficients from EQ-5D-3L models and utility values for the most common health states in the total sample.

Domain	Value set							
	Danish [28]	Dutch [25,30]	French [29]	Italian [32]	Portuguese [33]	Spanish [25,31]	Swedish [27]	UK [24]
Ranked domains for health state 21222 (MO, SC, UA, PD, and AD) (most frequent health state at EDSS levels 4, 5, and 6)								
1	Anxiety/ depression	Anxiety/ depression	Usual activities	Pain/ discomfort	Mobility	Mobility	Usual activities	Pain/ discomfort
2	Pain/discomfort	Pain/ discomfort	Mobility	Anxiety/ depression	Pain/ discomfort	Pain/ discomfort	Mobility	Anxiety/ depression
3	Mobility	Mobility	Pain/ discomfort	Usual activities	Usual activities	Usual activities	Anxiety/ depression	Mobility
4*	Usual activities	Usual activities	Anxiety/ depression	Mobility	Anxiety/ depression	Anxiety/ depression	Pain/ discomfort	Usual activities
21222 Utility	0.6548	0.651	0.487	0.775	0.449	0.648	0.7119	0.62
Ranked domains for health state 22222 (most frequent health state at EDSS levels 6.5 and 7)								
1	Anxiety/ depression	Anxiety/ depression	Self-care	Self-care	Self-care	Self-care	Usual activities	Pain/ discomfort
2	Self-care	Pain/ discomfort	Usual activities	Pain/ discomfort	Mobility	Mobility	Mobility	Self-care
3	Pain/discomfort	Self-care	Mobility	Anxiety/ depression	Pain/ discomfort	Pain/ discomfort	Anxiety/ depression	Anxiety/ depression
4	Mobility	Mobility	Pain/ discomfort	Usual activities	Usual activities	Usual activities	Pain/ discomfort	Mobility
5	Usual activities	Usual activities	Anxiety/ depression	Mobility	Anxiety/ depression	Anxiety/ depression	Self-care	Usual activities
22222 Utility	0.5919	0.569	0.275	0.718	0.292	0.514	0.6843	0.516
Ranked domains for health state 33322 (most frequent health state at EDSS levels 8 and 9)								
1	Mobility	Mobility	Mobility	Mobility	Mobility	Mobility	Mobility	Mobility
2	Anxiety/ depression	Self-care	Self-care	Self-care	Self-care	Self-care	Usual activities	Self-care
3	Self-care	Pain/ discomfort	Usual activities	Usual activities	Usual activities	Usual activities	Anxiety/ depression	Pain/ discomfort
4	Pain/discomfort	Anxiety/ depression	Pain/ discomfort	Pain/ discomfort	Pain/ discomfort	Pain/ discomfort	Pain/ discomfort	Usual activities
5	Usual activities	Usual activities	Anxiety/ depression	Anxiety/ depression	Anxiety/ depression	Anxiety/ depression	Self-care	Anxiety/ depression
33322 Utility	0.3371	0.115	−0.263	−0.026	−0.34	−0.4	0.5486	−0.166

Note. Regression coefficients from each country value set were ranked from the largest to the lowest utility decrement within each of the health states 22222, 21222, and 33322 (1 = most influential domain; 5 = least influential domain). Utility denotes the utility associated with the health state.

Domains: MO, mobility; SC, self-care; UA, usual activities; PD, pain/discomfort; AD anxiety/depression; EDSS, Expanded Disability Status Scale; EQ-5D-3L, three-level EuroQol five-dimensional questionnaire.

* Because there were “no problems” with self-care in health state 21222, this domain was not ranked.

This may be a result of study methodology or patients misclassifying their MS type. The coefficients of MS type in the utility regression model should therefore be interpreted with caution.

The analysis also demonstrates that different value sets lead to substantially different utilities, in particular for the more severe disease states, with expected higher utilities for experience-based utilities (Sweden) [27]. In the context of patients with MS, this is in line with the findings of Takemoto et al. [45], who found that the UK and Brazilian value sets led to diverging utilities in patients with MS. The statistical significance of predictors of utility and direction was similar overall in regression models of utility in the UK, Swedish, and French value sets. Controlling for confounding factors, disability had the largest impact on utility as measured by the magnitude of the coefficients. Regression analyses further showed that fatigue and cognitive difficulties are significant predictors of utility even when controlling for disability, although the statistical significance could be a result of the large sample size. In a health policy context this means that fatigue and cognitive difficulties are symptoms that are important to address because improvements would positively impact on utility values.

The importance of the different domains within each value set was illustrated by ranking the most influential domains for a few common health states in this MS population. Although our study did not systematically and quantitatively compare the relative ranking of domains within each value set across the entire spectrum of EQ-5D-3L health states, our analysis could serve as an illustration of which domains are influential in the value sets of worsening health states relevant to patients with MS in connection to which domains are actually problematic in patients with MS. Whether these differences in ranking between value sets reflect actual differences in preferences, in combination with differences in methodology, cannot be determined by our analysis. Our descriptive comparison shows that there is a variation between value sets in the ranking of the most influential domains. This is of relevance from a policy perspective. For example, targeting improvements in levels of pain, which is an important domain in MS, would lead to a higher absolute increase in utility in those value sets in which pain/discomfort is an important domain (e.g., the UK value set) but less so in other value sets (e.g., the Swedish value set).

From a policy perspective, the diverging utilities are an important point of consideration because the large differences in utility will lead to large differences in effect as measured by QALYs when using utility values in economic evaluations, given that the length of time spent in the severe health states will be long from a lifetime perspective. Another difference between value sets lies in the health states worse than death, which are not present in all value sets. As a consequence of the larger utility range when health states worse than death are possible, potential health and QALY gains may be more substantial in these cases.

Several limitations of this study were noted. Limitations of the study methodology have been elaborated elsewhere [18]. Patients were recruited from patient organizations, which tend to result in a sample of patients with more severe disease. The study sample is therefore not representative of the general MS population. Fatigue and cognitive difficulties were measured by VAS in this study so as to not overburden patients because other validated instruments are rather lengthy. VAS has been criticized for providing no interpretable meaning to specific points on the scale [55]; we, however, analyzed only the presence of symptoms, and not the severity as such.

Key variables in the regression models were self-reported by patients, which may be affected by, for example, recall bias or "unsure" answers. Others have found relapse to be associated with utility [17,40].

Areas for future research include exploring preferences for new interventions, such as disease-modifying treatments, in terms of which symptoms should be targeted from a patient perspective. In addition, it would be interesting to explore the impact of different country value sets on the outcome of economic evaluations and its implications on funding decisions.

Conclusions

The strong relationship of disability with utility was confirmed. Fatigue and cognitive difficulties are highly prevalent symptoms that are weakly correlated to disability, but are significant predictors of utility. Utilities derived with different value sets lead to considerably different utilities, in particular for more severe disability levels. The precise reasons for these differences and the impact of the different value sets on the outcome of economic evaluations and funding decisions are important areas for further research.

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Supplemental Materials

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