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Self-perceived physical functioning and health status among fully ambulatory multiple sclerosis patients

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Running title: Self-perceived health status in mild MS

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Abstract

We investigated the self-perceived health status among multiple sclerosis (MS) patients with no or mild disability according to the Expanded Disability Status Scale (EDSS) and the impact of self-rated physical functioning. A sample of fully ambulatory (EDSS ≤3.5) consecutive patients with MS was included after screening for major cognitive impairment. The EDSS was used to measure nervous system signs or disability, and the self-rated health status was assessed using the SF-36 Health Survey. The normative SF-36 data for the general population of Italy were used for comparison. **The 197 MS patients analyzed (150 women and 47 men) had significantly lower mean SF-36 scores than the general population, except for bodily pain.** The patients did not differ significantly by gender. The same analysis performed on a subsample of 107 patients (81 women and 26 men) with minimal disability in one functional system (EDSS ≤2.0) yielded similar results. EDSS was weakly correlated with the physical functioning subscale and explained only 2% of the variance in the physical functioning subscale. The regression of the physical functioning subscale on the other seven SF-36 subscales was significantly lower among MS patients than in the general population for all subscales, except for role limitation due to physical health problems and social functioning. Neither disease course nor duration correlated significantly with SF-36 subscales**.** The SF-36 physical functioning subscale seemed to indicate physical functioning more sensitively than EDSS. These findings should encourage the implementation of specific strategies aimed at improving the quality of the self-perceived health status already in the early disease stage.

Key words: multiple sclerosis · health status · SF-36 · EDSS · Italy

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Introduction

Multiple sclerosis (MS) is a chronic nervous system disorder affecting young adults. The disease course is heterogeneous, characterized by a wide spectrum of symptoms and uncertainty. The initial relapsing-remitting phase with minor disability is usually followed by progression and increased physical impairment within a quite unpredictable number of years [36].

MS patients have worse self-rated physical and mental health status than the general population, which affects the patients' overall quality of life [14, 15]. In clinical practice, the strategies aimed at improving MS patients' health-related well-being most frequently focus on patients with greater disability. Although health professionals perceive physical impairment as a relevant cause of patients' poorer quality of life [25], self-perceived physical functioning among nondisabled or mildly disabled MS patients does not usually lead to concern. Further, the rating scales commonly used to measure physical impairment, such as the Expanded Disability Status Scale (EDSS) [11], almost exclusively reflect health professionals' objective assessment, and the patients' actual self-perception of their health status can be overlooked, particularly among those with no or little physical impairment. The studies aimed at investigating health-related quality of life and self-perceived health status among MS patients have mostly been conducted on patients with a wide range of disability, thus including more physically impaired ones [17].

This study investigated the self-perceived health status of MS patients with no or mild disability at neurological examination. The impact of perceived physical functioning on different health-related domains in this subset of MS patients was assessed and its relevance compared with a reference population.

Material and methods

Study population

The study was conducted on a sample of MS patients residing in northern Sardinia, Italy, an area at high risk for the disease [22, 23]. The patients were recruited through the MS Centre registry at the Institute of Clinical Neurology, University Hospital of Sassari, the main referral specialized health structure for MS patients residing in northern Sardinia. Details on the Sassari MS Centre case registry are reported elsewhere [22].

Patients affected by MS according to the Poser Committee criteria [20] were enrolled among those consecutively referring to the Centre for clinical follow-up from January 1

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to December 31, 2004. Inclusion criteria comprised fully ambulatory status (EDSS score 3.5 or less) and MS clinical onset [21] between 1965 and 2004. Exclusion criteria were comorbidity (chronic disorders) and an exacerbating phase of the disease within the previous 3 months. An appointed ethics committee approved the study. Clinical information, including EDSS scores and disease course [13], was purposely updated during a neurological examination performed at the time of the study. The disease course was categorized into three classes: relapsing-remitting, relapsing-progressive/secondary progressive and primary progressive [13]. Disease duration was expressed as the time elapsing from clinical onset to the time of the study.

Measures

The EDSS was used to assess disability. This instrument enables numerical evaluation of patients' global physical impairment from partial scores attributed to determined nervous system functions detected at clinical neurological examination [11].

The patients' self-perceived mental and physical health status was measured using the 36-Item Short Form Health Survey (SF-36) [31, 32], a generic health survey assessing the most relevant health domains to both diseased and healthy individuals. SF-36 was purposely chosen as it allows comparisons between MS patients and a reference population by virtue of its construct, psychometric properties and external validity (robustness and generalizability) [32, 34]. The SF-36 is among the most widely used rating scales for measuring self-perceived health status among MS patients [17]. The SF-36 explores eight main domains [32]: physical functioning, role limitations due to physical health problems (role–physical), bodily pain, general health, vitality, social functioning, role limitations due to emotional health problems (role–emotional) and mental health. The first four subscales primarily measure physical health and the last four primarily measure mental health. The general health and vitality subscales are sensitive to both physical and mental health [32].

Normative SF-36 data by gender and age are available for the general population of Italy [1, 2, 35]. The normative sample was studied in 1995 and consisted of 2031 individuals, 1032 (50.8%) women and 999 (49.2%) men with a mean age of 47.7 years. The sample is representative of the general population, with 37% of respondents residing in southern Italy. Detailed sampling procedures and further sample features are reported elsewhere [2, 8].

Procedures

The SF-36 Italian standard version [2] was administered to the patients at the hospital setting. The questionnaire content was outlined to the patients in a standardized way. Cognitive impairment can also be detected in mildly disabled MS patients [12, 27]. To

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overcome potential interference with reliable responses to questionnaires, the Raven Coloured Progressive Matrices (RCPM) test [24] was used to screen for major intellectual deficits. RCPM is a nonverbal intelligence test based on perceptual ability and visuospatial reasoning. RCPM raw scores were age-adjusted according to normative data [24]. MS patients with an RCPM score corresponding to an intelligence quotient (IQ) of 69 or higher [24] were included in the study.

Statistical analysis

The SF-36 scores and substitutions for missing values were calculated according to standardized procedures described elsewhere [32]. Scores were transformed to a 0 (minimum) to 100 (maximum) scale. The statistical analysis was performed only for the domains with 50% or more complete items and after substituting missing values. The single subscale scores and not the composite ones were analyzed due to their better psychometric properties. The analysis was based on 35 items, as the transitional health status item was not included.

SF-36 subscale scores were then standardized to the general population of Italy, and *z* scores were calculated for each subscale using the mean (SD) of the age and gender-specific reference norms. These scores were then rescaled to a mean (SD) of 50 (10), which was therefore the average score for the general population of Italy on any subscale. These standardized scores were then compared between the MS patients and general population. One-sample *t*-tests were used in comparing the standardized subscale scores for the MS population with the data from the general population.

The association between EDSS and the physical functioning subscale was estimated using Pearson correlation coefficients. The impact of physical functioning on self-perceived health status was assessed by estimating the regression coefficients using physical functioning as an independent variable and each of the other subscales as a dependent variable in separate regression analyses. The regression coefficients between the physical functioning subscale and the other SF-36 subscales were estimated for the MS patients and the general population and also by gender. Significant differences in these regression coefficients between the subgroups were tested using univariate analysis of covariance (ANCOVA) with each SF-36 subscale score as dependent variable, group (MS patients and the general population) and gender as a fixed factors and the physical functioning subscale as covariate. A significant interaction effect between the physical functioning subscale and group status in this model was interpreted as a significant difference in the corresponding regression coefficients. Significance was set at $P < 0.05$, two-tailed tests. The SPSS for Windows version 13 statistical software (SPSS Inc., Chicago, IL, USA) was used for all analyses. For ANCOVA the general linear model procedure was used.

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Results

According to inclusion criteria, 218 MS patients with EDSS ≤3.5 were eligible for the study. Of these, 203 patients (93%) (156 women and 47 men) consented to participate in the study and underwent clinical neurological examination and the RCPM test. A total of 197 patients (150 women and 47 men, female-male ratio 3.2) scored a corresponding IQ > 69 on the RCPM test and were thus administered the SF-36 questionnaire and considered for statistical analysis. **The clinical and demographic characteristics are reported in Table 1.**

Table 1 should be inserted here.

SF-36 was completed thoroughly by 183 (93%) patients. Of 6895 items (197 times 35), 66 were missing (1.0%). Substitution could be performed for 41 (0.6%) of these items.

Figure 1 should be inserted here.

All mean subscale scores for MS patients were significantly reduced, except for bodily pain (Figure 1). The mean score for physical functioning was especially reduced, almost one SD below the mean score for the general population. Mean scores of male and female MS patients did not differ significantly (data not shown).

Mean standardized SF-36 subscale scores were also analyzed for a subgroup of 105 patients (79 women and 26 men) with EDSS ≤2.0: "minimal disability in one functional system". They were also significantly lower than in the general population, except for bodily pain and mental health.

The correlation between EDSS and the physical functioning subscale in the total MS sample was rather low (Pearson correlation coefficient = –0.14, $P = 0.05$), with EDSS explaining only 2.0% of the variation in the physical functioning subscale. EDSS also correlated, though poorly, with role–physical, general health and vitality (correlation coefficients of –0.17, –0.19 and –0.17, respectively). EDSS did not correlate significantly with the other SF-36 subscales. Neither disease course nor disease duration correlated significantly with any SF-36 subscale.

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Benzodiazepines and antidepressants were assumed by 24 (14.2%) patients as symptomatic treatment. No main effect of such therapies was found on the SF-36 subscales, adjusting for EDSS scores and disease duration (data not shown).

Running regression analyses with the physical functioning subscale as the independent variable and each of the other 7 subscales as the dependent variable showed significantly smaller regression coefficients among the MS patients compared with the general population for all subscales except for role–physical and social functioning (**Table 2**). Among men, the regression coefficient was significantly lower for general health among MS patients compared with the general population, whereas the other subscales did not differ. Among women, the MS patients had a significantly lower regression coefficient for all SF-36 subscales except for role–physical and social functioning.

Table 2 should be inserted here.

Discussion

The study showed that MS patients with no to mild disability according to EDSS score ≤3.5 rate their health status as poorer than the general population for all relevant health status domains except for bodily pain. This was true even for a subsample of MS patients with minimal disability in only one functional system on EDSS (score ≤2.0). **Interestingly, among MS patients physical functioning and the role limitation due to physical health problems were rated especially poorly compared with the other subscales, and were reduced compared with the general population despite no or mild disability.** Self-perceived general health and vitality were also worse in this subset of patients. Their emotional status interfered more with concentration, work productivity and other activities than among the general population. Physical and emotional health status had a greater impact on the quantity and quality of normal social activities compared with the general population in this group of non disabled to mildly disabled MS patients.

Further, this subset of MS patients also had lower scores than the general population in mental health status, although to lesser degree than for the other scales. Three of the five questions included in this scale are related to depression and the lower score might indicate that also this group of patients has a slightly higher rate of depression than found in the general population. Fatigue and

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depression are generally highly frequent among MS patients and probably also affect the other domains of the health-related quality of life [10]. I.e. fatigue might likely be an important component of self-rated poor physical functioning, which is not captured by the more objective disability measurement EDSS in mild MS.

In accordance with other studies [10, 18] self-rated bodily pain in our patients did not differ from that of the general population and for both genders. Physical pain is not a common clinical feature of MS, with the exception of pain due to spasticity for EDSS scores higher than those used as inclusion criteria for the study. SF-36 bodily pain subscale has proved to be a reliable measure for painful chronic conditions, such as fibromyalgia, rheumatoid and chronic arthritis, osteoporosis [19], migraine and cluster headache [6]. Given the characteristics of pain in MS and the subscale dependence on physical scores, this subscale might not represent a suitable instrument for self-rating health status in these patients.

In agreement with other studies [9, 10], the self-perceived health status among our patients did not depend on the number of years with the disease, **nor the disease course significantly affected the patients' self-rated health status. No differences were found between those receiving symptomatic treatment and those did not receive such treatment.**

In this fully ambulatory MS sample, physical functioning was especially perceived worse among MS patients than among the general population. This was true even for patients with minimal disability according to EDSS.
Because the SF-36 physical functioning subscale measures among other perceived daily ambulatory functioning, such as climbing stairs and walking different distances, our study results conceptually disagreed with the EDSS definition of fully ambulatory. Such discrepancy was further corroborated by the weak statistical correlation (2.0%) found between the EDSS and the SF-36 physical functioning subscale, raising uncertainty about EDSS sensitivity in measuring physical impairment at this disease stage and indicating the higher sensitivity of SF-36 physical functioning subscale. This is in accordance with other authors reporting on EDSS as an instrument to assess nervous system impairment but not overall mobility [26, 29]. Interestingly, by means of movement analysis technique, subclinical evidence of gait control dysfunction has been reported for MS patients with even "minimal disability in one functional system" (EDSS score of 0 to 2), who therefore had no objective walking restriction, signs of motor involvement or clinical spasticity [4].

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The objective versus subjective measurement of physical functioning in MS may differ in the same patient. The patients may be able to catch their own impaired physical functioning at an earlier stage than neurologists objectively can. Nortvedt et al. [16] have shown that self-rated health can predict a change in MS disability measured using EDSS. In this study, high scores for the SF-36 general health subscale and the mental health subscale at baseline were correlated with decreased EDSS after 12 months. The risk of worsening in EDSS after 1 year was two-fold among patients with poor or fair self-rated health status at baseline versus those rating their health as good, very good or excellent. More objective measures such as EDSS itself had no predictive value at baseline. The authors concluded that self-rated health might partly reflect disease activity and thus represent a risk factor in the natural history of the disease.
The meaningfulness of physical impairment on overall self-rated health status has been reported to differ between patients and evaluators [25]. In the study by Rothwell et al. [25], both clinicians and patients rated the impact of physical impairment differently compared with the general population and for the most relevant health domains. However, clinicians weighted the physical involvement of the disease more strongly on overall health status than patients did, whereas patients weighted their mental health and vitality as being more important than the clinicians did. The study included patients with moderate to severe disability (EDSS score ranged from 1 to 8). This evidence points to factors other than physical functioning playing a significant role in these patients' self-perceived health status.

Our study population did not comprise all MS patients living in the study area with the specific inclusion criterion of fully ambulatory status, and was a hospital-based sample of consecutive MS patients. These are the patients who undergo immune prophylaxis and need periodic follow-up visits at the Centre, and are therefore highly representative of a MS population with low disability scores.
Cultural differences between Sardinians and mainland Italians [7] might influence self-rated health status. Nevertheless, due to its cross-cultural validity, appropriateness and content comparability in tests on different Caucasian populations [5, 30, 33], the SF-36 was chosen to also avoid capturing the effect of such differences Further, more than one third of the normative SF-36 data for Italy were collected from southern Italy [2], where Sardinia is located.

Conclusions

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MS patients with no to mild disability on EDSS rate their health status as being significantly worse than the general population does. This is especially true for self-rated physical functioning in both genders with MS. Nevertheless, factors other than physical functioning contribute to the low scores for the other dimensions compared with the general population. In non to mildly disabled MS patients, the SF-36 physical functioning subscale seems to detect subclinical physical impairment and is thus a more sensitive indicator of physical functioning than EDSS. **These findings should encourage the implementation of disease-specific interventions targeting a broad spectrum of health issues for MS patients even in the early stages of the disease.**

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Figure legend

Figure 1. The mean standardized scores and 95% confidence interval for each SF-36 domain in MS patients versus the mean score of 50 in the general population of Italy

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Tables

Table 1. Clinical and demographic characteristics of 197 MS patients in Sardinia in the study

	n	%	Mean (SD)
Gender			
Men	47	23.9	–
Women	150	76.1	–
Mean age at examination (SD), years			
Men	–	–	41.0 (9.8)
Women	–	–	41.3 (9.7)
MS classification			
Clinically definite MS	180	91.4	–
Laboratory-supported definite MS	2	1.0	–
Chronic progressive MS	14	7.1	–
Laboratory-supported progressive MS	1	0.5	–
Clinical course			
Relapsing-remitting	180	91.4	–
Relapsing-progressive/secondary progressive	12	6.1	–
Primary progressive	–	–	–
Mean EDSS score (SD)			
Men	–	–	2.0 (1.2)
Women	–	–	2.2 (0.9)
Mean age at onset (SD), years			
Men	–	–	29.2 (8.8)
Women	–	–	28.5 (9.3)
Mean disease duration since onset, years (SD)			
Men	–	–	11.8 (8.4)
Women	–	–	12.8 (7.8)
Mean disease duration since diagnosis, years (SD)			
Men	–	–	8.9 (6.3)
Women	–	–	9.3 (5.7)
Mean raw scores on Raven Coloured Progressive Matrices (SD)	–	–	32.1 (4.2)
Men	–	–	31.0 (4.2)
Women			

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Table 2. Total and gender-specific regression coefficients between physical functioning and the other SF-36 subscales (ANCOVA) in MS patients (n = 197) and in the general population (n = 2031) [2]

	Physical functioning	Role–physical	Bodily pain	General health	Vitality	Social functioning	Role–emotional	Mental health
Physical functioning								
Total								
MS	–	0.56	0.41	0.39	0.48	0.40	0.27	0.23
General population	–	0.59	0.60	0.63	0.60	0.50	0.46	0.48
P[a]	–	NS	0.0001	<0.0001	0.02	NS	<0.002	<0.0001
Men								
MS	–	0.74	0.46	0.41	0.65	0.47	0.46	0.42
General population	–	0.57	0.57	0.59	0.58	0.56	0.48	0.47
P[a]	–	NS	NS	0.04	NS	NS	NS	NS
Women								
MS	–	0.50	0.39	0.38	0.42	0.36	0.22	0.17
General population	–	0.61	0.63	0.66	0.61	0.45	0.44	0.48
P[a]	–	NS	0.0002	<0.0001	0.003	NS	0.003	<0.0001

[a] Statistical significance of the interaction effect between the physical functioning subscale and group status on SF-36 subscale scores (ANCOVA).

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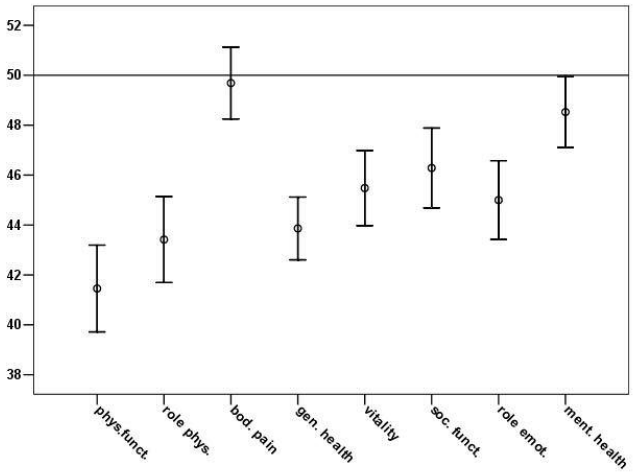
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