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Change in disability profile and quality of life in multiple sclerosis patients: a five-year longitudinal study using the Multiple Sclerosis Impact Profile (MSIP)

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Abstract

Background: Evidence on the progress of disease severity in Multiple Sclerosis (MS) is generally limited in scope.
Objectives: To examine the course of a broad spectrum of MS-related disabilities and quality of life (QOL) in relation to disease severity, and responsiveness of the Multiple Sclerosis Impact Profile (MSIP).
Methods: The mortality rate was calculated after checking the national population register for vital status of the initial cohort. We performed a longitudinal study among 245 patients with MS attending the Groningen MS Center in the Netherlands. We assessed these patients in 2004 and 2009 using a postal survey including the MSIP to evaluate disabilities, the World Health Organization Quality of Life-Abbreviation version (WHOQOL-BREF) to evaluate QOL, and the ambulation question of the Expanded Disability Status Scale (EDSS) to evaluate disease severity. Responsiveness of the MSIP was estimated using standardized response mean (SRM).
Results: Increase of disability in the MSIP disability domains and loss of QOL were most prevalent and pronounced in patients with EDSS 0 to < 4.5 in 2004. MSIP and QOL scores were remarkably stable in the higher disease severity groups. Mortality rates were highest (24%) in patients with EDSS ≥ 7 to < 10 in 2004. SRM indices for the MSIP ranged between 0.26 and 0.56.
Conclusions: Prominent increases in multiple aspects of disability and loss of QOL occur especially in the early stages in MS. Health care interventions may lead to health and QOL gains, in particular when offered to patients in the first stage of the MS process. Responsiveness was sufficient for nine of the 11 MSIP domains.

Keywords

disability, longitudinal study, mortality, multiple sclerosis, Multiple Sclerosis Impact Profile, quality of life

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Introduction

Multiple Sclerosis (MS) is a chronic neurological disease of the central nervous system and is potentially the most common cause of neurological disability in young adults.[1] The disease course is characterized by either acute periods of deterioration or relapses (about 85% of patients initially), or gradual progressive deterioration of neurological functioning, or combinations of the two.

Understanding the course of chronic diseases is a recurrent objective in research. Natural history studies, for example, are follow-up studies that provide the strongest evidence. These studies thoroughly examine the course of the disease among a large number of patients for a period of about 30–40 years. Natural history studies in MS have

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resulted in clearly defined courses of the disease and identified landmarks or disability milestones related to these courses. Milestones are clinically detectable thresholds of irreversible disability in the disease process regarding MS, usually defined using the Expanded Disability Status Scale (EDSS).[2] Examples of these milestones are EDSS score 4 (limited walking but without aid), score 6 (walking with unilateral aid) and score 7 (wheelchair-bound). Two recently published studies reported comparable findings about the relationship between age and reaching disability milestones. Confavreux and Vukusic[3] followed a cohort of patients with MS (n = 1844) for about 30 years and estimated the median age at reaching milestones: 44 years for EDSS score 4, 55 years for score 6, and 63 years for score 7. Kremenchutzky et al. [4] followed a cohort of patients (n = 505) for about 25 years and found, despite considerable individual variation, that the mean age at reaching EDSS score 4 was 40 years. From the first milestone onwards, time between disability milestones was remarkably comparable with the findings of Confavreux and Vukusic.[3]

Studies with a shorter follow-up period have provided weaker evidence than did natural history studies. Another difference compared with natural history studies is that results in these studies took into account the recently available disease-modifying therapies. Pittock et al.,[5] for example, studied the change in disability over 10 years in a cohort of 161 patients with MS, of which 15% had received immunomodulatory therapy. Some 30% of these patients progressed, while most patients remained stable or minimally progressed. Trojano et al.[6] examined the impact of interferon-beta on disease progression in patients with relapsing–remitting MS (n = 1504) during a 7-year follow-up study and found significant delays in reaching disability milestones (EDSS scores 4 and 6). Bermel et al.[7] examined 122 patients an average of 15 years after participation in an interferon trial and found that EDSS scores highly correlated with quality of life (QOL) and self-care independence. Finally, Stenager et al. found at 5-year follow-up a significant increase in the number of acute and chronic pain syndromes[8] and sexual dysfunction,[9] especially in patients with increasing disability, while Pfleger and colleagues reported a negative impact of MS on economic aspects of living even within a few years of disease onset.[10,11]

Evidence on long-term follow-up of QOL among patients with MS is lacking, but cross-sectional studies have shown that MS patients experience lower levels of QOL than the general population.[12,13] MS-related symptoms and disabilities are a likely explanation for this reduced QOL. This has been demonstrated for a number of symptoms and disabilities, such as fatigue,[14-16] cognitive and emotional functioning,[17] depression,[14,15,18,19] chronic pain,[20] and bladder and sexual dysfunction.[21]

Risk of suicide, probably related with a poor QOL, among persons with MS is about three times higher during the first years after diagnosis as expected in the general population.[22] Furthermore, among patients diagnosed with MS more than 20 years ago, the suicide risk is almost twice as high as expected, probably because these patients experience the most serious consequences of the disease.[22]

In our previous study,[23] in which we examined the relative impact of MS-related disabilities on QOL, using the Multiple Sclerosis Impact Profile (MSIP) we found that impairment in mental functioning was the most important predictor for QOL.

The MSIP is a disability measure based on the International Classification of Functioning, Disabilities and Health (ICF).[24] Items for the MSIP were selected by a expert panel (n = 98) consisting of patients and proxies, medical and non-medical experts.[25] The MSIP is an outcome measure reflecting MS-specific disabilities meeting psychometric criteria concerning reliability (internal consistency, mean inter-item correlation and test–retest reliability) and validity (convergent, discriminant, known groups and relative validity).[26,27] Concerning relative validity, the MSIP was more sensitive and more powerful in detecting differences between disease severity subgroups and QOL subgroups than generic QOL measures. Advantages of the MSIP compared with other disease-specific measurements such as the EDSS[2,28] or the Multiple Sclerosis Impact Scale (MSIS-29)[29,30] are that the MSIP combines psychometric quality with a broad assessment of MS-related health problems in more detail. The most important limitation in evaluating the MSIP properties was that we could not examine the responsiveness, the ability of a measure to detect change over time. Although relative validity is a good indicator for sensitivity to change, this does not substitute for responsiveness tests. Therefore, because this is the first longitudinal study in which we used the MSIP, we estimated the responsiveness.

In summary, previous longitudinal studies generated important information about progress in disease severity but are limited for several reasons. First, regarding disability, they have mainly reported about limitations in walking and provided limited information about other clinically relevant MS-related disabilities. Second, these studies rarely include the course of QOL during disease progression. Therefore, the objective of this study was to examine the course of a broad spectrum of MS-related disabilities and QOL in relation to disease severity. Because longitudinal studies are not complete without a detailed analysis of patients passing disability milestones and MS-related mortality rate, we also examined the characteristics of patients who passed disability milestones and calculated the mortality rate.

Methods

Design

We performed a 5-year follow-up study in a cohort of 276 patients with MS initially assessed in 2004.

Patients and procedures

Our initial sample in 2004 consisted of 378 MS patients attending the Groningen MS Center, part of the Neurology department of the University Medical Hospital Groningen in the Netherlands. These patients were checked for vital status using the national population register. This yielded 31 deaths (8%) during the 5-year period. The remaining patients were eligible for follow-up re-assessment in 2009 and received a postal invitation to participate in the survey and to answer demographic and disease-related questions, and to complete questionnaires for disease severity, a broad range of MS-related disabilities and QOL. Non-responders received a reminder after 2 weeks.

Of the 347 patients in our follow-up re-assessment, 245 patients (71% response rate) completed the questionnaires. The 102 non-responders did not differ from the responding patients regarding age, gender, marital status, educational level and years since MS diagnosis.

Measures

To evaluate disease severity we used the Ambulation question from the self-report version of the EDSS.[31] The EDSS score is an ordinal variable starting at 0 (no disability) and increasing at half point increments to a maximum score of 10 (death due to MS). The Ambulation question reflects EDSS scores in the range 4.5–10.[31]

For this study, patients were classified into three clinically relevant and recognizable 'disease severity subgroups': the low-severity subgroup (EDSS 0 to < 4.5) comprising persons able to walk more than 500 m with no assistance; moderate-severity subgroup (EDSS ≥ 4.5 to < 7) comprising persons limited in walking; and high-severity subgroup (EDSS ≥ 7 to < 10) comprising persons at least partially restricted to a wheelchair or bed. We defined 'passing a disability milestone' as the progress to the next, more severe, disease severity subgroup.

We applied the Measures (MSIP) to assess MS-related disabilities.[26,27] The MSIP measures the prevalence and severity of a broad range of MS-related disabilities concerning body functions, execution of activities by the individual, involvement in life situations and lack of support from the environment. It consists of 36 items divided over seven scales and four additional impairment items (fatigue, pain and impairment in seeing functions and impairment in speech functions). Scoring options range from 0 (no disability/full support) to 3 or 4 (complete disability/no support). Summed scores for each scale indicate the extent of disability or lack of support from the environment. For the purpose of this study the sum scores and the scores on the single impairment items were multiplied to obtain a result ranging from 0–100. The internal consistency tests of the MSIP scales were good for most scales (Cronbach's alphas: 0.80 and 0.90), satisfactory for the 'Mental functioning' scale (0.62) and weak for the 'Environmental factors' scale (0.49). Mean inter-item correlation coefficients were good for both 'Mental functioning' scale (0.35) and 'Environmental factors' scale (0.19).[26,32]

To measure QOL we applied the World Health Organization Quality Of Life, abbreviated version (WHOQOL-BREF), a generic QOL measure with a broad scope, including environmental aspects. It consists of 26 items, divided into four domains covering 'Physical health and autonomy', 'Psychological health', 'Social relationships' and 'Environmental aspects' and has two single-item questions ('Overall quality of life' and 'Overall satisfaction with health'). For each scale, item scores were coded, summed and transferred to a scale of 0 (worst health) to 20 (best health). In our previous study in patients with MS the WHOQOL-BREF showed satisfactory levels of internal consistency with Cronbach's alpha between 0.63 and 0.81.[26]

Analysis

To calculate the mortality rate in our 2004 cohort these patients were checked for vital status using the national population register.

For comparison of mean scores for demographic and disease-related variables between groups of respondents and non-respondents, and between deceased patients and survivors, we used *t*-tests for continuous variables and non-parametric tests to compare scores on ordinal variables. The difference of proportions test was used to compare scores on nominal variables. To examine the changes during the 5-year period concerning disabilities and QOL we used the paired samples *t*-test.

Responsiveness of the MSIP was estimated by the standardized response mean (SRM) for assessing of an outcome measure's ability to detect change over time. In the SRM formula, the mean change in scores over time are divided by the standard deviation (SD) of these change scores. Next, with the aim to quantify the change in disability and QOL over time as 'trivial', 'small', 'moderate' or 'large', the Effect Size (ES) indicator was used (mean change in scores over time divided by the pooled SD of baseline and follow-up scores). According to Cohen's thresholds[33] an ES of < 0.20 indicates a trivial change, an ES of ≥ 0.20 to < 0.50 a small change, an ES of ≥ 0.50 to < 0.80 a moderate change, and an ES ≥ 0.80 a large change. These two methods of standardizing mean changes in outcomes were used since the interpretation of the SRM with Cohen's thresholds[34] leads to overestimation or underestimation, as these thresholds were developed on standardizing mean differences between baseline and follow-up by using the pooled standard deviation (SD_p). It has been convincingly argued that only the SD_p should be used to interpret ES for correlated designs.[35,36]

All statistical tests were two-tailed. A value of $p < 0.05$ was used for all tests to indicate statistical significance.

SRM and ES were calculated for statistically significant differences. It was shown that, according to an external criterion, SRM ≥ 0.20 reflects a clinical relevant change.[37]

Results

Cohort

Demographic and disease-related characteristics of the 245 participants in both measurements in 2004 and 2009 are presented in Table 1. Four patients were excluded from further analysis because their EDSS scores were not known.

Sensitivity to change over time

Nine of the 11 MSIP disability domains were able to detect change over time (See Table 2), while three of the four WHOQOL-BREF scales were, due to random variation ($p > 0.05$), not able to detect change over time.

Overall change in disability profile and QOL

The overall cohort showed a statistically significant and clinically relevant increase in disability in eight out of 11 MSIP disability domains when compared with baseline (Table 2). 'Lack of support from environmental factors' showed the largest, but moderate increase, followed by 'Impairment in speech' and both 'limitations in activities' domains with a small increase.

Patients reported a small worsening in QOL concerning 'Physical health and autonomy' compared with 5 years earlier.

Table 1. Patients characteristics of participants in both measures in 2004 (n = 245)

	Cohort
Gender (%)	
Female	165 (67)
Male	80 (33)
Age	
Mean (SD)	51 (11)
Range	23–85
Marital status (%)	
Married / partnership	196 (81)
Unmarried / widowed / divorced	45 (19)
Educational level (highest level) (%)	
Primary or secondary school / vocational training	188 (77)
Higher professional education / university	54 (23)
Employment status (more answers possible) (%)	
Employment	59 (24)
Voluntary work	14 (6)
(partially) retired due to MS	144 (60)
Housewife / househusband	74 (31)
Retired due to age	25 (10)
Years since MS diagnosis	
Mean (SD)	13 (8)
Range	1–42
EDSS score (range 0–10) (%)	
0 to < 4.5	96 (39)
≥ 4.5 to < 7	99 (40)
≥ 7 to < 10	46 (19)

Change in disease severity, disability profile and QOL in the low disease severity subgroup (EDSS 0 to < 4.5)

In total 96 patients in the low disease severity subgroup in 2004 participated in both measurements. After 5 years 66 patients (69%) were still unlimited in walking. MS was leading to limitations in walking for 18 patients (19%): median age in 2004 for these patients was 44.5 years (range 27–68 years). MS was leading to wheelchair dependency for 12 patients (13%): median age in 2004 was 46 years (range 35–67 years).

Patients in this subgroup showed an increase in disability in seven out of 10 MSIP disability domains (Table 3). 'Lack of support from environmental factors' showed a moderate increase. All other changes were of a small magnitude and concerned 'Impairments in body functions', 'Limitations in activities', and 'Restrictions in participation in life situations'.

Patients reported a small worsening in QOL concerning 'Physical health and autonomy' and a trivial worsening in quality of 'Psychological health' and quality of the 'Environment' compared with 5 years earlier.

Change in disease severity, disability profile and QOL in the moderate disease severity subgroup (EDSS ≥ 4.5 to < 7)

In total 99 patients with moderate disease severity in 2004 participated in both measurements. During the intervening 5 years the mean EDSS score increased from 6.0 to 6.5 (p-value 0.000). After 5 years 51 patients (52%) experienced ambulatory limitations but were still able to walk, while disease severity in 35 patients (35%) increased to wheelchair dependency. Median age in 2004 for these patients was 51 years (range 29–69 years). Walking ability improved for 13 patients (13%) who reported being not limited in walking.

Patients in this subgroup showed a clinically relevant increase in disability in five out of 10 MSIP disability domains (Table 3). 'Lack of support from environmental factors' showed a moderate increase. All other changes were of a small magnitude and concerned 'Impairment in speech functions', 'Limitations in activities', and 'Restrictions in participation in life situations'.

QOL among patients in this subgroup did not change during the 5-year period.

Table 2. Changes over 5 years in disabilities and QOL in a cohort of MS patients (n = 241)

	2004 Mean (SD)	Change Mean (SD)	SRM
MSIP Disabilities			
Impairments in …			
Muscle and Movement Functions	28.3 (21.2)	2.3 (15.0)	0.26
Excretion and Reproductive Functions	28.2 (23.5)	3.7 (16.7)	0.32
Mental Functions	21.5 (17.8)	0.9 (14.3)	ns
Speech functions	6.3 (13.0)	4.7 (13.9)	0.26
Seeing functions	18.6 (22.3)	3.3 (22.3)	0.27
Fatigue	45.2 (23.2)	4.0 (21.8)	0.56
Pain	22.5 (23.5)	0.8 (18.9)	ns
Limitations in …			
Basic Movement Activities	29.0 (29.3)	7.1 (19.3)	0.53
Activities of Daily Living	32.6 (30.1)	7.1 (18.1)	0.55
Restrictions in …			
Participation in life situations	16.9 (22.5)	2.7 (21.2)	0.48
Lack of support in …			
Environmental Factors	19.7 (22.0)	11.6 (27.2)	0.51
WHOQOL-BREF			
Physical Health and Autonomy	13.9 (2.8)	−0.6 (2.6)	0.33
Psychological Health	14.4 (2.5)	−0.2 (2.1)	ns
Social Relations	15.0 (3.0)	−0.3 (3.9)	ns
Environment	15.5 (2.4)	−0.2 (2.6)	ns

SRM, Standardized Response Mean;
MSIP (range 0–100): higher scores = more disability / less support;
WHOQOL-BREF (range 0–20): higher scores = better Quality of life;
ns = not significant

Change in disease severity, disability profile and QOL in the high disease severity subgroup (EDSS ≥ 7 to < 10)

In total 46 patients within this subgroup participated in both measurements. During the intervening 5 years the mean EDSS score of these patients increased from 8.5 to 9.0 (p-value 0.001). After 5 years 44 patients (96%) in this subgroup were still wheelchair dependent, while two patients (4%) improved and were able to walk while using assist devices.

Patients showed a small increase in 'Impairment in speech functions' (Table 3). Other MSIP disability domains, as well as all QOL domains, did not change during the 5-year period.

Mortality rates

From the 378 patients in our original cohort 31 patients (8%) had died in 2009: 15 female and 16 male patients. Mean age at time of death was 58.1 years (SD 14.0, range 33–83 years) for the total sample of patients who had deceased in the period 2004–2009. There was no difference between male and female patients. The mortality rate was highest in the highest disease severity subgroup: out of the 89 MS patients with EDSS ≥ 7 to < 10 in 2004, 21 patients (23.6%) died. Out of the 138 MS patients with EDSS ≥ 4.5 to < 7 in 2004, eight patients (5.8%) died, and among the 143 MS patients with EDSS 0 to < 4.5 in 2004, two patients (1.4%) were deceased.

Discussion

In this study we found that the increase of disability in the MSIP domains and loss of QOL were most pronounced in the low disease severity subgroup (EDSS 0 to < 4.5), while there was no clinically relevant increase of MSIP disabilities or worsening of QOL in the highest disease severity subgroup (EDSS ≥ 7 to < 10). Concerning the progress of disease severity, we found that the median age of patients who passed the first disability milestone (EDSS 4) was 44 years in 2004 and of patients who passed the second disability milestone (EDSS 7) was 51 years in 2004. As expected, mortality was highest (24%) among those in the highest disease severity subgroup in 2004.

We examined the responsiveness of the MSIP. The MSIP was shown to be sensitive to detect change over time for 9 out of 11 MSIP domains. Compared with the WHOQOL-BREF, the MSIP performed better in detecting changes over time.

Our study was the first to examine the change in a broad spectrum of MS-related disabilities using the MSIP. We

Table 3. Changes over 5 years in disabilities and QOL in the disease severity subgroups (*n* = 241)

	EDSS score 0 to <4.5 (*n* = 96)			EDSS score ≥4.5 to <7 (*n* = 99)			EDSS score ≥7 to <10 (*n* = 46)		
	2004	Change		2004	Change		2004	Change	
	Mean (SD)	Mean (SD)	ES	Mean (SD)	Mean (SD)	ES	Mean (SD)	Mean (SD)	ES
MSIP Disabilities									
Impairments in …									
Muscle and Movement Functions	13.0 (13.2)	5.4 (10.0)	0.40	30.9 (13.6)	0.0 (14.0)	ns	54.2 (21.6)	0.7 (23.4)	ns
Excretion and Reproductive Functions	15.9 (17.0)	3.5 (11.9)	0.20	31.6 (19.2)	3.7 (16.0)	ns	52.8 (27.4)	4.2 (27.3)	ns
Mental Functions	16.7 (18.1)	1.6 (14.1)	ns	24.6 (17.1)	0.4 (13.9)	ns	26.1 (16.4)	0.5 (16.2)	ns
Speech functions	4.7 (10.5)	2.2 (9.6)	0.20	4.7 (9.8)	3.6 (11.5)	0.30	14.0 (19.9)	12.2 (22.1)	0.47
Seeing functions	13.7 (15.9)	1.1 (16.6)	ns	18.3 (21.1)	5.0 (24.6)	ns	29.2 (31.2)	5.4 (27.4)	ns
Fatigue	35.5 (21.6)	6.5 (20.2)	0.27	51.0 (19.2)	−0.8 (19.7)	ns	54.6 (27.4)	8.1 (27.7)	ns
Pain	15.9 (21.9)	2.2 (18.5)	ns	28.3 (23.8)	−1.9 (19.0)	ns	25.0 (23.4)	3.6 (20.3)	ns
Limitations in …									
Basis Movement Activities	7.8 (10.8)	5.7 (15.8)	0.39	27.8 (18.3)	9.6 (22.7)	0.45	73.6 (24.1)	4.9 (18.0)	ns
Activities of Daily Living	9.6 (11.1)	6.1 (16.4)	0.38	33.2 (19.5)	10.3 (19.6)	0.47	80.2 (19.3)	2.0 (17.7)	ns
Restrictions in ….									
Participation in life situations	6.0 (10.0)	4.1 (15.0)	0.32	16.6 (18.3)	4.8 (20.9)	0.25	45.1 (29.9)	−6.1 (31.3)	ns
Lack of support from									
Environmental Factors	26.4 (26.1)	16.0 (30.1)	0.60	17.6 (20.2)	13.7 (26.1)	0.65	15.2 (18.0)	1.9 (24.3)	ns
WHOQOL-BREF									
Physical Health and Autonomy	15.5 (2.7)	−0.9 (2.5)	0.36	13.2 (2.2)	−0.2 (2.3)	ns	11.8 (2.5)	−0.6 (3.2)	ns
Psychological Health	15.1 (2.6)	−0.6 (2.0)	0.19	14.2 (2.3)	−0.0 (2.0)	ns	12.9 (2.3)	−0.0 (2.3)	ns
Social Relations	15.5 (3.1)	−0.5 (2.7)	ns	15.2 (2.6)	−0.4 (2.8)	ns	13.2 (3.0)	0.4 (3.4)	ns
Environment	16.5 (2.5)	−0.5 (2.2)	0.15	15.1 (2.0)	−0.1 (1.8)	ns	14.1 (2.2)	0.1 (2.5)	ns

ES = Effect Size; MSIP (range 0–100): higher scores = more disability / less support; WHOQOL-BREF (range 0–20): higher scores = better Quality of life; ns = not significant

found that the increase of disability in the MSIP disability domains was most prevalent and most pronounced in the low disease severity subgroup. We also found that there was no clinically relevant increase of MSIP disabilities or worsening of QOL in the highest disease severity subgroup and a moderate increase of disabilities in the moderate disease severity subgroup. This study also was the first to examine change in QOL in MS over time. Again, we found that the lowest disease severity group was the group that seemed to suffer most. QOL in this group worsened for all domains, except for the domain of 'Social relations', while QOL in the other subgroups did not change.

Our findings that the low disease severity group experienced the largest increase in disability and the largest loss in QOL may be an explanation for the high suicide risk during the years after diagnosis.[22] Therefore, these findings suggest that patients who are in the first phase of the disease process might be in more need for support from the health care system than is generally expected. Our finding that patients in the low disease severity subgroup might need more support was confirmed by the high increase in the MSIP domain 'Lack of support from the environment' (support from family, professionals, social and health care systems) in both the lowest and moderate disease severity subgroups, while the patients in the highest disease severity subgroup showed no increase in lack of support. This finding is likely to apply to all developed countries. Although the introduction of immunomodulatory treatment may have resulted in more support to eligible patients in the low-severity group, despite this additional support (that focuses on the therapy and side effects of therapy) patients are still reporting a lack of support from the environment in this early disease stage. For the broad range of consequences of MS, a more integrated, patient-centred, proactive and preventive care system is needed.

Our finding of a median age of 44 years for patients who passed the first disability milestone (EDSS 4) was similar to that found by Confavreux and Vukusic[3] and Kremenchutzky et al.[4] However, the median age of 51 years for passing the disability milestone EDSS 7 was lower than

reported in the studies of Confavreux and Vukusic,[3] who found a median age of 63 years, and Kremenchutzky et al.,[4] who found that time between disability milestones was 'remarkably comparable' with the findings of Confavreux and Vukusic.[3] These findings may be indicative of the fact that advances in disease severity in our cohort were faster than in the natural history studies. There are several reasons that could explain this difference. First, there is an ongoing discussion about when progression in MS can be defined as 'sustained progression'. Kremenchutzky et al.[4] even suggested that a final decision that recovery from exacerbations does not occur is just possible after a year of follow-up. Our finding that 15 patients in the 2004 cohort were recovered to a lower, less severe, disease severity subgroup fits with this. Furthermore, the precision of the results in our study concerning the median age at time of passing a disability milestone is limited due to the fact that the exact moment of passing the milestone is 'somewhere' between both measurements. Second, the range between minimum and maximum age for passing a milestone in our sample was large (about 40 years), a finding that was also reported by Kremenchutzky et al.[4] Nevertheless, this broad range might affect the median age. Finally, our findings are based on self-report questionnaires. Although this method is recognized as a valid and reliable method, results are similar but not equal to observation-based measures.

Mortality was highest (24%) among those in the highest disease severity subgroup, while there was a increase in disease severity but no increase in disability profile among survivors in this subgroup. Mean age at time of death in our cohort was 10 years lower (55 years, SD 14) compared with the results in the study of Hirst et al.,[38] who found a mean age of 65 years (SD 15). This finding, in combination with a relatively shorter time between two disability milestones, could suggest that progress of disease severity in our cohort was relatively stronger compared with findings in other studies.

There are some (potential) limitations in this study. First, there is the lack of information about the use of immunomodulatory treatment among patients in our cohort. This treatment may have a positive impact on the course of the disease,[6,7] and on the time before and between disability milestones. Another limitation was the incompleteness and limited quality of the information on causes of death that we obtained regarding our cohort.

In summary, we succeeded in examining the course of a broad range of MS-related disabilities and QOL in relation to disease severity. This information resulted in a precise insight into the consequences of MS, and subsequently provided valuable information that can guide the selection of health care interventions. The responsiveness of the MSIP, which is a relatively new measure, was found to be sufficient for 9 out of the 11 MSIP domains.

Based on our findings we conclude that prominent increases in multiple aspects of disability and loss of QOL occur in early stages in MS in particular. Health care interventions may lead to large health and QOL gains in particular when offered to patients who are in the first stage of the MS process. Furthermore, health care professionals should be aware of the high risk of death in the high disease severity subgroup.

Based on our findings we recommend that future follow-up studies include a detailed assessment of disabilities and QOL for a better understanding of the consequences of MS. Furthermore, with this broader range of disease-related variables more options are available for prognostic studies with the aim to select predictive variables and to assess their impact on disease progression.

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Conflict of interest

The authors declare that they have no conflicts of interest.

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