

VU Research Portal

The initial course of daily functioning in multiple sclerosis: a three-year follow-up study

de Groot, V.; Beckerman-Boiten, H.; Lankhorst, G.J.; Polman, C.H.; Bouter, L.M.

published in

Multiple Sclerosis
2005

DOI (link to publisher)

[10.1191/1352458505ms1238oa](https://doi.org/10.1191/1352458505ms1238oa)

document version

Publisher's PDF, also known as Version of record

[Link to publication in VU Research Portal](#)

citation for published version (APA)

de Groot, V., Beckerman-Boiten, H., Lankhorst, G. J., Polman, C. H., & Bouter, L. M. (2005). The initial course of daily functioning in multiple sclerosis: a three-year follow-up study. *Multiple Sclerosis*, 11(6), 713-718.
<https://doi.org/10.1191/1352458505ms1238oa>

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

E-mail address:

vuresearchportal.ub@vu.nl

Multiple Sclerosis

<http://msj.sagepub.com/>

The initial course of daily functioning in multiple sclerosis: a three-year follow-up study

V de Groot, H Beckerman, G J Lankhorst, C H Polman and L M Bouter

Mult Scler 2005 11: 713

DOI: 10.1191/1352458505ms1238oa

The online version of this article can be found at:

<http://msj.sagepub.com/content/11/6/713>

Published by:



<http://www.sagepublications.com>

Additional services and information for *Multiple Sclerosis* can be found at:

Email Alerts: <http://msj.sagepub.com/cgi/alerts>

Subscriptions: <http://msj.sagepub.com/subscriptions>

Reprints: <http://www.sagepub.com/journalsReprints.nav>

Permissions: <http://www.sagepub.com/journalsPermissions.nav>

Citations: <http://msj.sagepub.com/content/11/6/713.refs.html>

The initial course of daily functioning in multiple sclerosis: a three-year follow-up study

V de Groot^{*,1,2}, H Beckerman^{1,2}, GJ Lankhorst^{1,2}, CH Polman³ and LM Bouter²

¹Department of Rehabilitation Medicine, VU University Medical Center, P.O. Box 7057, 1007 MB Amsterdam, The Netherlands; ²Institute for Research in Extramural Medicine, VU University Medical Center, P.O. Box 7057, 1007 MB Amsterdam, The Netherlands; ³Department of Neurology, VU University Medical Center, P.O. Box 7057, 1007 MB Amsterdam, The Netherlands

We studied the initial course of daily functioning in multiple sclerosis (MS). A cohort of 156 recently diagnosed patients was prospectively followed for three years (five measurements). Domains of interest were neurological deficits, physical functioning, mental health, social functioning and general health. An a priori distinction was made between a relapse onset group (n = 128) and a non-relapse onset group (n = 28). At baseline, neurological deficits are relatively minor for most patients, 26.3% have aberrant physical functioning scores, 38.5% have aberrant social functioning scores, 9% have aberrant mental health scores and 25% have aberrant general health scores. The neurological deficits and physical functioning deteriorated significantly over time. This deterioration was more pronounced and clinically relevant in the non-relapse onset group only. Mental health showed a significant, but not clinically relevant deterioration over time. Social functioning and general health showed non-significant effects for time. It is concluded that in the initial stage of MS, when neurological deficits are relatively minor and mental health is relatively unaffected, patients in both groups experience limitations in daily functioning. Patients in the non-relapse onset group have progressive neurological symptoms that are accompanied by progressive limitations in physical functioning, but not by progressive limitations in the other domains.

Multiple Sclerosis (2005) 11, 713–718

Key words: clinical course; Expanded Disability Status Scale; Functional Independence Measure; longitudinal study; Medical Outcome Study Short Form 36; multiple sclerosis; prognosis

Introduction

Most longitudinal studies on the clinical course of multiple sclerosis (MS) in large study populations have only used the Expanded Disability Status Scale (EDSS) as outcome measure,^{1–7} which is subject to criticism.^{8–10} A clear limitation is that it combines impairments and disability into one scale. Moreover, the instrument is heavily biased towards locomotor function, and does not cover other relevant domains of functioning. Studies that address other domains of functioning are predominately cross-sectional,¹¹ thereby not providing insight into the course of MS in these domains. Although the information obtained in these studies is certainly of value, longitudinal studies of carefully and comprehensively documented cohorts of patients with MS would improve our knowledge on the course of MS in relevant domains of daily functioning.

We studied the initial course of MS in the domains of neurological deficits, physical functioning, mental health, social functioning and general health for the relapse onset

group (RO, Relapsing Remitting MS (RRMS) and Secondary Progressive MS (SPMS)) and the non-relapse onset group (NRO, Primary Progressive MS (PPMS) and patients for whom the type is unknown at six months) in the first three years.

Methods

All consecutive potentially eligible patients visiting the outpatient clinics of five participating neurology departments were invited to participate in the study. A cohort of 156 MS patients, diagnosed less than six months previously and aged 16–55 years, was recruited and prospectively followed for three years. Diagnoses were made according to the Poser-criteria for definite MS.¹² Patients with other neurological disorders, systemic or malignant neoplastic diseases were excluded. Measurements took place at baseline, after six months, and after one, two and three years. In case of a relapse, the measurements were postponed for a few weeks until the relapse had subsided. Patients were visited at home in order to minimize drop-out.

The cohort was sub-divided into two a priori defined groups on the basis of disease type, determined six months after inclusion in the study.¹³ The RO group consisted of patients with RRMS or SPMS, and was the reference category in the analysis. The NRO group con-

*Correspondence: Vincent de Groot, Department of Rehabilitation Medicine, VU University Medical Center, P.O. Box 7057, 1007 MB Amsterdam, The Netherlands.
E-mail: v.degroot@vumc.nl

Received 31 January 2005; accepted 24 May 2005

sisted of patients with PPMS and patients with MS for which the disease type was unknown at six months.

The EDSS,¹⁴ the Functional Independence Measure (FIM)¹⁵ and the Medical Outcome Study Short Form 36 (SF36),^{16,17} or their sub-scales, were used to assess the domains of neurological deficits, physical functioning, mental health, social functioning and general health (Table 1). The FIM and SF36 scores were transformed to a scale that ranged from 0 (worst) to 100 (best). The EDSS was used in its original format, where 0 indicates no neurological deficits and 10 indicates death due to MS.

The EDSS¹⁴ consists of a thorough neurological assessment of the seven neurological systems (visual/optic, brainstem, pyramidal, cerebellar, bowel/bladder, mental and other) and provides information about walking ability, use of walking aids and ability to perform self-care activities. Lower scores on the EDSS are determined with a scoring paradigm based on the scores obtained from the neurological systems, intermediate scores are predominantly based on walking ability and higher scores are mainly based on the inability to perform self-care activities. Reliability has been shown to be moderate.¹⁰ Therefore, only experienced raters were involved in the scoring.

The FIM consists of a motor function (FIMmf, 13 items) and a cognitive function (FIMcf, five items) sub-scale.¹⁵ The items address the activities of daily living and are scored on the basis of a semi-structured interview. The validity of the FIM has been established for use in inpatient and outpatient rehabilitation settings, and its reliability is good.^{18,19}

The SF36^{16,17} is a questionnaire that assesses eight domains (physical functioning (SF36pf), mental health (SF36mh), bodily pain, vitality, social functioning (SF36sf), role physical (SF36rp), role emotional (SF36re), general health perception (SF36gh)). Its validity and reliability have been extensively studied.^{16,17} For MS it is not recommended to calculate physical and mental component scores because scaling assumptions would be violated.²⁰

To study the differences in SF36 scores between a healthy population and the study population, we used reference data on an age-matched healthy Dutch reference population, derived from Aaronson *et al.*¹⁷ The cut-off was set at

1.96 standard deviations below the mean of the reference population. EDSS scores >0 and FIM scores <100 were considered aberrant. We calculated 95% confidence intervals (95% CI) around the proportion of patients with aberrant scores.

For the longitudinal analysis of the domains of neurological deficits, physical functioning, mental health and general health perception, data is presented on six models, using raw data for the graphs and 'linear' generalized estimating equations (GEE)²¹ from the Statistical Package for Interactive Data Analysis (SPIDA) version 6.05 from the Statistical Computing Laboratory for the analysis. The correlation structure was chosen on the basis of the correlation matrix of the outcome measures, and set at exchangeable (i.e., correlation coefficients between the first and successive measurements are approximately equal) for all outcomes except the cognitive sub-scale of the FIM that was set at four-dependence (i.e., correlation coefficients between the first and successive measurements are progressively smaller). For the domain of social functioning (SF36rp, SF36re and SF36sf) data is presented on three models using raw data for the graphs and 'binomial' GEE for the analysis. Because the data showed strong floor and ceiling effects, we distinguished a group scoring within the norm and a group with scores deviating from the norm, using a cut-off of 1.96 standard deviations below the mean of an age-matched Dutch reference population.¹⁷ Time was modelled as a continuous variable expressed in years. To test for differences in the course of both groups we used an interaction term time \times group. The significance level for time, group and time \times group was set at 0.05. Determining the minimally clinically important difference (MCID) depends on numerous factors and assumptions.²² For the present study, the MCID was set at a 10% difference for all outcome measures.

Results

Table 2 shows the baseline characteristics of the patients. Most characteristics comply with the expected pattern: 64% females, approximately 80% with a relapse onset, more females than males in the RRMS group, more males

Table 1 Domains of interest, (sub-scales of) outcome measures used and percentage (95% CI) of MS patients with aberrant scores at baseline

Domain	Outcome measures	Abbreviation	Percentage with aberrant scores at baseline (%)
Neurological deficits	Expanded Disability Status Scale	EDSS	96.8 (98.2–95.4)*
Physical functioning	Functional Independence Measure motor function	FIMmf	74.4 (70.9–87.9)**
	SF36 physical functioning	SF36pf	26.3 (19.4–33.2)***
Mental health	FIM cognitive function	FIMcf	64.7 (60.9–68.5)**
	SF36 mental health	SF36mh	9 (4.5–13.5)***
Social functioning	SF36 role physical	SF36rp	38.5 (30.8–46.1)***
	SF36 role emotional	SF36re	12.2 (7–17.3)***
	SF36 social functioning	SF36sf	12.8 (7.6–18.1)***
General health	SF36 general health perception	SF36gh	25 (18.2–31.8)***

SF36, Medical Outcome Study Short Form 36; *Percentage scoring ≥ 1 ; **Percentage scoring <100 ; ***Percentage scoring worse than 1.96 standard deviations below the mean of the reference data obtained from Aaronson *et al.*¹⁷

Table 2 Baseline characteristics of patients with multiple sclerosis

	<i>Relapse onset</i>		<i>Non-relapse onset</i>		<i>Total</i>
	<i>RR</i>	<i>SP</i>	<i>PP</i>	<i>Unknown at six months</i>	
<i>n</i> (%)	120 (77)	8 (5)	25 (16)	3 (2)	156 (100)
Age	35.5 (8.9)	48.2 (6.7)	43.2 (8.9)	45.5 (6.9)	37.6 (9.5)
Female (%)	84 (70.0)	3 (37.5)	11 (44)	3 (100)	101 (64)
Time since diagnosis (year)	0.26 (0.15–0.41)	0.33 (0.24–0.48)	0.28 (0.15–0.33)	0.14 (0.14–0.17)	0.26 (0.15–0.40)
Time since symptoms (year)	1.83 (0.67–4.40)	7.50 (3.35–14.51)	2.10 (1.07–3.15)	3.62 (3.53–0.63)	2.15 (0.79–4.36)
Number of exacerbations	2.0 (1.0–3.0)	2.0 (1.0–7.0)	0 (0–0)	0 (0–0)	2.0 (1.0–3.0)
EDSS	2.0 (2.0–3.0)	3.0 (2.5–3.9)	3.0 (2.5–4.0)	2.5 (2.0–4.0)	2.5 (2.0–3.0)

n (percentage), mean (SD) or median (IQR). RR, relapsing remitting multiple sclerosis; SP, secondary progressive multiple sclerosis; PP, primary progressive multiple sclerosis.

than females in the PPMS group, and more severe neurological deficits in the groups with a progressive disease course.^{1,4,6} Seven patients were lost to follow-up (three after one year, one after two years and three after three years) and only 1.9% of the measurements were missing.

Table 1 shows the proportion of patients with aberrant scores for all outcome measures. Only 3% of the patients have no neurological symptoms. Although it seems as if major problems exist on the FIM sub-scales, only 17.3% of patients score <90 points on the FIMmf and 10.2% of patients score <90 points on the FIMcf. This indicates that current disabilities are relatively minor for most patients. Deviations from normal are most pronounced for the sub-scales SF36pf, SF36rp and SF36gh.

The course of MS for the two groups can be found in Figure 1 (raw data) and the corresponding results of the GEE analysis can be found in Table 3. The neurological deficits (EDSS) and physical functioning (FIMmf and SF36pf) deteriorate in the first three years (time is significant: see Table 3 and Figure 1A, B). For the FIMmf there is a difference between the two groups that does not change over time (group is significant: see Table 3), but for the EDSS and the SF36pf the deterioration is more pronounced in the NRO group (time × group is significant: see Table 3). In the NRO group, the change in EDSS and SF36pf over the first three years exceeds the MCID (EDSS 1.2 and SF36pf 15 units). In the first three years mental health, as measured with the FIMcf, shows a deterioration (3.6 units, statistically significant but smaller than the MCID) that is the same in both groups (time is significant: see Table 3 and Figure 1C). Mental health, as measured with the SF36mh, does not change significantly. For the other scales no change occurs in the first three years (time is not significant: see Table 3 and Figure 1C, D, E and F).

Scores for a specific group at a specific point in time can be calculated using the results from Table 3 in a linear regression formula. As an example, we will calculate the EDSS, FIMmf and SFrp of a patient with MS in the NRO group two years after inclusion.

$$\begin{aligned} \text{EDSS} &= 2.4 + 0.2 \times \text{time (years)} + 1.0 \times \text{group} \\ & \quad (\text{RO} = 0, \text{NRO} = 1) + 0.2 \times \text{time} \times \text{group} \\ &= 2.4 + 0.2 \times 2 + 1.0 \times 1 + 0.2 \times 2 \times 1 = 4.2 \end{aligned}$$

$$\begin{aligned} \text{FIMmf} &= 96.1 - 1.3 \times \text{time (in years)} - 6.0 \times \text{group} \\ & \quad (\text{RO} = 0, \text{NRO} = 1) \\ &= 96.1 - 1.3 \times 2 - 6.0 \times 1 = 87.5 \end{aligned}$$

The situation regarding SF36rp is slightly more complex because the results are presented as an odds ratio (OR). First, the OR from Table 3 is reverted to the original logistic coefficient by taking the natural log (ln). This logistic coefficient is then multiplied by time (in years), and finally *e* is raised to the power of this coefficient.

$$\begin{aligned} \text{SFrp} &= e^{\text{time (in years)} \times \ln(1.1)} = e^{\text{time} \times 0.095} = e^{2 \times 0.095} \\ &= e^{0.19} = 1.2 \end{aligned}$$

The number obtained (1.2) is an estimate of the odds (ratio of the probability that the patient deviates from the norm to the probability that he does not) that this patient will have an aberrant social functioning score.

Discussion

At baseline, the domains of physical functioning (SF36pf), social functioning (SF36rp) and general health (SF36gh) are markedly affected. Although both groups are affected, in the domains of physical functioning and general health the NRO group is more severely affected than the RO group, whereas in the domain of social functioning there is no difference between both groups. Surprisingly, mental health is relatively unaffected. These results show that in the initial stage of the disease, when the neurological deficits are relatively minor and mental health is relatively unaffected, patients in both groups do already experience limitations in daily functioning.

In the first three years after diagnosis, the course differs not only between the RO and the NRO group, but also between the five domains. In the domains of neurological deficits and physical functioning the NRO group shows clinically relevant deterioration, whereas the RO groups stays relatively stable. In the domains of mental health, social functioning and general health, neither the RO nor the NRO group show any clinically relevant changes. This indicates that patients in the NRO group have progressive neurological symptoms that are accompanied by progres-

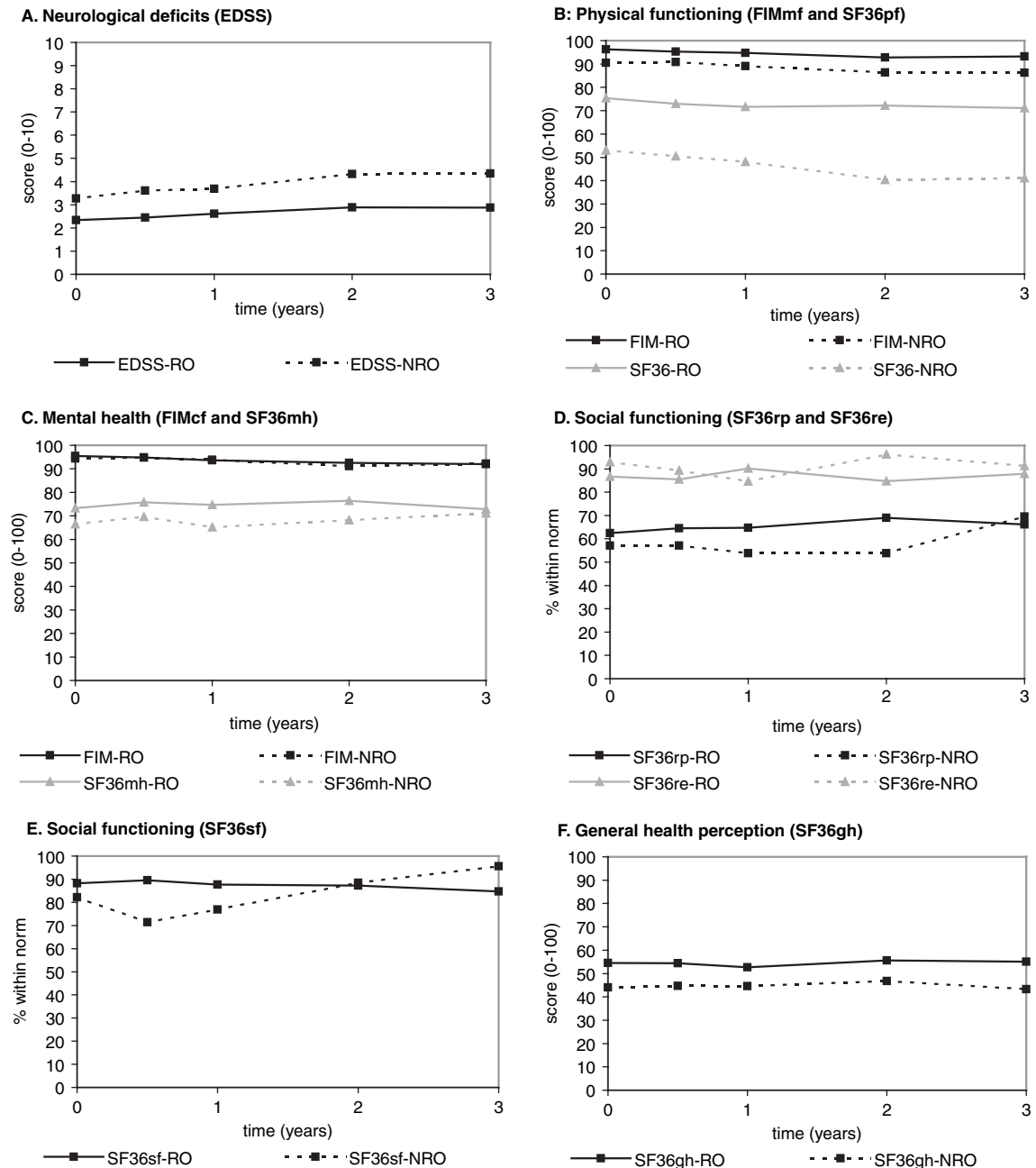


Figure 1 Initial course of MS in the domains of neurological deficits, physical functioning, mental health, social functioning and general health perception. *Graphs are based on raw data. EDSS, Expanded Disability Status Scale; FIMmf, Functional Independence Measure motor function; SF36pf, Medical Outcome Study Short Form 36 items physical functioning; FIMcf, FIM cognitive function; SF36mh, SF36 mental health; SF36rp, SF36 role physical; SF36re, SF36 role emotional; SF36sf, SF36 social functioning; SF36gh, SF36 general health perception; RO, relapse onset group; NRO, non-relapse onset group.

sive limitations in physical functioning, but not by progressive limitations in the other domains.

In the later stages of MS, mental health is negatively affected and there is a relationship between disease severity and mental health.²³ In contrast to what we expected, we found that mental health was relatively unaffected at baseline or after three years, for which there is no good explanation. Even though the majority of the study population showed only mild neurological symptoms at baseline, we expected that the emotional burden

shortly after the diagnosis would have a negative influence on mental health. However, the interval between making the diagnosis and inclusion in the study (maximal six months) may be long enough for patients to recover from an initial deterioration in mental health. Another explanation might be that the outcome measure that was used was not sensitive enough to detect problems in this area.

There are some important strengths of this study. The cohort consists of incident cases of MS, which means that the start of participation in this cohort is clearly defined.

Table 3 Results (regression coefficient, odds ratios and 95% confidence intervals) of GEE analysis for the different outcome measures

Outcome measure	Intercept	Time	Group	Time × group
Linear GEE				
EDSS	2.4 (2.2–2.6)	0.2 (0.1–0.3)	1 (0.5–1.4)	0.2 (0.1–0.4)
FIM motor function	96.1 (95.2–96.9)	–1.3 (–1.6 to–1.0)	–6.0 (–8.1 to–3.8)	
SF36 physical functioning	74.3 (70.5–78.0)	–1.4 (–2.5 to–0.2)	–21.9 (–31.4 to–12.4)	–3.9 (–6.2 to–1.6)
FIM cognitive function	95.0 (94.2–95.8)	–1.0 (–1.4 to–0.7)		
SF36 mental health	73.3 (70.7–75.9)	–0.1 (–0.1 to–0.1)		
SF36 general health perception	54.0 (50.9–57.1)	0.4 (–0.5–1.2)	–9.9 (–17.6 to–2.2)	
Logistic GEE				
SF36 role physical		1.1 (1.0–1.2)*		
SF36 role emotional		1.0 (0.9–1.2)*		
SF36 social functioning		1.0 (0.8–1.2)*		

GEE, generalized estimating equations; EDSS, Expanded Disability Status Scale; FIM, Functional Independence Measure; SF36, Medical Outcome Study Short Form 36; Time, time of measurement in years; Group, relapse onset is reference category; Time × Group: interaction term Time with Group.

*Odds ratios, logistic GEE models.

Only seven patients were lost to follow-up. Finally, we used a powerful design to study daily functioning. To our knowledge, this is the first longitudinal study that simultaneously assesses several domains of daily functioning. The longitudinal measurements, the concurrent use of several outcome measures at the same points in time, and the use of longitudinal data analysis techniques enable us to make a detailed and comprehensive description of the course of daily functioning in MS.

A potential weakness is the definition of the type of MS. RRMS is relatively easy to recognize and accounts for the majority of the cases. In practice, PPMS is more difficult to recognize. Furthermore, there is a small sub-group that cannot be classified in the early stages of the disease. During follow-up, it is easier to determine the type of MS, so we chose to dichotomize the patients on the basis of their disease onset type determined six months after inclusion in the study.

Another potential problem in this study is that five patients were classified as SPMS at baseline. This is rather unexpected in this incidence cohort, because this type of MS is normally preceded by RRMS. Table 2 shows a long time since the first symptoms for these patients. Looking carefully at their history, it became clear that for all of these patients there was a delay in making the diagnosis, either caused by the patient or the physician. This delay might lead to onset confounding,^{24,25} because time since first symptoms is related to disease progression and to conversion of RRMS into SPMS. To study the possibility of onset confounding, we repeated the analysis and adjusted for time since first symptoms at baseline (a logarithmic transformation was applied to obtain a normal distribution). Because none of the coefficients showed a considerable change, it is concluded that onset confounding did not play a major role in the present study.

Although this study clearly shows that in the early phase of MS, functioning is already seriously affected, knowledge about the precise mechanisms underlying this limited functioning is scarce. Clinicians might be encouraged to pay special attention to daily functioning in patients who visit their clinic, and explore the possible causes, beside neurological deficits, of the problems in daily

functioning. Factors that might contribute to problems in daily functioning might be patient-related, such as fatigue, personality, depression, and uncertainty about the future, or more related to the environment, such as social support and work related factors. Future studies should focus on the determinants of this limited functioning in order to enhance our understanding of these mechanisms and to provide clinicians with information that can be used in the development of effective treatments.

Acknowledgements

We would like to thank the neurologists in the participating hospitals (VU University Medical Center, Academic Medical Center Amsterdam, Sint Lucas Andreas Hospital Amsterdam, OLVG Hospital Amsterdam, Erasmus Medical Center Rotterdam) for recruiting the patients, and M van der Bruggen, M Schothorst, and T Wedding for performing the measurements. The Netherlands Organization for Scientific Research (NWO 940-33-009) supported this study. It was performed on behalf of the Functional prognostication and disability (FuPro) study group: GJ Lankhorst, J Dekker, AJ Dallmeijer, MJ IJzerman, H Beckerman, V de Groot: VU University Medical Center Amsterdam (project coordination); AJH Prevo, E Lindeman, VPM Schepers: University Medical Center, Utrecht; HJ Stam, E Odding, B van Baalen: Erasmus Medical Center, Rotterdam; A Beelen, IJM de Groot: Amsterdam Medical Center, Amsterdam.

References

- Runmarker B, Andersen O. Prognostic factors in a multiple sclerosis incidence cohort with twenty-five years of follow-up. *Brain* 1993; **116**: 117–34.
- Weinshenker BG, Bass B, Rice GPA, Noseworthy J, Carriere W, Baskerville J *et al.* The natural history of multiple sclerosis: a geographically based study. 2. Predictive value of the early clinical course. *Brain* 1989; **112**: 1419–28.
- Weinshenker BG, Bass B, Rice GPA, Noseworthy J, Carriere W, Baskerville J *et al.* The natural history of multiple sclerosis: a

- geographically based study. I. Clinical course and disability. *Brain* 1989; **112**: 133–46.
- 4 Weinschenker BG, Rice GPA, Noseworthy JH, Carriere W, Baskerville J, Ebers GC. The natural history of multiple sclerosis: a geographically based study. 3. Multivariate analysis of predictive factors and models of outcome. *Brain* 1991; **114**: 1045–56.
 - 5 Amato MP, Ponziani G. A prospective study on the prognosis of multiple sclerosis. *Neurol Sci* 2000; **21**: S831–S838.
 - 6 Confavreux C, Vukusic S, Adeleine P. Early clinical predictors and progression of irreversible disability in multiple sclerosis: an amnesic process. *Brain* 2003; **126**: 770–82.
 - 7 Pittock SJ, Mayr WT, McClelland RL, Jorgensen NW, Weigand SD, Noseworthy JH *et al.* Change in MS-related disability in a population-based cohort: a 10-year follow-up study. *Neurology* 2004; **62**: 51–59.
 - 8 Noseworthy JH. Clinical scoring methods for multiple sclerosis. *Ann Neurol* 1994; **36**: S80–S85.
 - 9 Sharrack B, Hughes RA, Soudain S, Dunn G. The psychometric properties of clinical rating scales used in multiple sclerosis. *Brain* 1999; **122**: 141–59.
 - 10 Hobart J, Freeman J, Thompson A. Kurtzke scales revisited: the application of psychometric methods to clinical intuition. *Brain* 2000; **123**: 1027–40.
 - 11 Nortvedt MW, Riise T. The use of quality of life measures in multiple sclerosis research. *Mult Scler* 2003; **9**: 63–72.
 - 12 Poser CM, Paty DW, Scheinberg L, McDonald WI, Davis FA, Ebers GC *et al.* New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Ann Neurol* 1983; **13**: 227–31.
 - 13 Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis: results of an international survey. National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis. *Neurology* 1996; **46**: 907–11.
 - 14 Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1983; **33**: 1444–52.
 - 15 Granger CV, Cotter AC, Hamilton BB, Fiedler RC, Hens MM. Functional assessment scales: a study of persons with multiple sclerosis. *Arch Phys Med Rehabil* 1990; **71**: 870–75.
 - 16 Freeman JA, Hobart JC, Langdon DW, Thompson AJ. Clinical appropriateness: a key factor in outcome measure selection: the 36 item short form health survey in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2000; **68**: 150–56.
 - 17 Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R *et al.* Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. *J Clin Epidemiol* 1998; **51**: 1055–68.
 - 18 Kidd D, Stewart G, Baldry J, Johnson J, Rossiter D, Petruckevitch A *et al.* The Functional Independence Measure: a comparative validity and reliability study. *Disabil Rehabil* 1995; **17**: 10–14.
 - 19 Ottenbacher KJ, Hsu Y, Granger CV, Fiedler RC. The reliability of the functional independence measure: a quantitative review. *Arch Phys Med Rehabil* 1996; **77**: 1226–32.
 - 20 Hobart J, Freeman J, Lamping D, Fitzpatrick R, Thompson A. The SF-36 in multiple sclerosis: why basic assumptions must be tested. *J Neurol Neurosurg Psychiatry* 2001; **71**: 363–70.
 - 21 Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics* 1986; **42**: 121–30.
 - 22 Terwee CB, Dekker FW, Wiersinga WM, Prummel MF, Bossuyt PM. On assessing responsiveness of health-related quality of life instruments: guidelines for instrument evaluation. *Qual Life Res* 2003; **12**: 349–62.
 - 23 Nortvedt MW, Riise T, Myhr KM, Nyland HI. Quality of life in multiple sclerosis: measuring the disease effects more broadly. *Neurology* 1999; **53**: 1098–103.
 - 24 Prins M, Geskus RB, Coutinho RA. [Roaming through methodology. XXXV. Bias in prevalent cohort studies of the natural course of disease]. *Ned Tijdschr Geneesk* 2001; **145**: 2170–72.
 - 25 Alcabas P, Pezzotti P, Phillips AN, Rezza G, Vlahov D. Long-term perspective on the prevalent-cohort biases in studies of human immunodeficiency virus progression. *Am J Epidemiol* 1997; **146**: 543–51.