2

METHODS

Design of the study

This study on perception of risk of MS (PROMS) is a longitudinal study comprising four time points in two years at which patients underwent neurological and neuropsychological examinations and completed psychological questionnaires. An overview of the study is presented in Table 1.

Participants

The PROMS study was conducted among recently diagnosed MS patients and their partners. Patients were recruited through the Departments of Neurology of the Erasmus MC, three hospitals within the region of this academic hospital, and the VU Medical Center in the period of March 1999 – December 2000. Patients were eligible if they had a definite or probable diagnosis of MS,[1] were diagnosed within two years before study entry, were between 18 and 55 years old and had signed informed consent. The diagnoses were verified by senior neurologists of the academic hospitals. Patients with serious comorbidity or with insufficient understanding of the Dutch language were excluded. Partners were eligible if they had sufficient understanding of the Dutch language.

Part of this study was conducted in collaboration with the FUPRO-MS study of the department of rehabilitation of the VU Medical Center (Amsterdam), a large-scale study on the clinimetric evaluation and determinants of functional prognosis. The PROMS and FUPRO-MS studies had different research questions but a comparable schedule of measurements and a considerable overlap in the

Table 1 Overview of assessments in the PROMS study

Measurement	1	2	3	4
Follow-up in years	0	½	1	2
Patients				
General characteristics	X			
Disease characteristics				
MRI*	X			
MS-related medical history	X			
Neurological examination	X	X		X
Neuropsychological examination*	X	X		X
Personality traits				
Optimism, neuroticism	X			
Psychological outcome variables				
Perception of risk and seriousness, health-related quality of life, anxiety, depression, disease-related distress, illness representations, uncertainty	X	X	X	X
Psychological interview	X			
Partners				
Psychological outcome variables				
Perception of risk and seriousness, health-related quality of life, anxiety, depression, disease-related distress, illness representations, uncertainty	X		X	X
Psychological interview	X			

* The MRI and neuropsychological examinations were conducted to study the predictive value of cognitive function on progression of disease. This research question is outside the scope of this thesis.

examinations and questionnaires. The inclusion criteria of the FUPRO-MS study were limited to patients with definite MS who were diagnosed no longer than six months before study entry. Patients with definite MS who were diagnosed between 6-24 months and those with probable MS were eligible for the PROMS study only. Patients who met the criteria for both studies were invited to participate in both.

Of the 120 patients who met the inclusion criteria, 101 agreed to participate in the study. Patients who declined participation further mentioned the emotional burden (n=3) or a lack of interest (n=3). Nine patients declined without additional comments and four never responded to our reminders. Ninety of 101 (89%) had a partner of whom 78 did participate. Others were excluded due to insufficient understanding of the Dutch language (n = 2), were not living together and for that reason not invited by the patient (n = 6) or declined for unknown reasons (n = 4).

Fifty-nine patients were recruited through the Erasmus MC, 32 through the VU Medical Center and 10 through hospitals within the region of the Erasmus MC.

Half of the patients (57/101) participated in the PROMS-study only, and the other half (54/101) participated in both the PROMS- and FUPRO-MS study.

Of the 101 patients who started, two declined further participation after the first measurement and one after the second (Table 2). Reasons for withdrawing were the high emotional burden (n = 1), problems with disability payment procedures (n = 1), loss to follow-up (n = 1). Patients who missed one assessment often did not respond to several reminders or repeatedly postponed visits. Loss of follow-up in partners was mainly explained by the non-participation of patients (n = 5) and broken relationships (n = 3).

Procedure

Patients were informed about the study by their treating physician. When they showed interest, patients were given an information letter and a reply form. The letter included additional information about the study, as well as explanations on the protection of privacy and the non-interference of study participation with their treatment by the neurologist. At the same time and with permission of the patient, the neurologist completed a form with general and clinical characteristics of the patient, which was returned to the investigators. Patients were asked to return the reply form within two weeks. Those who did not respond were phoned by the investigator to hear their decision.

Patients who agreed to participate were scheduled for a neurological and neuropsychological examination and an interview. These appointments were planned one week apart with the examinations preceding the interview. Patients participating in both studies were visited at home for the neurological and

Table 2 Participation at follow-up measurements

	Time point	Resigned (cumulative)	Missing assessments at one time point	Available data
Patients	1	-	-	101
	2	2	1	98
	3	3	1	97
	4	9 *	-	72 *
Partners	1	-	-	78
	3	3	3	72
	4	11 *	-	55 *

* Measurement 4 was scheduled to finish in March 2003. Numbers are based on available data by December 2002. At that time, 81 patients and 66 partners had been scheduled for measurement 4.

neuropsychological examinations, whereas PROMS participants were invited to visit the hospital. All interviews were held at home by the same psychologist (CJ). One week before the examinations, questionnaires for the patients were sent by mail. These had to be completed one week after the examination and handed in before the interview. Partners were given their questionnaires prior to the patient's interview and were asked to complete these in another room during the patient's interview. After the patient's interview, the partner was interviewed in absence of the patient. At follow-up, all questionnaires were sent to the patients and partners by mail with an explicit request to complete the questionnaires on their own. The questionnaires could be handed in at the neurological examinations or returned by mail. If necessary, repeated phone calls were made to remind participants of returning their questionnaires. The study protocol was approved by the medical ethical committees of the participating hospitals.

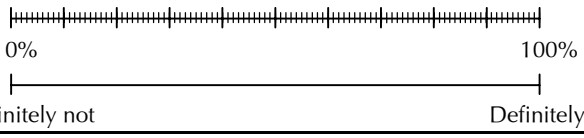
Instruments

Description of instruments

Perception of risk and seriousness – Expectations about prognosis were operationalized as perception of prognostic risk and perceived seriousness of prognosis. There is no widely-used instrument or gold standard for the assessment of risk perception. Instead, researchers have developed their own instruments, which differ considerably from one another. It is known that different assessments yield different impressions of perceptions of risk, implying that the choice of measurement has a significant impact on the findings of the study.[2-5] For example, women at increased risk of breast cancer appeared to have more accurate perceptions of their risks when these were measured as comparative risks than when measured as absolute risks.[5] Table 3 provides an overview of aspects that define measurements of risk perception. These aspects can be categorized as three major decisions: the definition of the prognostic outcome, the choice of the risk format, and the choice of scale or answer format.

In this study, wheelchair dependence was selected as the prognostic outcome because it is a well-known consequence of MS (see previous chapter). Wheelchair dependence was defined as the inability to walk beyond five meters, equaling a score of 7.0 on the EDSS. Because we were interested in the expectations of patients for the near and far future, we investigated the short (2-year), medium (10-year) and long term (lifetime) risk of wheelchair dependence. Risk perception was measured as an absolute and relative risk. In the relative risk, patients were asked to evaluate their risk compared to other patients of their age and sex who have similar limitations due to the disease. Since many patients reported problems of

Table 3 Definition and measurement of perception of risk

Definition of outcome	
Choice of outcome	Progressive course, wheelchair dependence, use of walking aids, blindness, cognitive decline, dying due to MS
Operationalization	Wheelchair dependence for distances over 5 meters, 100 meters, 1 kilometer
Time span	Wheelchair dependence within two years, ten years, lifetime
Definition of risk format	
Absolute versus relative risk	What do you think is your risk of wheelchair dependence? Compared to other women of your age and sex, what do you think is your risk of wheelchair dependence?
Unconditional versus conditional risk	What do you think is your risk of wheelchair dependence? Suppose you take interferon, what do you think is your risk of wheelchair dependence?
Definition of scale	
Dichotomous	Yes / No, Likely / Unlikely, Definitely / Definitely not
Percentage	1%, 20%, 50%
Frequency	1 in 100, 20 in 100, 50 in 100
Odds	1 to 100, 1 to 5, 1 to 2
Likert scale	3-, 5-, 7-, 9-, 11-point scale, e.g.: 5-point: No chance, unlikely, moderate, likely, certain to occur. 7-point: No chance, very unlikely, unlikely, 50/50 chance, likely, very likely, certain to occur.
Visual analogue scale	

Based on references[5-11]

understanding this relative risk format (see also Chapter 10), these questions are not discussed in the thesis.

The basic choice in response modes is that between numerical and verbal (non-numerical) scales.[6,12-16] This classification is in line with the two basic systems of reasoning: associative, intuitive and automatic processes versus rule-based, deliberative, controlled processes:[16,17] verbal assessments may be preferred in non-rational processes, and numerical in rule-based processes. Because we were interested in the impact of perceived risk on emotional well-being, we opted for verbal – or non-numerical – assessment of risk perception. A second, practical, reason is that we expected a high number of missing values with a numerical assessment, as patients emphasized in the pilot study that prognostic risks are

unknown. Therefore, we aimed to reduce any associations with numbers or counting in order to assess beliefs or ideas rather than knowledge about risks. We chose for blank visual analogue scales with verbally labeled end-points. Thus, patients were asked to what extent they thought they would become wheelchair-dependent for distances over five meters within two years, ten years and lifetime (see Appendix A). Answers had to be given by marking a blank 100mm visual analogue scale (VAS), which ends were anchored at 'Definitely not' and 'Definitely'. Marks on the scale were measured in millimeters from the left end of the scale. Answers ranged from 0 (definitely not) to 100 (definitely).

Perceived seriousness of wheelchair dependence was assessed in a similar way. Patients were asked for each of these periods how serious they thought it would be to be wheelchair-dependent by that time. Again, answers had to be given on a VAS anchored at 'Not serious at all' and 'The most serious thing I can imagine', with a possible range from 0 to 100, respectively.

Health-related quality of life – Quality of life was assessed using the SF-36.[18] The SF-36 comprises four physical health (physical functioning, role-physical functioning, bodily pain and general health) and four mental health scales (vitality, social functioning, role-emotional functioning and mental health). Items are summed per scale and transformed into scores between 0 (poor health) and 100 (optimal health).[18] For the bodily pain scale, higher scores mean less pain. The SF-36 was validated in a Dutch population and norm values were available.[19]

Anxiety and depression – Anxiety and depression were assessed by two 7-item scales of the Hospital Anxiety and Depression Scale (HADS).[20,21] Scale scores can vary from 0-21 with high scores indicating higher levels of anxiety and depression. This instrument was chosen because the HADS is relatively free of interference by coexisting general medical conditions.[22] Scores between 8 and 10 are considered clinically borderline and 11 or higher clinically definite levels of anxiety and depression.[20,21] Norm scores of the general population were available.[23]

Disease-related distress – Specific MS-related distress was assessed using the Impact of Event Scale.[24,25] This questionnaire addresses the psychological distress of having MS by focusing on the impact of thoughts and feelings. One scale measures being overwhelmed by thoughts and feelings about having MS (intrusion) and the other evaluates the tendency to avoid these thoughts and feelings (avoidance). The intrusion scale ranges from 0 to 35 with high scores indicating more intrusive thoughts and feelings. The avoidance scale ranges from 0 to 40 with high scores indicating a greater tendency to avoid MS-related feelings and thoughts. A total distress score was obtained by summing intrusion and avoidance scores. Scores of 26 and higher on the total scale indicate levels of severe distress.

Illness representations – Illness representations are the core determinant of coping behavior in the self-regulation theory of illness.[26] Illness representations were assessed using the Illness Perception Questionnaire (IPQ).[27] The illness identity, cause and timeline (cyclical) scales were derived from the revised version (IPQ-R).[28] Also, the coherence scale from the revised version was included to assess whether patients believe they have a clear understanding of their illness.

Optimism – Dispositional optimism, a generalized tendency to believe in positive outcome expectancies was assessed using the Life Orientation Test (LOT).[29,30] The scale consists of four positively formulated items (optimism), four negatively formulated items (pessimism) and four filler items. The optimism and pessimism sub-scales are summed into a total score, with a possible range from 8 to 40, with higher values indicating greater dispositional optimism and pessimism. Good validity has been demonstrated in a Dutch population sample.[30]

Neuroticism – Neuroticism refers to a stable dimension of personality consisting of negative emotions such as anxiety and anger, and cognitive and behavioral characteristics such as low self-esteem, preoccupation and insecurity.[31] Patients completed the 12-item neuroticism scale of the Eysenck Personality Questionnaire (EPQ).[32,33] The scale ranges from 0 – 12, with high scores indicating high neuroticism.

Illness uncertainty – The Mishel Uncertainty in Illness Scale (MUIS) was used to measure the patient's feelings of uncertainty about symptoms, diagnosis, treatment, relationships with caregivers and future plans.[34] The questionnaire comprises 33 items with 5-point Likert answer formats (strongly agree – strongly disagree). Items are summed into four scales: inconsistency, unpredictability, complexity and ambiguity with high scores indicating greater uncertainty.

MS-related disease history – Date of first symptoms, type of first symptoms and use of immunomodulatory drugs were registered at the neurological examination. Initial date of diagnosis and diagnostic certainty (probable or definite MS) were obtained from the treating physicians and the medical records. The diagnoses were confirmed at study entry by neurologists of the participating academic hospitals.

Disability status – Physical limitations were assessed by physicians of the academic hospitals following a standardized research protocol. Level of disability was rated on the widely-used Expanded Disability Status Scale (EDSS).[35] This scale ranges from 0.0 (no neurological symptoms) to 10.0 (death due to MS).

Psychological interview – A semi-structured interview was conducted to address experiences with the disease before and after diagnosis. Topics included the symptom history, disclosure of the diagnosis, uncertainty and worries about prognosis, beliefs about MS, expectations of prognosis, doctor-patient relationship,

and information needs. In this thesis, we will report about patients' explanations of their perceptions of risk and seriousness of wheelchair dependence. Patients were asked to elucidate their VAS scores (see perception of risk and seriousness). To prevent priming of the answers, questions were framed without interpreting the location of the mark on the VAS. For example, we asked 'can you explain why you put your mark *on that point of the line'* instead of '*in the middle'* or '*nearly at the end of the line'*. Explanations were recorded on audiotapes and transcribed verbatim.

Psychometric properties of instruments

Psychometric properties of the instruments used in this study are summarized in Table 4. We examined the following statistics:

Reliability – Reliability concerns the extent to which measurements are stable over a variety of conditions in which the same results should be obtained. We calculated Coefficient α as a measure of internal consistency which is based on the average inter-item correlation. When α is 0.80, at least 80% of the total score variance is due to true score variance.[36] For research purposes Coefficient α is acceptable at about 0.70 or higher, whereas for diagnostic purposes 0.90-0.95 may not even be high enough.[37] Reliabilities of the scales are calculated using the baseline data of patients. Based on these criteria, coefficient α of the IPQ cyclical timeline and personal control scales, the EPQ Neuroticism and the MUIS complexity and predictability scales were insufficient. The reliability of the IPQ cyclical timeline scale increased after items with the weakest item-total correlation were excluded. Since the remaining items ('My symptoms come and go in cycles' and 'I go through cycles in which my illness get better and worse') are most relevant in MS, it was decided to use the 2-item scale in further analyses. The low reliability of the personal control scale was not caused by errors in recoding of the items, but due to low inverse correlations between the items. Coefficient α of the EPQ Neuroticism scale increased to 0.74 when the scale was reduced by one item and to 0.80 when the two 'weakest' items were removed. Yet, the correlation coefficients of these scales with the original 12-item scale were 0.99 and 0.97, respectively. As this indicates that scale reduction will not yield different results, we decided to use the original scale.

Factor analysis – We performed principal component analysis with Varimax rotation to *screen* whether the original groupings of items (scales) were replicated in our study. The results of the factor analyses of the scales were compared with the original structure. When for a given scale, all (++) or all but one (+) of its items loaded on the same factor, we considered the original scale to be confirmed.

Table 4 Psychometric properties of the psychological instruments in this study

Questionnaire	Scale	Number of items	Reliability[1]	Factor analysis[2]	Skewness[3]
Perceived risk	2 years	1	NA	NA	1.17
	10 years	1	NA	NA	0.20
	Lifetime	1	NA	NA	-0.26
Perceived seriousness	2 years	1	NA	NA	-1.69
	10 years	1	NA	NA	-1.39
	Lifetime	1	NA	NA	-1.29
Health-related	Physical functioning	10	0.94	++	-0.81
quality of life	Role-physical functioning	4	0.84	++	0.05
– SF-36	Bodily pain	2	0.89	++	-0.61
	General health	5	0.77	++	-0.10
	Vitality	4	0.78	+	-0.11
	Social functioning	2	0.80	++	-0.81
	Role-emotional functioning	3	0.74	++	-0.94
	Mental health	5	0.82	+/-	-0.62
Anxiety / depression	Anxiety	7	0.83	++	1.03
– HADS	Depression	7	0.81	++	1.14
Disease-related	Avoidance	7	0.75	++	0.67
distress – IES	Intrusion	7	0.82	++	0.81
Illness representations	Causes	19	NA	NA	NA
– IPQ	Coherence	5	0.82	++	0.16
	Consequences	7	0.72	++	-0.07
	Chronic timeline	3	0.82	++	0.49
	Cyclical timeline	5	0.32	-	-0.03
		2	0.72	++	-0.74
	Personal control	3	0.00	+	0.14
	Treatment control	3	0.66	+	-0.10
	Identity	23	0.87	NA	0.93
Optimism – LOT	Optimism	4	0.72	++	-0.13
	Pessimism	4	0.68	++	-0.39
Neuroticism – EPQ	Neuroticism	12	0.64	++	-0.02
		11	0.74	++	-0.07
Illness uncertainty	Inconsistency	7	0.78	+	0.82
– MUIS	Unpredictability	5	0.28	+	-0.38
	Complexity	7	0.56	-	1.05
	Ambiguity	13	0.63	-	0.43

[1] Coefficient α; [2] ++ All items load on 1 factor, + all but 1 item load on one factor, +/- most items load on 1 factor, - items are divided over factors. NA = not applicable; [3] SE = 0.24.

When most of its items loaded on one factor (+/-) confirmation was considered moderate. When items of the original scale were dispersed over several factors (-), we considered the structure not confirmed. In our study, factor analyses could not reproduce the IPQ cyclical timeline scale and the MUIS ambiguity and complexity scales. Since the 2-item cyclical timeline scale of the IPQ loaded on one factor, this scale was used.

Normality – Although statistical tests generally require that data are normally distributed, it is tempting to conclude that most tests are robust for deviations from normal distributions.[38] For example, in multivariate regression analyses it is not required that individual variables are normally distributed, but that the residuals (unexplained variance) of analyses demonstrate a normal distribution. Yet, it is adviced to use transformations of variables to improve their normality unless there is some compelling reason not to.[38] One reason may be that results of transformed data are far more difficult to interpret from a clinical perspective. Therefore, we limited transformation to those analyses in which transformation of skewed variables yielded different conclusions. To examine which variables *might* need transformation, we evaluated normality by examination of the skewness of the distributions. As a rule of thumb, distributions are considered to deviate from normality when the skewness is higher than twice its standard error (SE). The distribution of perceived risk and seriousness, SF-36 quality of life, HAD anxiety and depression and IES intrusion and avoidance were all skewed. To examine whether these variables *do* need transformation, we inspected the normal probability plots of the residuals.

Based on inspection of the internal consistency reliability and factor analysis, it was decided that the psychometric properties of the illness uncertainty scale (MUIS) and the IPQ personal control scale were insufficient. These scales were not used in the analyses. The distributions of most SF-36 scales, the HADS, IES and perceptions of risk and seriousness were skewed. All analyses including these variables will be inspected on adverse effects of skewness.

Missing data handling

The percentage of missing data of the main follow-up variables (perception of risk and seriousness, quality of life, anxiety and depression and disease related distress) in patients was 0-3% at measurement 1, 0-3% at measurement 2, 0-5% at measurement 3, and 0-2% at measurement 4. In partners, the percentage of missing values was 0-5% at measurement 1, 0-7% at measurement 3, and 0-2% at measurement 4. Exception was perceived 2-year risk and seriousness, which were included later in the study and therefore missing at measurement 1 in thirteen

patients and eleven partners. Compared to those who did complete these questions, we found no differences in perceived 10-year and lifetime risk and seriousness. Thus, missing values were considered 'at random'. For the cross-sectional analyses, missing data of the perceived 2-year risk were imputed using the iterative expectation-maximization method based on their perceived 10-year and lifetime risk and seriousness.[39]

Statistical analysis

Statistical analyses were performed using SPSS 9.0-11.0 for Windows (SPSS Inc., www.spss.com) and SAS 8.0 for Windows (SAS Institute Inc., www.sas.com). All data were inspected for coding errors, outliers and extreme values. All multivariate analyses were inspected for multicollinearity and normality of the residuals. P-values (2-sided) lower than 0.05 were considered statistically significant.

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