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The aim of this study was to investigate expectations of prognosis in patients recently diagnosed with MS. Disease- and person-related determinants of perception of risk and seriousness of wheelchair dependence, as well as the relationship between risk perception, psychological well-being and QoL were investigated. In this chapter, the findings of the study are summarized and discussed. First, methodological issues with regard to the design of the study and the instruments used are reviewed. Then, the main findings of the study are discussed from a psychological and clinical perspective. And finally, topics for future research are addressed.

Methodological issues

Data collection: postal distribution of questionnaires

The first methodological issue to be discussed concerns the data collection within couples. To ensure the independent assessment of observations within couples, it is crucial that spouses fill out their questionnaires separately. In our study, procedures for completion of the questionnaires differed at baseline and follow-up. At baseline, patients filled out their questionnaires before the interview, whereas partners completed theirs while the patient was interviewed. At follow-up, all questionnaires were sent and returned by mail. Patients and partners had then more opportunity to confer their answers, which may have biased the follow-up assessments. It can be postulated that such bias would be revealed by higher correlations between patient and partner scores at follow-up. Table 1 demonstrates that correlations of the key variables were not consistently higher at follow-up, suggesting that the postal distribution of questionnaires has not biased the findings.

Table 1 Pearson correlation coefficients between patient and partner scores of major study variables at baseline and follow-up measurements

Measurement		Baseline	1-year follow-up	2-year follow-up
Anxiety		0.31	0.36	0.27
Depression		0.36	0.24	0.30
Intrusion		0.10	0.17	0.17
Avoidance		0.27	0.36	0.14
Perceived risk:	2-year	0.45	0.50	0.53
	10-year	0.48	0.46	0.57
	Lifetime	0.45	0.55	0.31
Perceived seriousness:	2-year	0.27	0.34	0.48
	10-year	0.31	0.23	0.38
	Lifetime	0.24	0.39	0.36

Selection of the study population

Our study aimed to include patients who were diagnosed with definite or probable MS within two years prior to study entry and were between 18 and 55 years old. Patients with serious comorbidity or insufficient understanding of the Dutch language were excluded. For the generalization of our findings, it is important to evaluate whether the participants were a representative sample of this patient population, and if not, whether the findings were biased by patient selection.

Second opinion

Since patients were recruited primarily through academic hospitals, an unknown number may have visited these centers for a second opinion. These patients either came on their own initiative or were referred by their treating neurologist. The potential overrepresentation of patients referred for a second opinion may have influenced several of the findings. First, it can be anticipated that these patients were the least satisfied with the diagnostic procedures at their local hospital. Hence, the percentage of patients who were dissatisfied with the timing of diagnosis (Chapter 3) may be lower in an unselected patient population not derived from an academic center. Yet, the conclusion that patients prefer an early diagnosis will remain unchanged, because this was primarily based on the group that was satisfied and had a short duration of the diagnostic workup. Second, the high level of anxiety and distress (Chapter 4) may be overestimated. Anxiety and distress may have been the reason to seek for confirmation in a second opinion, or the result from the uncertainty of being sent for one. This may imply that in an

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unselected population levels of anxiety and distress may be lower. The relationship between perception of risk and anxiety and distress will only be overestimated when in the latter patients low levels of anxiety and distress are associated with high perception of risk.

Emotional burden in non-responders

Of the 120 patients who were invited to participate in the study, 19 refused. The reasons for non-participation were known in six patients (Chapter 2), of whom three mentioned the high emotional burden of the disease and three others showed lack of interest. The emotional burden of being confronted with the disease is expected an important reason for non-participation in more patients, implying that the prevalence and mean levels of anxiety, depression, distress and QoL may be underestimated in our study. Again, the relationship between perception of risk and psychological outcomes will only be overestimated when in these patients high levels of anxiety and distress were associated with low perception of risk.

Definite and probable MS

To investigate the influence of diagnostic certainty on perception of risk and psychological well-being, the PROMS study included patients with definite and probable MS.^[1] Yet, only ten patients with probable MS were included, which number was not large enough to provide statistical power for comparisons with patients with definite MS. Although no clear conclusions can be drawn, the differences between patients with probable and definite MS tended to be small. This may be explained by the fact that the majority of patients with probable MS anticipated that their diagnosis would finally be definite: seven out of ten patients perceived their risk of developing definite MS as 80% or higher at each time point of the study. However, due to the low number of patients with probable MS, the findings of this study are primarily generalizable to patients with definite MS.

Validity and reliability of instruments

The majority of instruments used in this study were validated and known to be reliable. The validity of two instruments is discussed in more detail: the assessment of perceived risk and seriousness by visual analogue scales (VAS) and clinical disability by means of the Expanded Disability Status Scale (EDSS).

Perceived risk and seriousness

Perception of risk and seriousness of wheelchair dependence were measured on a blank VAS (see Appendix A). The VAS is a widely-used instrument for the

quantification of subjective phenomena including attitudes, pain, discomfort and perception of risk.^[2,3] In this study, comparisons between perceived risk and seriousness assessed by VAS scores and patients' explanations in the interview (Chapter 10) indicated good face validity. For example, when patients explained that they thought they would definitely not become wheelchair-dependent they marked the line between 0-5mm, and patients who said that 'it might happen or not' had scores between 45-55mm. Our interview findings confirmed that 50%-responders primarily stressed their uncertainty about the future, rather than explained that the numerical risk was actually 50% (see also Chapter 6).^[4] Although, for these patients as well as all others, there is a difference between this individual perspective (I don't know, low or high) and population perspective (the risk is 50%, 20% or 80%), this may not necessarily reduce the validity of the findings on perception of risk. In this light, it is important to realize that also the actual population risk is the mean of all individual risks, namely a 20% risk means that the risk is 100% in 20 out of 100 patients and 0% in 80 patients. Although individual perception of risk cannot be compared to this mean actual risk, it is valid to compare the latter with the mean perception of risk.

EDSS as a measure of disability status

Despite its widespread use as an instrument to rate disability in MS, the EDSS has many documented imperfections.^[5,6] The instrument has poor responsiveness, large inter-rater variability and is primarily focusing on mobility at the higher end of the scale.^[5,6] It can be argued that in a relatively homogenous population the EDSS is inadequate for the measurement of small differences in disability status. This may have implications for our study of patients' perception of their symptoms. The variation in *perceived* symptoms, given a certain level of objective limitations as assessed by the EDSS, may still reflect residual variation in *actual* functional limitations. If true, this could mean that the relationship between perceived symptoms and perception of risk, adjusted for EDSS (Chapter 8 and 9), is due to residual confounding of actual physical limitations. However, the significant adjusted association between perceived symptoms and personality (Chapter 9) indicates that perceived symptoms, at least in part, are subjective and less likely explained by residual confounding alone.

Main findings

Psychological well-being and quality of life in the early phase

At baseline, on average eight months after diagnosis (Chapter 4), patients and partners were substantially bothered by the intrusion of MS-related thoughts and

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feelings. In our study, 70% of the patients were satisfied with the timing of their diagnosis and 24% had preferred to be diagnosed earlier (Chapter 3). The probability of satisfaction with the timing of diagnosis significantly decreased with a longer duration of the diagnostic workup at the neurological clinics. This period may be crucial, because a referral to a medical specialist indicates that symptoms were serious enough to warrant further examination (Chapter 3). Patients commented that the burden of uncertainty was a major reason for preferring an earlier diagnosis. This burden of uncertainty before the diagnosis is in line with previous MS studies on the impact of diagnostic information.^[7-9] In two studies, levels of anxiety and distress tended to be lower after the diagnosis although this decrease was not as profoundly as anticipated.^[7,8] The third study reported an increase of these negative feelings after diagnosis, next to an increase in positive feelings such as courage for fighting the disease and clarity about their situation.^[9]

Intrusive thoughts and feelings decreased during the 2-year follow-up (Chapter 11). Patients also demonstrated high levels of avoidance at baseline, but not at follow-up. In comparison, the mean levels of distress in this study were higher than that found in patients and partners awaiting presymptomatic test results for Huntington's disease or hereditary breast and ovarian cancer.^[10] It has been argued that these high levels of distress may reflect coping processes and adaptive reactions in apparent stressful situations such as the early phase after diagnosis (see previous paragraph).^[11,12] The finding that distress was lower at follow-up supports this coping hypothesis.

Patients as well as partners also reported significantly more symptoms of anxiety than individuals from the general population (Chapter 4). These high levels of anxiety remained unchanged during the 2-year follow-up, despite the substantial decrease in disease-related distress (Chapter 11). In fact, 50% of the patients and 60% of the partners who had clinically high levels of anxiety at baseline still had these high levels at the two-year follow-up. In contrast to studies in later phases of MS,^[13-15] mean scores of depression were not higher in these recently-diagnosed patients compared to general population controls.

Quality of life (QoL) – Previous studies have demonstrated that patients with MS report poorer health-related QoL than individuals from the general population (see Introduction). The present study shows that patients, including those with no to minimal functional limitations, also reported poorer QoL in the early period after diagnosis (Chapter 4). The poorer QoL among patients with few functional limitations may be explained by increased feelings of anxiety or depression. Anxiety and depression may lower QoL or may lead to reporting poorer QoL (Chapter 5).^[16] An alternative explanation may be a lack of response shift,^[17,18]

which predicts that patients may still have compared their health status with the expectation of 'perfect' health. This phenomenon may explain the poorer QoL even in the absence of moderate to severe physical limitations (Chapter 5).

In summary, patients and partners experienced a high emotional burden in this early period after diagnosis. Although disease-related distress decreased during the 2-year follow-up, there was no significant reduction in the feelings of anxiety: at least 12% of the patients and 16% of the partners had clinically high levels of anxiety during the 2-year period of follow-up. This may have clinical implications as discussed in the section Clinical implications (Page 182).

Perception of risk and seriousness of wheelchair dependence

Perception of risk

The key question in this thesis was: what do patients recently diagnosed with MS expect of future disease progression? And how do these expectations change in the first years after diagnosis? Based on comparison of mean perception of risk and estimated risks, patients overestimated their 2-year and 10-year risks of wheelchair dependence, and underestimated their lifetime risk (Chapter 6). In the two-year follow-up, perception of the 2-year and 10-year risk slightly but significantly increased, whereas perceived lifetime risk remained unchanged (Chapter 11). Several findings are of interest in light of our understanding of perception of prognostic risk.

First, a significant number of patients perceived their risks to be about 50%. These patients predominantly explained in the interviews that they did not know what to expect: it might happen or it might not, confirming findings of others that 50%-answers indicated complete uncertainty of the future.^[19] Patients may have used this response, because 'this allows them to give a number without feeling that they have committed themselves to a specific answer'.^[20] Indeed, the 50%-response is equally defensible whatever actually happens.^[21] Patients may also have given a 50%-response, because they did not want to think about whether their risk would be higher or lower. Using the heuristic of anchoring and adjustment, Tversky and Kahneman predict that in such situations patients stick to scale anchors, e.g. the ends or the middle of the scale as the 50%-responders did.^[22]

Second, as expected, perceived risks were higher for the longer time periods. But despite the longer time interval between the 10-year and lifetime prognosis, the mean difference between perceived 10-year and lifetime risk approximated the mean difference between the perceived 2- and 10-year risk. That is, respondents did not discriminate between ten years and lifetime.

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Third, many studies on risk perception reported that individuals overestimated^[23-26] or underestimated^[27] their risks of e.g. cancer. In our study, conclusions of over- and underestimation varied with the time perspective: patients overestimated short- and medium-term risks and underestimated lifetime risks. These findings emphasize the importance of careful selection and definition of outcomes in studies of risk perception (see page 188).

Why did patients overestimate their short- and medium-term risks and underestimate their lifetime risk of wheelchair dependence? One may speculate that patients may overestimate their risks to prevent future disappointment or to anticipate coping with future disease progression. Alternatively, patients may underestimate their risks not because they believe it is low, but to prevent excessive or unnecessary worry, also referred to as defensive optimism.^[28] Our findings of the interview study are compatible with this view (Chapter 10). And finally, patients may deny that they are at increased risk. In our study, it is difficult to distinguish between these psychological motivations because patients were often not aware of their numerical risks and did not know whether they were under- or overestimating. Notwithstanding, patients were knowledgeable of the lifetime possibility of wheelchair dependence and of the unpredictability of their disease. In that light, the considerable underestimation of the lifetime risk in a subgroup of patients - several patients perceived the *lifetime* risk even lower than 5% (Chapter 6) - may be an indication of defensive optimism or denial.

Perception of seriousness

Patients considered wheelchair dependence to be a very serious consequence of their disease (Chapter 6). This opinion did not change during the 2-year follow-up. Although patients considered short-term wheelchair dependence to be more serious than long-term wheelchair dependence, the differences between periods were only small. This lack of variation may be a result of the seriousness of wheelchair dependence itself: a wheelchair would always disrupt life, no matter at what point in time. In the interviews, patients did mention that short-term wheelchair dependence would be particularly serious, because this would severely disrupt their life and future plans and moreover, that the disease in that case has an extremely progressive course (Chapter 10).

Associations between perceived risk and psychological well-being

Perceived risk

The most important finding of our studies of correlates with risk perception is that perception of the short-term risk of wheelchair dependence was most consistently

Table 2 Summary of results on psychological correlates of perceived risk

	↔	Time period								
		2 years			10 years			Lifetime		
		Baseline	All	Δ	Baseline	All	Δ	Baseline	All	Δ
Anxiety	↑	***	***	***	--	*	+	--	--	--
Depression	↑	**	***	*	--	***	**	--	--	--
Intrusion	↑	**	***	**	***	***	*	**	**	--
Avoidance	↑	*	***	*	--	*	--	--	--	--

↔ = Direction of the relationship, ↑ = Positive; Baseline = Cross-sectional associations at baseline (Chapter 7), All = Cross-sectional associations at all assessments (Chapter 12) Δ = Associations between changes in perception of risk and changes in psychological well-being (Chapter 12); *** p < 0.001, ** p < 0.01, * p < 0.05, + p < 0.10, -- p > 0.10.

and convincingly related to psychological well-being (Table 2). Moreover, changes in perception of the short-term risk were strongly associated with changes in psychological well-being. These results remained significant after adjustment for clinical disability status, indicating that the relationship between risk perception and emotional well-being is unlikely confounded by disability status (see comments on page 174). This particular association of short-term risk perception and psychological well-being is in line with the explanations of patients in the interviews that short-term disability may have a more disruptive and threatening impact on family life, work, and leisure activities than disability occurring in the remote future (see page 177).

The question remains whether risk perception influences psychological well-being or vice versa. This cannot be inferred directly from our study. In Chapter 7, we put forward that if psychological well-being had influenced perception of risk this effect was expected for each time perspective (2 years, 10 years and lifetime). Such consistent relationships were found with regard to the intrusion of MS-related thoughts and feelings, but not for anxiety, depression and avoidance. Thus, it was concluded that intrusive thoughts most likely had influenced perception of risk, while the latter most likely determined levels of anxiety, depression and avoidance. Even though most^[27,29,30] – but not all^[31] – previous studies have considered risk perception as a determinant of psychological well-being, the main direction of this relationship needs to be further explored.

Perceived seriousness

We found that perceived seriousness was consistently related to anxiety and disease-related distress (Table 3), whereas only patients who considered short-term

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Table 3 Summary of results on psychological correlates of perceived seriousness

	↔	Time period								
		2 years			10 years			Lifetime		
		Baseline	All	Δ	Baseline	All	Δ	Baseline	All	Δ
Anxiety	↑	*	***	***	+	***	**	+	***	**
Depression	↑	*	+	--	--	--	--	+	--	--
Intrusion	↑	*	**	--	**	***	--	***	**	--
Avoidance	↑	***	***	*	***	***	*	***	***	**

↔ = Direction of the relationship, ↑ = Positive; Baseline = Cross-sectional associations at baseline (Chapter 7), All = Cross-sectional associations in all assessments (Chapter 12) Δ = Associations between changes in perception of seriousness and changes in psychological well-being (Chapter 12); *** p < 0.001, ** p < 0.01, * p < 0.05, + p < 0.10, -- p > 0.10.

wheelchair dependence as more serious had higher levels of depression. A lower perception of perceived seriousness was associated with lower levels of anxiety and avoidance of MS-related thoughts and feelings. Previous studies that investigated the potential impact of MS on important life goals and financial security have demonstrated that patients who perceived the disease as more threatening reported more symptoms of depression, higher global distress and poorer subjective health status.^[32,33] Our findings on perceived seriousness are in line with those of previous studies.^[32,33]

Determinants of perceived risk and seriousness

To understand how patients came to their expectations of prognosis, we investigated what factors influenced their perception of the risk and seriousness of wheelchair dependence. Disease-related characteristics, illness beliefs and personality factors were examined in a cross-sectional (Chapter 6, 8, 9) and longitudinal design (Chapter 11). In addition, perceptions were elucidated in the interviews (Chapter 10).

Determinants of perceived risk

Not surprisingly, patients who had more physical limitations as a result of their disease symptoms, rated on the EDSS, had higher perceptions of risk (Table 4). This relationship was found for the short-, medium- and long-term prognosis of wheelchair dependence, albeit that the correlation between disability status and perceived risk was stronger for the short term. This is likely explained by the unpredictability of the disease: also patients with no to minimal disability in this early phase may develop a progressive course on the long term. Of note is that a

Table 4 Summary of results on determinants of perceived risk

	↔	Time period								
		2 years			10 years			Lifetime		
		Baseline	All	Δ	Baseline	All	Δ	Baseline	All	Δ
Disability status	↑	***	***	--	***	***	--	***	***	--
Perceived symptoms	↑	***	***	***	***	***	***	--	--	***
Neuroticism	↓↑	+	--	*	+	--	*	+	--	*
Perceived symptoms * neuroticism	↑	**	***	+	**	***	+	**	***	+
Coherence	↑	+	*	--	+	*	--	+	*	--

↔ = Direction of the relationship, ↑ = Positive, ↓ = Inverse; Baseline = Cross-sectional associations at baseline (Chapter 6, 8, 9), All = Cross-sectional associations at all assessments (Chapter 11), Δ = Associations between change in determinants and changes in perception of risk (Chapter 11); *** p < 0.001, ** p < 0.01, * p < 0.05, + p < 0.10, -- p > 0.10.

change in EDSS was not significantly associated to changes in perception of risk, which, as discussed, may reflect the lack of sensitivity of the EDSS (see page 174).

Of all illness beliefs studied only illness identity, or perceived symptoms, was consistently related to perception of risk after adjustment for disability status (Chapter 8). That is, in patients with similar functional limitations those who perceived more physical limitations had higher perception of risk. This relationship of perceived symptoms was primarily found with regard to the short- and medium-term risk of wheelchair dependence. Although the association with perceived symptoms may be due to residual confounding of disability status (page 174), several psychological explanations may also be considered (Chapter 10). First, patients may extrapolate present or past experiences, e.g. the presence of risk factors or symptoms, into predictions about future disease status.^[34-36] Second, patients who reported more physical limitations may consider themselves to be more similar to patients who will likely become wheelchair-dependent. These explanations refer to the heuristic of representativeness, which would predict a higher perception of risk among patients who reported more symptoms.^[22] And third, the (perceived) presence of symptoms, MS-related or not, may elicit higher perceptions of risk by a reminder process in which vulnerability beliefs are aroused by somatic cues.^[37] In other words, patients will be more aware of their higher risk of wheelchair dependence because they are repeatedly reminded of it by the presence of their physical limitations. Tversky and Kahneman explained such reminding process by the heuristic of cognitive availability.^[22]

Of the three personality factors studied – optimism, pessimism and neuroticism – only neuroticism was a significant determinant of perceived risk.

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That is, perceived symptoms appeared to have a stronger relationship with perception of risk in high-neuroticism patients. It is thought that persons scoring high on this personality dimension are more likely to be self-focused and therefore more likely to detect changes in physical status.^[38] Above that, this attention for physical symptoms is loaded with anxiety and uncertainty, through which these patients may interpret minor symptoms as having major consequences more than do patients scoring low on neuroticism.^[38-40] For this reason, perceived symptoms may be stronger related to perception of risk in high-neuroticism patients.

Contrary to our expectations, there was no consistent association between risk perception and time since diagnosis, time since first symptoms and illness beliefs other than perceived symptoms. Time since diagnosis was probably not associated because this period was relatively short for all participants. Time since first symptoms was not directly, but indirectly related to risk perception: patients with longer time since first symptoms tended to have higher disability (Chapter 4). Further, of the eight illness beliefs studied, only perceived symptoms was associated with perception of risk (Chapter 8). A problem with the interpretation of these findings is that these illness beliefs may have been too general to relate to the perceived risk of a specific disease complication. For example, a patient may believe that the disease is a chronic condition (high IPQ Chronic timeline), which cannot be treated effectively by medication (low IPQ Treatment control), without expecting to become wheelchair-dependent.

Determinants of perceived seriousness

Similar to the analyses performed on perceived risk, we investigated the determinants of perceived seriousness. The findings are summarized in Table 5. Paradoxically, patients with a relatively good physical condition considered the prospect of wheelchair dependence as more serious than did patients with higher disability (Chapter 6). An explanation for this finding may be that patients with few neurological symptoms have more to lose than patients with advanced functional limitations. Alternatively one can argue that patients with higher disability may recognize that a wheelchair finally extends rather than reduces mobility, even though compared to their present physical condition, this may still be a major step backwards.

Patients who were less pessimistic considered wheelchair dependence as less serious. The fact that wheelchair dependence is a negative event may possibly explain why pessimism rather than optimism was associated with perceived seriousness (see also Chapter 9). The findings for the other determinants were equivocal. The baseline analysis suggested that pessimism strengthened the

Table 5 Summary of results on determinants of perceived seriousness

	↔	Time period								
		2 years			10 years			Lifetime		
		Baseline	All	Δ	Baseline	All	Δ	Baseline	All	Δ
Disability status	↓	***	**	--	***	**	--	***	**	--
Pessimism	↑	***	*	--	***	*	--	***	*	--
Disability status * pessimism	↕	**	--	**	**	--	**	**	--	**
Perceived symptoms	↕	--	--	--	--	--	--	--	*	--
Neuroticism	↓	--	--	--	--	--	--	--	--	--
Perceived symptoms * neuroticism	↓	***	--	--	***	--	--	***	--	--
Chronic timeline	↓	+	*	+	+	*	+	+	*	+
Treatment control	↓	+	+	--	+	+	--	+	+	--
Coherence	↓	*	+	--	*	+	--	*	+	--

↔ = Direction of the relationship, ↑ = Positive, ↓ = Inverse; Baseline = Cross-sectional associations at baseline (Chapter 6, 8, 9), All = cross-sectional associations at all assessments (Chapter 11), Δ = Associations between change in determinants and perception of seriousness (Chapter 11); *** p < 0.001, ** p < 0.01, * p < 0.05, + p < 0.10, -- p > 0.10.

association between disability status and perceived seriousness, but the longitudinal analyses showed the opposite. Also, illness beliefs (chronic timeline, treatment control and coherence) were not consistently associated with perception of seriousness.

Most variables considered were not significantly or consistently associated with perception of seriousness. As discussed earlier, variation in perception of seriousness was limited which may have affected the statistical power of our study. Based on the findings from the interview study (Chapter 10), it may be argued that psychosocial factors such as family life (having young children or care for family members) job activities (being breadwinner or having career perspectives), leisure activities, housing and social life may have a stronger impact. These factors determine whether and to what extent the lives of patients are threatened by the prospects of wheelchair dependence.

Clinical implications

Preference for an early diagnosis

Our study demonstrates that the probability of patients being satisfied with the timing of diagnosis decreases with a longer duration of the diagnostic workup at the neurological clinics. Yet, this probability did not substantially decrease within

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twelve months after the first visit to the neurologist. On the one hand, these findings indicate that there is no need to delay diagnostic procedures to prevent psychological harm in patients, as was advocated in neurological practice.^[41,42] On the other hand, our data also show that there is no need to rashly conduct investigations.

Patients clarified that a long duration of the diagnostic workup was stressful because they had symptoms and did not know what caused them. This suggests that patients may benefit when neurologists explain the symptoms and probable diagnoses that are considered. The latter seems counter-intuitive as discussing the possibility of disabling diseases may increase anxiety and worry for diagnoses that will not be confirmed later on. However, a previous study in cancer revealed that patients had lower levels of anxiety after disclosure of the diagnosis when they were prepared for a possible diagnosis of cancer.^[43] Another reason is that in light of rapid developments at the Internet it may be better to discuss the possibilities with the patients. Consider a patient with a first presentation of optic neuritis who has a 50% risk of developing MS within 20 years.^[44] It is still common practice to tell these patients that they have a temporary inflammation of the optic nerve.^[42] However, when patients search at the Internet for more information they will easily learn about the possibility of MS: an Internet search at www.google.nl using the Dutch keyword 'oogzenuwontsteking', i.e., inflammation of the optic nerve, yielded no less than six out of ten results at page one that referred to specific MS sites (see Appendix B). So, withholding this information may increase anxiety, as patients are not able to discuss this with their neurologist. Needless to say there also is a high risk that patients will (mis)diagnose themselves.

High levels of anxiety and distress in patients and partners.

Where the initially high levels of disease-related distress in patients and partners significantly decreased over time, such a decrease was not found for anxiety: at least 12% of the patients and 16% of the partners had clinically high levels of anxiety (HADS \geq 8.0 at all assessments during this study). Monitoring symptoms of anxiety during the first years after diagnosis using the 7-item HADS Anxiety scale can be a short and effective strategy to identify patients who may need psychological support in order to deal with the psychological burden of disease. Such screening can be readily incorporated in the regular visits with for example the MS nurse.

Equally important is the finding that feelings of anxiety did decrease below that cut-off score in most patients and partners. These participants managed to deal with the emotional burden of the disease within a reasonable period of time. As

most patients will continuously face disappointments and losses in the future, it is important that they get the feeling of being able to deal with this on their own. It can be argued that professional psychological support in such early phase may be unnecessary or even unwanted as this interferes with natural coping processes of the patients. This merits a restraint approach in the offer of psychological support to all patients in the very early phase after diagnosis.

Overestimation of short-and medium-term risks

The significant relationship of the 'pessimistic' short-term expectations with anxiety, depression and disease-related distress demonstrates that patients were bothered more by short-term than by long-term prognosis. This finding predicts that reassurance about the low risk of wheelchair dependence at the short term may take away major worries. Based on their clinical experience, treating neurologists can inform individual patients about the probability of specific prognostic outcomes. Even though actual numerical risks may not be available, neurologists can inform recently diagnosed patients based on the clinical features that e.g. their 2-year risk of wheelchair dependence risk is rather low or unlikely. Although such approach is not yet evaluated by appropriate controlled studies in MS, it has been demonstrated that perception of risk can be altered by individualized information,^[45-49] particularly when risks are poorly controllable by preventive behavior.^[50] It is obvious that such individualized information is optimized when it focuses on major concerns about the disease of patients and partners. Although for many patients the possibility of wheelchair dependence was most serious, our interview data show that some patients considered other outcomes more threatening. It is therefore recommended to verify this prior to discussion of prognosis.

Symptom reporting

In the present study, patients' perceptions of their symptoms were significantly related to perceived short- and medium-term risks of wheelchair dependence. This relationship may in part be explained by the lack of responsiveness of the EDSS (see page 174). Yet, the overestimation of the presence of symptoms can also imply that patients considered themselves to be more ill than they actually were and consequently overestimated their risks of future complications. For the clinical care of patients it is important to realize that patients may not evidently know what symptoms are a result of their illness. As MS is a highly variable disease, it may be very difficult for patients to determine which symptoms are due to their disease and which are common problems not related to MS but e.g. due to the flu, stress or

infections. Patients may gain in understanding about their illness and prognosis when they are informed about the relevance of symptoms and their relation to the course of MS by their neurologist or MS nurse. This may lower their perception of prognostic risk and hence improve psychological well-being.

In summary, in the early period after diagnosis general information about prognosis and specific information concerning perception of symptoms may lead to more optimistic expectations about short-term disease progression and decrease disease-related distress. Patients who will remain anxious for a prolonged time may benefit from professional psychological support.

Suggestions for future research

Clinical studies

In the previous section, it was recommended that neurologists should inform patients about their short-term prognosis and explain the significance of their symptoms. Although it may be expected that this may be beneficial to patients, we need to investigate how such information is best addressed in the context of prognostic risks.

The first topic for further research addresses the communication of uncertain information of prognosis. Since changes in perception of the short-term risk of wheelchair dependence were significantly associated with changes in anxiety and distress (Chapter 12), the first question to be addressed is whether reassuring about short-term prognosis may improve psychological well-being. Several recent studies have demonstrated that perception of risk can be altered by individualized information.^[45-49] A possible strategy to be followed may be that neurologists ask patients and partners about their major concerns with regard to the future course of disease and discuss short- and long-term expectations for these complications or consequences. In this discussion, it will be important – where possible – to distinguish uncertain expectations ('we don't know for sure') rather than absolute uncertainty about prognosis ('we don't know at all'). It will be a challenge to investigate possibilities to communicate such uncertain information in a clinical trial. These studies may not only be limited to patients with MS, but also to other chronic diseases.

Another point of further research in MS addresses the fact that the patients' overestimation of the presence of their symptoms may underlie their pessimistic expectations of short-term disease progression (Chapter 8). Given the variability of symptoms in MS, it is important to find out whether patients are able to accurately evaluate the presence of MS symptoms and to monitor their disease activity. A first

step to follow is to investigate patients' beliefs about their illness in a qualitative study. Such study has the best chance to bring to light the common misunderstandings, which can consequently be used as a starting point for further quantitative research and for strategies on how to inform patients. In a randomized controlled study, the effect of such intervention on expectations can be evaluated. If proven successful, such information procedures may be included in the regular care of patients, e.g., the follow-up visits with the MS nurse.

Studies of perception of prognostic risk

Perception of prognostic risk is an unexplored area in clinical research. To our knowledge, this is the first study that addressed the determinants of perceived prognostic risk and its associations with psychological well-being. Where findings on the associations may be similar to those found in genetic risks, the determinants of prognostic risks may be considerably different. This study demonstrated that presence of symptoms determined perceived risk of wheelchair dependence, and that the relationship of perceived symptoms was different for the three time perspectives (2 years, 10 years and lifetime) and for patients with high and low neuroticism. These findings are summarized in a model (Figure 1).

The qualitative analysis of the interview data confirmed the role of present symptoms, but added many other factors such as disease history, the future availability of treatment and psychological factors such as hope and mental attitude. How patients think about future disease progression can be schematically

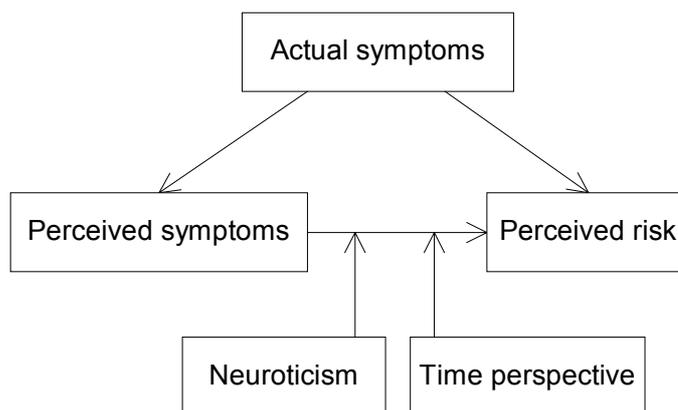


Figure 1 Schematic model of perceived risk of wheelchair dependence based on our correlational studies (directions assumed)

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represented in a mental model. Mental models summarize the major lines of reasoning employed by patients, and have been previously employed in risk perception of breast cancer and in the design of risk communication strategies.^[51-54] Such qualitative approach can bring to light how patients think about their risks more efficiently than correlational studies. The explanations that patients employed

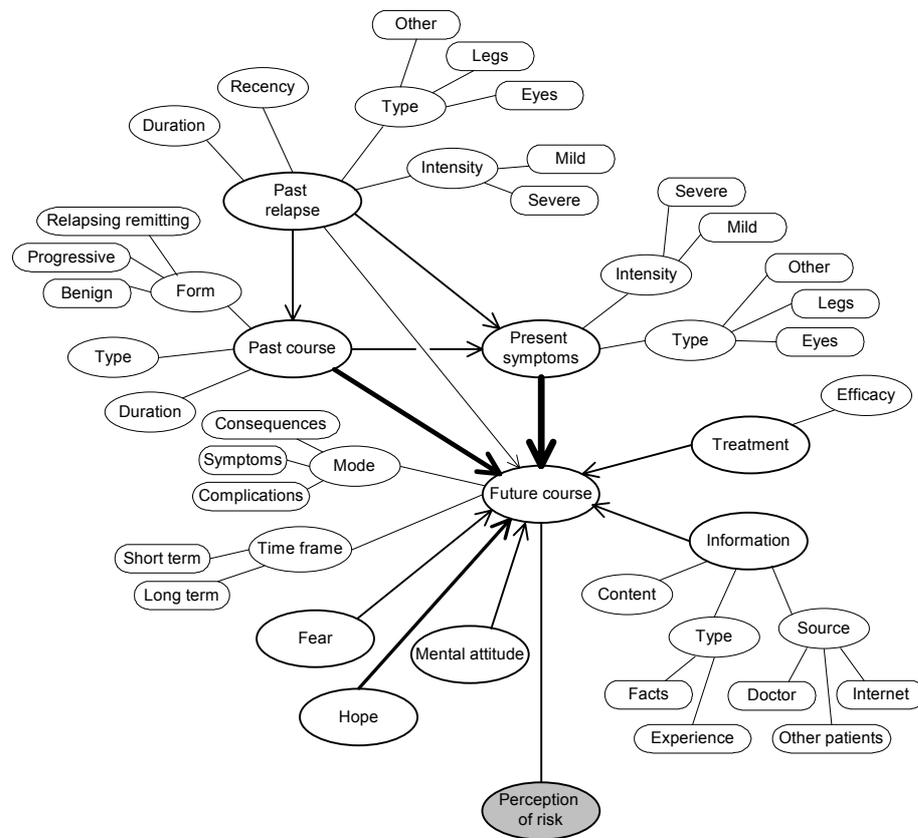


Figure 2 Towards a mental model of patients’ expectations of future disease progression based on data from the interview study

Bold ellipses are key constructs, normal ellipses are attributes of these constructs and rounded squares are values of the attributes. The thickness of the arrow or line represents the frequency of use of the explanation. Perception of risk is presented as an operationalization of expectations of future disease course. For example, patients perceived their short-term (time frame) risk of wheelchair dependence as low because their past course of disease had been benign (form) or that their symptoms (past relapse) had only included their eyes (type) and not their legs (type).

with regard to their expectations about future disease progression in our study are outlined in a preliminary model in Figure 2. In this figure, perception of risk is presented as an isolated construct, as in our view it is an operationalization of patients' expectations. This model is preliminary and based on interviews with recently diagnosed patients on their risk of wheelchair dependence only. Although the model remains to be confirmed, it may be helpful as a starting point in our understanding of patients' expectations. Future studies should be broadened by investigating the risk of wheelchair dependence in later phases of disease, but also by investigating other risks in MS and other risks in other chronic diseases as it can be assumed that patients generally extrapolate past disease course into future expectations. On the other hand, hope and fear may be more important in diseases with uncontrollable prognosis as MS, whereas behavioral influences such as diet and exercise may prevail with regard to preventable complications in for example cardiovascular diseases. Also, differences may be expected between predictable and unpredictable diseases, risk of short- and long-term complications. Unraveling the major lines of reasoning will help understanding perceived risks of patients over a potentially wide range of diseases. These studies may serve as a starting point for new quantitative studies including follow-up studies and clinical trials.

Recommendations for risk perception research

Perception of risk is an alternative way to study expectations with regard to specific (health) outcomes. This part of the discussion provides several considerations to determine whether perception of risk is a suitable operationalization of expectations in a particular clinical study.

Perception of risk can be the strategy of choice when the aim is to compare expectations between or within patients to investigate and/or to determine what factors influence expectations, or to investigate the relationship between expectations and psychological well-being. Several factors determine whether risk perception is an adequate operationalization for patients' expectations. First, a necessary condition is that there is one or a limited number of specific health outcome that are of major concern to the patient population. An outcome that is not of major concern will not affect health decisions or psychological well-being of patients. As for many people MS is associated with a wheelchair, it was anticipated in our study that this could be a major concern for recently diagnosed patients, but this may be less obvious in later phases of the disease as suggested by the decrease in seriousness of wheelchair dependence in patients with more disability. Also in the context of genetic testing, the outcome of interest may vary, as persons at the same time are at risk of being a mutation carrier, at risk of developing the disease

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and at risk of dying of the disease. Second, the outcome should be relevant in the context of the research question. In MS, there are many prognostic risks that are considered as serious, but not all of them would affect psychological well-being or decision making in the early phase of disease. Relevance does also concern the time perspective. In our study, we found significant associations between perceived risk and psychological well-being only for the short-term, but not for the long-term risk of wheelchair dependence. Third, for the validity of the assessment it is important that the outcome can be described in an unambiguous way, so that all participants will have the same interpretation. For this reason, in this thesis wheelchair dependence was specified for short distances, namely 5 meters and over. Unambiguous description may be less straightforward for cognitive decline, sensory problems or psychological consequences. Finally, patients should be aware of the outcome being a consequence of the disease. In our study, wheelchair dependence was a consequence of disease that all patients knew, but it would have been unethical to ask for their perceived risk of sexual dysfunction, cognitive decline or death due to MS, as patients may not be aware of these complications or outcomes of MS.

Final remarks

This study demonstrated that patients overestimated their short- and medium-term risks of wheelchair dependence and that these perceptions were significantly related to subjective symptom reporting, higher levels of anxiety and distress. Moreover, the longitudinal data confirmed that changes in these short- and medium-term risk perception were convincingly related with changes in psychological well-being. As this is the first study on perception of prognostic risk, not only in MS but also in other chronic diseases, it is evident that replication of our findings is needed. Notwithstanding, the findings highlight the importance of addressing short-term prognosis in the clinical consultation with patients. Further intervention studies of the confirmation of uncertain information about prognosis and information on symptoms may provide opportunities to adjust patients' expectations about their future disease progression. This may help patients to cope with the prognostic uncertainty of MS and ultimately improve the health-related quality of life of patients.

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