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## PERCEPTION OF PROGNOSTIC RISK IN PATIENTS WITH MULTIPLE SCLEROSIS: THE RELATIONSHIP WITH ANXIETY, DEPRESSION AND DISEASE-RELATED DISTRESS

### Abstract

**Objectives:** The aim of the study was to investigate the impact of perception of prognostic risk on anxiety, depression and disease-related distress in patients with multiple sclerosis (MS). **Method:** Perceived risk and perceived seriousness of the 2-year, 10-year and lifetime prognosis of wheelchair dependence, disability status (EDSS), disease-related distress (IES) and anxiety and depression (HADS) were assessed in 101 patients. **Results:** Patients with higher perceptions of 2-year, 10-year or lifetime risk were bothered by more intrusion of MS-related thoughts and feelings ( $p < 0.01$ ). Only higher perception of the 2-year risk of wheelchair dependence was significantly related with higher levels of anxiety, depression and avoidance. Similarly, higher perception of the seriousness of wheelchair dependence was consistently associated with more intrusion and avoidance (IES), but only perceived seriousness of the 2-year prospect of wheelchair dependence was significantly correlated with anxiety and depression. All relations were independent of clinically assessed disability status. **Conclusions:** Perceptions of the *short-term* risk and seriousness of wheelchair dependence were significantly related to anxiety, depression and disease-related distress in patients with MS. These findings underscore the importance of informing patients with chronic disorders, such as MS, about the short-term prognosis of important long-term consequences of disease.

## Introduction

Patients with multiple sclerosis (MS) experience considerable prognostic uncertainty.<sup>[1-4]</sup> The course of the disease is variable and unpredictable and can lead to serious consequences such as wheelchair dependence and cognitive decline. Patients often are aware of these disease prospects, but cannot be informed about what complications they themselves will develop. How patients perceive their risks of major disease complications may determine their decisions about treatment and future planning, and also affect their mental health. Studies in cancer and cardiovascular diseases showed that patients' expectations about treatment outcome and their general health condition – whether realistic or not – may enhance mental health when expectations are positive, but may have adverse effects when they are negative.<sup>[5-9]</sup> In MS, it has been demonstrated that patients who generally hold positive expectations in life reported less symptoms of depression.<sup>[6]</sup> The relation between expectations about *specific* disease consequences and mental health has not yet been studied in MS or in other chronic diseases. From a clinical perspective, this may be more relevant because health care professionals can discuss these specific consequences with patients, in order to adjust apparent unrealistic expectations. This may be particularly important in the early phase after diagnosis, when patients are in the need for information about the disease.

The aim of the present paper is to investigate the impact of perception of prognostic risk and seriousness on mental health, as assessed by anxiety, depression and disease-related distress in patients diagnosed with MS no longer than two years before study entry. We particularly focused on perception of the risk of wheelchair dependence, as this is one of the major and most recognized consequences of MS by patients. Since the impact of expectations on psychological outcomes may differ for prospects about the near or far future, we examined perception of the short (two years), medium (ten years) and long-term (lifetime) risk of wheelchair dependence.

## Methods

### Participants and procedures

Patients were recruited through the Departments of Neurology of the Erasmus MC (Rotterdam), three hospitals within the region of this academic hospital, and the VU Medical Center (Amsterdam) in the period of March 1999 – December 2000. Patients were eligible to participate in the study if they were diagnosed as having definite or probable MS<sup>[10]</sup> within two years before study entry, were explicitly informed about the diagnosis, were between 18 and 55 years old and had signed

informed consent. Diagnoses were verified by senior neurologists of the academic hospitals. Patients with serious comorbidity or with insufficient understanding of the Dutch language were excluded. Of the 120 patients who met the criteria, 101 agreed to participate in the study. Patients who declined participation 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. Patients underwent a neurological examination and filled out questionnaires. The questionnaires were sent one week before the neurological examination and had to be completed one week after the examination. The study protocol was approved by the medical ethical committees of the participating hospitals.

### Measurements

Patients underwent a neurological examination following a standardized research protocol. Functional limitations were assessed by a trained physician, and rated on the Expanded Disability Status Scale (EDSS).<sup>[11]</sup> This scale ranges from 0.0 (no neurological symptoms) to 10.0 (death due to MS). None of the patients were hospitalized at the time of data collection. Assessments of the EDSS were postponed when patients experienced a relapse at the time of the scheduled examination. Date of first symptoms was registered together with the neurological examination, whereas date of diagnosis and diagnostic certainty (probable or definite MS) were obtained from the medical records.

Perception of prognostic risk was assessed for the short (2-year), medium (10-year) and long-term (lifetime) risk of wheelchair dependence. Wheelchair dependence was defined as the inability to walk beyond five meters, which equals a score of 7.0 on the EDSS.<sup>[11]</sup> Patients were asked to what extent they expected to become wheelchair-dependent for this distance within two years, ten years and lifetime. Perception of risk was assessed by marking a 100mm visual analogue scale (VAS)<sup>[12,13]</sup> from 'Definitely not' (0%) and 'Definitely' (100%). Next, patients were asked for each prognosis how serious they considered being wheelchair-dependent by that time. Perception of seriousness was scored on a VAS anchored at 'Not serious at all' (0) and 'The most serious thing I can imagine' (100).

Anxiety and depression were assessed by the Hospital Anxiety and Depression Scale (HADS).<sup>[14]</sup> This scale has been reviewed as a reliable and valid instrument for assessing anxiety and depression in patients with various diseases.<sup>[15]</sup> The anxiety and depression scales range from 0-21 with high scores indicating higher levels of anxiety and depression. Internal consistency reliability was high in our study:<sup>[16]</sup> coefficient  $\alpha$  was 0.83 for the anxiety and 0.81 for the depression scale. Scale scores of 8 and higher indicate a high risk of anxiety and depressive

disorder.<sup>[14]</sup> Disease-related distress was assessed using the Impact of Event Scale (IES).<sup>[17]</sup> This questionnaire addresses psychological distress by focusing on the intensity of thoughts and feelings that relate to specific negative events or concerns, in this study being diagnosed with MS. Though designed to assess the impact of traumatic events, the scale has been also used to assess the psychological burden of being at high risk of hereditary prostate cancer and breast cancer.<sup>[18-20]</sup> The questionnaire comprises two scales: intrusion (range 0 – 35) and avoidance (0 – 40). Intrusion refers to the degree of being overwhelmed by thoughts and feelings about MS. Items include 'Any reminder brought back feelings about it' and 'I had dreams about it'. Avoidance refers to tendency to keep off these thoughts and feelings and is measured by items such as 'I tried not to think about it' and 'I stayed away from any reminders of it'. In our study, coefficient  $\alpha$  was 0.82 for the intrusion scale and 0.75 for the avoidance scale. Intrusion and avoidance are positively correlated.<sup>[21]</sup> Although this seems paradoxical, avoidance can be thought of as a way of coping with high levels of intrusive thoughts: if disease-related thoughts and feelings are too disturbing, patients may restore emotional equilibrium by avoidance.

### **Statistical analysis**

Spearman correlations were computed to examine the crude association of disability status (EDSS) with psychological outcomes and perceived of risk and seriousness of wheelchair dependence. Differences in perceived risk, perceived seriousness and mental health between the two academic hospitals and the non-academic hospitals were tested using ANOVA. To investigate the relationship of perceived risk and seriousness with psychological outcomes, we performed a series of multiple regression analyses with adjustment for disability status (EDSS), time since diagnosis, time since first symptoms, age and sex. These analyses were conducted for the 2-year, 10-year and lifetime prognosis separately. Results are presented as regression coefficients (B) with 95% confidence intervals. The correlation ( $\rho$ ) between time since diagnosis and time since first symptoms was 0.19 so no problems of collinearity between these time variables were expected. Descriptive statistics demonstrated that the distributions of the main study variables were skewed. For multivariate regression analyses this does not need to be a problem if it can be assumed that the residuals of the analyses are normally distributed.<sup>[22]</sup> This is indicated by straight diagonals in the normal-probability plots. For all regression analyses, these scatterplots produced reasonably straight lines, so there was no compelling need to transform the distributions of the study variables. Finally, the relationship of perceived risk and perceived seriousness with

psychological outcomes were compared between groups with a high and low disability by evaluation of their interaction effects. These groups were defined by an EDSS cut-off score of 3.0 to make a distinction between no to minimal disability (EDSS 0-2.5) and moderate to severe disability (EDSS 3.0-10.0).<sup>[11]</sup> P-values lower than 0.05 were considered statistically significant.

## Results

### Characteristics of patients

Mean age of the patients was 37.5 years (SD 9.5) and 70% were women. Patients were diagnosed with definite MS (90%) or probable MS (10%), on average 7.8 months (median 5.1, inter-quartile range IRQ [2.4, 12.2]) before entry in the study. The median time since first symptoms was 2.1 years (IQR [1.1, 4.5], mean 3.7). EDSS-scores ranged from 0.0 to 7.0 (median 2.5). Fifty-nine patients were recruited through the Erasmus MC, 32 through the VU medical center and 10 through non-academic hospitals. Patients with more physical limitations had significantly higher perception of the 2-year, 10-year and lifetime risk of wheelchair dependence ( $p < 0.05$ ), but considered wheelchair dependence to be less serious ( $p < 0.007$ ; Table 1). Patients with higher disability reported significantly more symptoms of anxiety ( $p = 0.24$ ,  $p = 0.02$ ) and depression ( $p = 0.43$ ,  $p < 0.001$ ). Thirty-four percent of the patients had clinically relevant levels of anxiety and 10% of depression (HADS scores  $\geq 8$ ). They were also significantly more distressed, as indicated by the positive correlations of EDSS with intrusion ( $p = 0.27$ ,  $p = 0.006$ ) and avoidance ( $p = 0.28$ ,  $p = 0.005$ ). No significant differences in perceived risk, perceived seriousness and psychological well-being were observed between patients from the two academic centers and the hospitals within the region.

### Expectations about wheelchair dependence and psychological distress

Table 2 shows regression coefficients (B) of the relationship between patients' perception of the risk and seriousness of wheelchair dependence and their levels of disease-related distress. After adjustment for disability status (EDSS), time since first symptoms, time since diagnosis, age and sex, we found that patients with higher perception of risk were bothered by more intrusion of MS-related thoughts and feelings ( $p < 0.01$ ). This relationship was found for the 2-year, 10-year and lifetime risks of wheelchair dependence. In contrast, only higher perception of the 2-year risk was significantly associated with avoidance of MS-related thoughts and feelings ( $B = 1.00$ ,  $p = 0.03$ ). Patients who considered wheelchair dependence as more serious had higher levels of intrusion and avoidance ( $p < 0.05$ ), irrespective whether this concerns the 2-year, 10-year or lifetime prognosis.

**Table 1** Perception of risk and seriousness of wheelchair dependence and psychological outcomes: means and correlations with disability status (EDSS)

	Median [IQR]	Correlation with EDSS	
		$\rho$	p-Value
<b>Prognosis of wheelchair dependence:</b>			
Short-term expectations			
Perceived 2-year risk	20 [4, 33]	0.39	< 0.001
Perceived 2-year seriousness	90 [78, 97]	-0.32	0.001
Medium-term expectations			
Perceived 10-year risk	46 [16, 52]	0.42	< 0.001
Perceived 10-year seriousness	79 [66, 92]	-0.29	0.004
Long-term expectations			
Perceived lifetime risk	52 [44, 73]	0.20	0.05
Perceived lifetime seriousness	77 [66, 88]	-0.27	0.007
<b>Psychological outcomes:</b>			
Anxiety	5 [4, 9]	0.24	0.02
Depression	2 [1, 6]	0.43	< 0.001
MS-related distress: Intrusion	8 [4, 15]	0.27	0.006
Avoidance	9 [4, 17]	0.28	0.005

IQR = inter-quartile range;  $\rho$  = Spearman correlations.

### Expectations about wheelchair dependence and anxiety and depression

Patients who thought it more likely to become wheelchair-dependent within two years showed increased levels of anxiety ( $B = 0.78$ ,  $p < 0.001$ ) and depression ( $B = 0.45$ ,  $p = 0.007$ ; Table 2), after adjustment for neurological status (EDSS), time since diagnosis, time since first symptoms, age and sex. Higher perception of the 10-year and lifetime risk was not significantly associated with more symptoms of anxiety or depression. Similarly, patients who considered wheelchair dependence within two years as more serious reported more symptoms of anxiety ( $B = 0.53$ ,  $p = 0.02$ ) and depression ( $B = 0.37$ ,  $p = 0.02$ ). Perceived seriousness of the 10-year and lifetime prognosis of wheelchair dependence was not significantly associated with these psychological variables. The findings on the relationships of perceived risk and seriousness with psychological well-being remained unchanged when only patients with definite MS were included in the analyses.

### Comparison between high and low disability groups

To examine the differences between patients with high and low disability, mental health scores were plotted against perception of the 2-year risk (Figure 1) and seriousness of wheelchair dependence. Although patients with more physical

**Table 2** Perceived risk and seriousness of wheelchair dependence in relation to disease-related distress, anxiety and depression

	Intrusion	Avoidance	Anxiety	Depression
<b>Short-term expectations</b>				
Perceived 2-year risk	1.16 ** [0.38, 1.94]	1.00 * [0.05, 1.94]	0.78 *** [0.33, 1.23]	0.45 ** [0.12, 0.77]
Perceived 2-year seriousness	1.09 ** [0.32, 1.87]	1.61 *** [0.68, 2.55]	0.53 * [0.08, 0.98]	0.37 * [0.05, 0.69]
<b>Medium-term expectations</b>				
Perceived 10-year risk	1.04 *** [0.43, 1.64]	0.26 [-0.49, 1.00]	0.09 [-0.28, 0.47]	0.10 [-0.16, 0.36]
Perceived 10-year seriousness	0.76 * [0.16, 1.37]	1.31 *** [0.58, 2.06]	0.31 [-0.07, 0.68]	0.20 [-0.06, 0.47]
<b>Long-term expectations</b>				
Perceived lifetime risk	0.78 ** [0.21, 1.35]	0.00 [-0.70, 0.70]	-0.11 [-0.46, 0.24]	0.03 [-0.22, 0.27]
Perceived lifetime seriousness	1.02 *** [0.44, 1.60]	1.32 *** [0.61, 2.03]	0.32 [-0.03, 0.68]	0.21 [-0.04, 0.46]

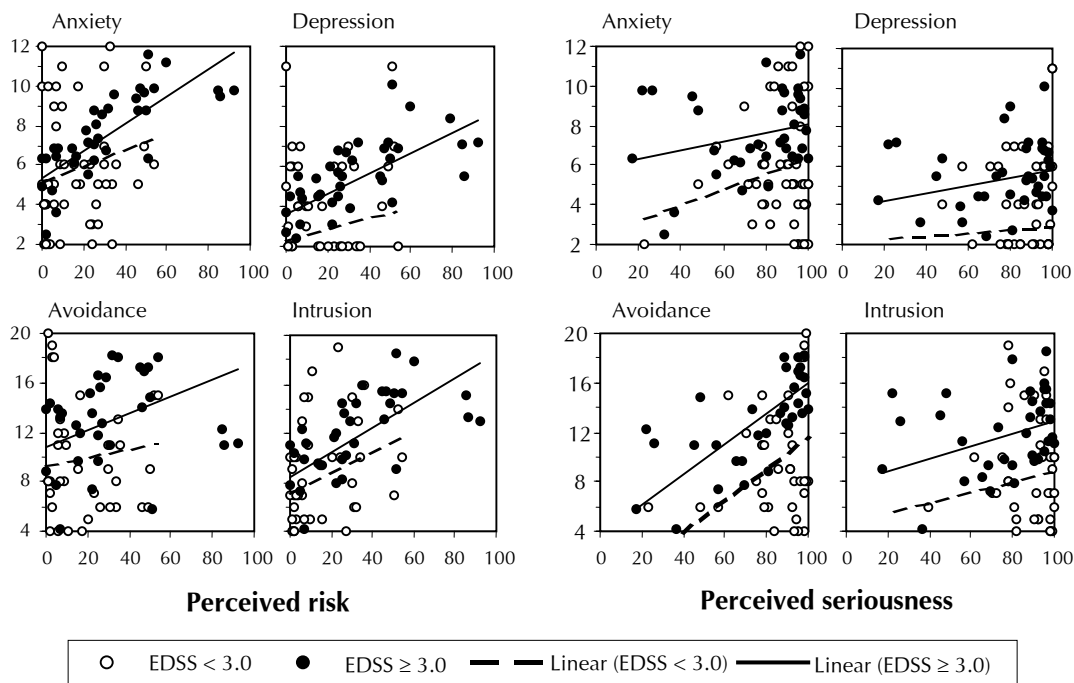
Intrusion refers to the degree of being overwhelmed by thoughts and feelings about MS, and avoidance to tendency to keep off these thoughts and feelings. Values are regression coefficients [95% confidence interval] representing the changes in scores per 10 points on the visual analogue scale. Coefficients are adjusted for disability status, time since first symptoms, time since diagnosis, age and sex. \*  $p < 0.05$ , \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$ .

limitations had higher scores of all four mental health indicators, the difference was only significant for depression ( $p = 0.002$ ). None of the interaction effects for perceived risk and seriousness with EDSS was statistically significant in the regression analyses ( $p > 0.50$ ).

## Discussion

This study demonstrates that patients with higher perception of the risk and seriousness of wheelchair dependence had higher levels of MS-related distress. This relation was found for the 2-year, 10-year and lifetime prognosis of wheelchair dependence. Yet, only perception of the 2-year risk and seriousness were related to anxiety and depression. All associations were independent of clinically assessed disability status.

Before interpreting the data from a clinical perspective, two issues are to be elucidated. First, perceived seriousness was assessed for each prognosis separately, because we hypothesized that patients would consider wheelchair dependence more serious when occurring in the near future. Although perceived seriousness was higher for the 2-year prognosis, the three assessments of perceived seriousness



**Figure 1** Mental health scores by perceived 2-year risk and seriousness of wheelchair dependence in patients with high and low disability

were highly correlated ( $0.72 < r < 0.89$ ,  $p < 0.001$ ). This suggests that patients perceived wheelchair dependence a serious consequence of their disease, no matter when it would happen. The consistency in the relationships between perceived seriousness and distress (intrusion and avoidance) for each prognosis may therefore be explained by a similar evaluation of seriousness for each period.

Second, the results of this study should be viewed within the limitations of a cross-sectional study design: we cannot prove whether higher perception of risk and seriousness increase distress, anxiety and depression, or vice versa. Nevertheless, our data may be indicative for the direction of the relationship. It can be argued that, if distress, anxiety or depression had determined perception of risk, this would have affected the short- as well as long-term risk perception. Following this reasoning, the significant relationship with intrusion for each prognosis is consistent with the hypothesis that risk perception is in part determined by intrusive thoughts and feelings about the disease. On the contrary, avoidance, anxiety and depression were significantly related only to the perceived two-year risk. This would imply that anxiety, depression and avoidance are more likely



determined by risk perception, than vice versa. Yet, these hypotheses are to be confirmed in experimental follow-up studies.

To our knowledge, this is the first study that addressed perception of prognostic risk in relation to mental health in chronically ill patients. Nevertheless, the findings of our study may be compared to those that have investigated risk of disease in healthy subjects, because both groups face uncertain adverse health prospects. In persons at high-risk of developing breast cancer, prostate cancer or diabetes, higher perception of risk was associated with more psychological distress, as was found in the present study.<sup>[18,23,24]</sup>

The most important finding of this study is that perception of the 2-year risk was strongly related to anxiety and depression while perception of the 10-year and lifetime risk were not. This may be explained by the fact that short-term disability may have a more disruptive impact on family life, work, and leisure activities than disability occurring in the remote future. In that light, our findings are in line with earlier studies reporting that patients who perceived MS as a major threat had higher levels of distress, more feelings of depression, poorer subjective health status and poorer social adjustment.<sup>[25,26]</sup> Further, as in previous studies,<sup>[27-30]</sup> we found that patients with more physical limitations were significantly more anxious and depressed than patients with fewer limitations. However, the association of perceived 2-year risk and seriousness of wheelchair dependence with psychological outcomes was independent of the patients' disability status.

The finding that perceived short-term risk influenced feelings of anxiety, depression and distress may have implications for the clinical care of patients. It can be argued that informing recently diagnosed patients about the low probability of wheelchair dependence within the short term – or about other consequences they consider important – may decrease their feelings of anxiety and depression. This will be particularly relevant, because in our study patients overestimated their short-term risks (Chapter 6): mean perception of the 2-year risk of wheelchair dependence was 22.4% compared to an actual risk of 5-10% based on epidemiological studies.<sup>[31]</sup> The challenge for future research will be to investigate whether it is feasible to communicate low probabilities of short-term prognosis to patients without raising false hope for the long-term prospects of the disease.

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## CHAPTER 7

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