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## THE ASSOCIATION BETWEEN PERCEPTION OF PROGNOSTIC RISK AND ANXIETY, DEPRESSION AND DISTRESS IN RECENTLY DIAGNOSED MULTIPLE SCLEROSIS: A 2-YEAR FOLLOW-UP STUDY

### Abstract

**Background:** In a 2-year follow-up study of recently diagnosed patients with MS and their partners, we investigated the association between perception of risk and seriousness of wheelchair dependence and feelings of anxiety, depression and distress. **Methods:** Perceived risk and seriousness were assessed for the 2-year, 10-year and lifetime prognosis of wheelchair dependence. Anxiety, depression and disease-related distress were measured at baseline, 6-month, 1-year and 2-year follow-up. **Results:** Mean levels of disease-related distress decreased both in patients and their partners during the 2-year follow-up, but levels of anxiety and depression remained unchanged. In patients, higher perception of the 2-year and 10-year risk of wheel-chair dependency was significantly related to poorer psychological well-being, whereas higher perception of seriousness was consistently related to higher distress and anxiety. An increase in perception of the 2-year risk of wheelchair dependence was associated with a significant increase in levels of anxiety, depression and distress. **Conclusion:** Patients' perception of the short- and medium-term risk of wheelchair dependence was consistently related to psychological well-being. Our findings raise the question whether the psychological well-being of patients with MS may be improved by adjusting their perception of risk of wheelchair dependence.

## Introduction

Expectations about future disease or complications of disease are important determinants of psychological well-being.<sup>[1-4]</sup> In our cohort of patients recently diagnosed with multiple sclerosis (MS), higher perception of the short-term risk of wheelchair dependence was associated with increased levels of anxiety, depression and disease-related distress. Of note is that MS patients shortly after diagnosis particularly overestimated their short- and medium term risks of wheelchair dependence (Chapter 6) and that their levels of anxiety were significantly higher than in controls from the general population (Chapter 4).

In the previous chapter, it was demonstrated that patients' perception of their short-term risk of wheelchair dependence increased during follow-up. Given the association between perceived short-term risk and psychological well-being (Chapter 7), this raises the question whether levels of anxiety, depression and disease-related distress also increased during follow-up. Several psychological reactions are possible. First, following the associations observed at baseline, one expects that, due to the increase in perception of the short-term risk, patients also have higher levels of anxiety, depression and distress at follow-up. Second, the strong correlations between perceived risk and well-being found at baseline may have been a finding that is typical for the early period after diagnosis, because that period is generally characterized by both uncertainty and high levels of stress. Such a confounding effect may not be present at follow-up. Third, when patients manage to cope with the uncertain prospects of their disease, one may argue that they may face their high risks of future wheelchair dependence without emotional disturbances. In the last two situations, the increased perception of the short-term risk will not be accompanied by a decrease in emotional well-being.

In this paper, we investigated the association between perception of prognostic risk and psychological outcomes in a longitudinal study to confirm and extend our previous cross-sectional findings. First, the course of anxiety, depression and MS-related distress in patients and their partners is examined. Second, in patients the relation between perception of risk and seriousness and these psychological outcomes is investigated cross-sectionally during follow-up. And third, we investigated whether changes in perceived risk and seriousness were accompanied by changes in psychological outcomes.

## 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 if they were diagnosed with definite or probable MS<sup>[5]</sup> within two years before entry in this study, were between 18 and 55 years old, and had given informed consent. 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. This prospective study consisted of four time points: baseline, 6-month, 1-year and 2-year follow-up. At present, the data collection for the 2-year follow-up is still ongoing. Of the 101 patients who entered the study, 98 completed the half-year follow-up, 97 the one-year and, to date, 72 (out of 81 patients invited) have finished the 2-year follow-up. Ninety out of 101 patients had a partner, of whom 78 (87%) did participate. Of the 78 partners who started the study, 72 completed the one-year and, up until now, 55 (out of 66 partners invited) have finished the two-year follow-up. Baseline characteristics of patients and partners are presented in Chapter 11 (Page 145).

Patients completed questionnaires at all assessments and were scheduled for neurological examination at baseline, 1-year and 2-year follow-up. At these visits, also partners filled out questionnaires. Questionnaires for patients and partners were sent by mail one week prior to the neurological examinations and had to be handed in at the time of the psychological interview (baseline), at the neurological examinations (follow-up) or returned by mail. At baseline, partners were given their questionnaires at the time of the patient's interview, which was scheduled one week after the neurological examination, and were asked to complete these in another room. At one- and two-year follow-up patients and partners were mailed their questionnaires simultaneously, with an explicit request to complete the questionnaires on their own. The study protocol was approved by the medical ethical committees of the participating hospitals.

### Measurements

*Perceptions of prognostic risk.* Perception of risk and seriousness were assessed for the risk of becoming wheelchair-dependent as a consequence of the disease. Wheelchair dependence was defined as the inability to walk beyond five meters. This definition equals a score of 7.0 on the Expanded Disability Status Scale (EDSS).<sup>[6]</sup> Perception of risk and seriousness were assessed for the short- (2-year), medium- (10-year) and long-term (lifetime) prospects of wheelchair dependence. Perception of risk was measured using a 100mm visual analogue scale (VAS) from 'Definitely not' (0%) and 'Definitely' (100%). Patients were asked for each prognostic period how serious they think it is to be wheelchair-dependent by that time. Perceived seriousness was measured using a VAS anchored at 'Not serious at

all' (0) and 'The most serious thing I can imagine' (100). Partners completed the same questions, addressing the patient's risk of wheelchair dependence and the seriousness of their partner becoming wheelchair-dependent.

*Psychological outcomes.* Anxiety and depression were assessed by the Hospital Anxiety and Depression Scale (HADS).<sup>[7]</sup> The anxiety and depression scales range from 0-21 with high scores indicating higher levels of anxiety and depression. Internal consistency reliability at baseline in our study was high:<sup>[8]</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. Disease-related distress was assessed using the Impact of Event Scale (IES).<sup>[9]</sup> This questionnaire addresses the psychological distress of having MS by focusing on the intensity of thoughts and feelings that relate to the disease. The questionnaire comprises two scales addressing the intrusion (range 0 - 35) and avoidance (0 - 40) of MS-related thoughts and feelings. 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  $\alpha$  at baseline was 0.82 for the intrusion scale and 0.75 for the avoidance scale. Intrusion and avoidance are always positively correlated.<sup>[10]</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.

*Clinical data.* Present disability was assessed by physicians from the academic hospitals following a standardized research protocol. Functional limitations were rated on the EDSS,<sup>[6]</sup> which ranges from 0.0 (no neurological symptoms) to 10.0 (death due to MS). Date of first symptoms was assessed during the neurological examination. Date of diagnosis and diagnostic certainty (probable or definite MS) were obtained from the medical records and verified by senior neurologists.

### **Statistical analyses**

We used the SAS Proc Mixed Repeated measurement procedure for the analyses of longitudinal data. This procedure takes into account that the same individual contributes data to the analysis at different time points and allows the inclusion of subjects with incomplete follow-up. This likelihood-based procedure generates more accurate estimates of the parameters than analysis of available data or of patients who completed all assessments only by using the available data to predict the missing data of subjects who are censored.<sup>[11]</sup>

We first examined the course of anxiety, depression and MS-related distress in patients and partners by comparison of estimated means using SAS Proc Mixed with time (0, ½, 1 and 2 years) and time since diagnosis (0-3, 4-6, 7-12 and 13-24 months) as independent categorical variables. Analyses were conducted for patients and partners separately. To test for a linear and quadratic trend, the analyses were repeated using time since diagnosis as a continuous variable.

Second, in patients the association between their perception of risk and seriousness and psychological outcomes was analyzed in the follow-up data. Using SAS Proc Mixed, the following strategy was used for each period of prognosis (2 years, 10 years and lifetime) and each psychological outcome (anxiety, depression, intrusion and avoidance). A full model was tested including perceived risk and seriousness of wheelchair dependence, disability status (EDSS), a linear and quadratic time effect, all first-order interaction effects and the covariates (time since diagnosis, time since first symptoms, age and sex). To simplify the model, this saturated model was reduced by eliminating non-significant interaction effects and covariates. Elimination was based on the significance of the difference in  $-2 \log$  likelihood goodness of fit between the reduced and the saturated model. If the p-value was greater than 0.05 ( $\chi^2$ -test), the parsimonious model was considered not significantly different from the saturated model, and was used for further simplification. Regression coefficients (B) for the final model were estimated using the restricted maximum likelihood procedure.

Third, to determine whether changes in perception of risk and seriousness were associated with changes in anxiety, depression and MS-related distress, the analyses were repeated using difference scores. Difference scores were obtained by subtracting baseline values from scores at 1-year and 2-year follow-up. The full model included change in perception of risk, perception of seriousness and disability status, and their interaction effects between these main effects and time. For this purpose, time was recoded into 0 and 1 representing the first and second year of follow-up. The model was reduced using the aforementioned procedure. P-values lower than 0.05 were considered statistically significant. Analyses were performed in SAS 8.0 ([www.sas.com](http://www.sas.com)) and SPSS 11.0 ([www.spss.com](http://www.spss.com)).

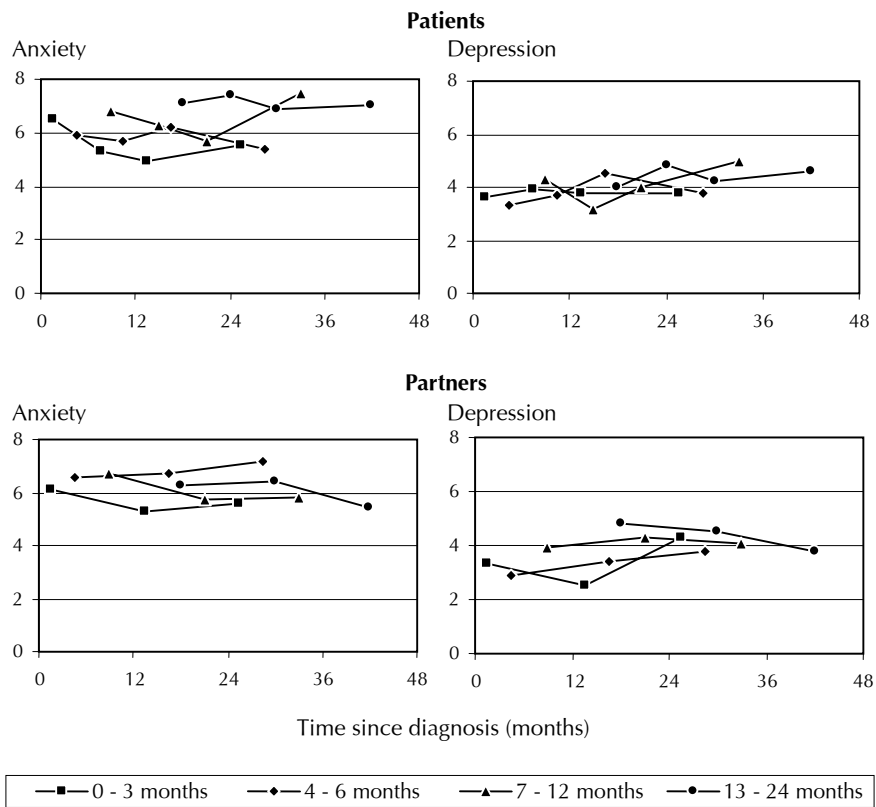
## Results

### Course of anxiety, depression and distress

Figure 1 shows the course of anxiety and depression in the 2-year follow-up of patients and their partners. Means are presented for four groups defined by time since diagnosis (0-3, 4-6, 7-12 and 13-24 months). Because patients were diagnosed up to 2 years prior to entry in the study, the present data cover the first

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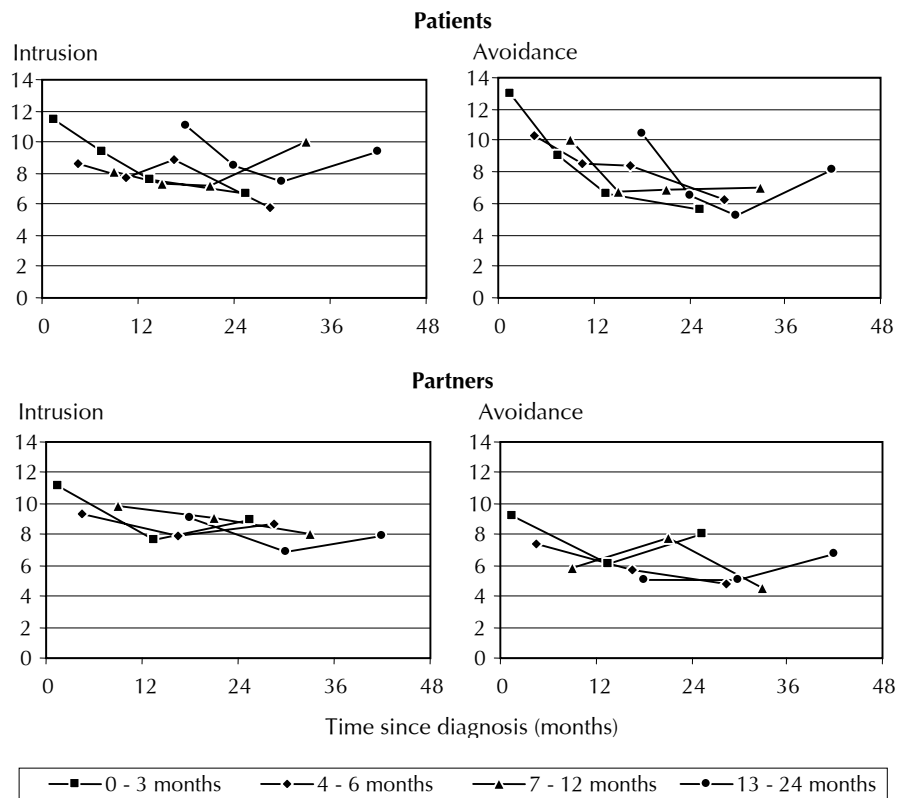
four years after diagnosis. Neither in patients nor in partners, a significant change in anxiety or depression was found ( $p$  for trends  $> 0.05$ , see Figure 1). Of the patients who had clinically relevant levels of anxiety (scores  $\geq 8.0$ ) at baseline, 63% (20/32) also showed these high scores at 1-year and 55% (12/22) at 2-year follow-up. Also in partners, these percentages remained high at 1-year (57%; 16/28) and 2-year follow-up (62%; 13/22). Of the patients who had clinically relevant levels of depression (scores  $\geq 8.0$ ) at baseline, 80% (8/10) also had high depression scores at 1-year and 38% (3/8) at 2-year follow-up. In partners, these percentages were 60% (6/10) and 38% (3/8). Intrusion of MS-related thoughts and feelings (Figure 2) significantly decreased in this 2-year follow-up in patients ( $p < 0.0005$ ) and in partners ( $p = 0.02$ ). Patients also showed significantly lower scores of avoidance at follow-up ( $p < 0.0001$ ).



**Figure 1** Anxiety and depression of patients and partners during 2-year follow-up. Groups are defined by time since diagnosis at baseline (see Methods).

**Perceived risk and seriousness and psychological well-being**

Table 1 shows the cross-sectional relation between perception of risk and seriousness of wheelchair dependence and the psychological outcomes assessed at different points of follow-up. Perception of risk and seriousness of the 2-year and 10-year prognosis were significantly and consistently related to intrusion, avoidance, anxiety and depression. In contrast, perceived risk of the lifetime prognosis was only related to intrusion of MS-related thoughts and feelings. Perceived seriousness was significantly related to all outcomes, except depression. Disability status was a significant predictor of psychological outcomes in all analyses ( $p < 0.03$ ). The effect of EDSS on psychological outcomes remained statistically significant in all analysis, but was stronger in the analyses of perceived risk and seriousness of lifetime prognosis compared to short-term prognosis.



**Figure 2** Disease-related distress of patients and partners during 2-year follow-up  
Groups are defined by time since diagnosis at baseline (see Methods).

**Table 1** Association between perception of risk and seriousness of wheelchair dependence and psychological outcomes in patients (cross-sectional analysis)

	Intrusion	Avoidance	Anxiety	Depression
<b>Short-term prognosis</b>				
Perceived 2-year risk	0.86 [0.48, 1.24] ***	0.72 [0.27, 1.17] ***	0.46 [0.26, 0.66] ***	0.30 [0.14, 0.47] ***
Perceived 2-year seriousness	0.54 [0.15, 0.92] **	0.89 [0.43, 1.34] ***	0.45 [0.24, 0.66] ***	0.15 [-0.02, 0.32]
<b>Medium-term prognosis</b>				
Perceived 10-year risk	0.78 [0.42, 1.13] ***	0.49 [0.06, 0.90] *	0.21 [0.02, 0.40] *	0.26 [0.11, 0.41] ***
Perceived 10-year seriousness	0.62 [0.27, 0.97] ***	0.91 [0.49, 1.32] ***	0.38 [0.19, 0.58] ***	0.07 [-0.08, 0.23]
<b>Long-term prognosis</b>				
Perceived lifetime risk	0.46 [0.11, 0.81] **	-0.03 [-0.44, 0.37]	0.04 [-0.15, 0.23]	0.08 [-0.08, 0.23]
Perceived lifetime seriousness	0.48 [0.15, 0.80] **	0.83 [0.45, 1.21] ***	0.33 [0.15, 0.51] ***	0.04 [-0.10, 0.19]

B (95% CI) is presented per 10 points increase in perception of risk and seriousness. Analyses are adjusted for disability status, age, sex, time since diagnosis, time since first symptoms. \*  $p < 0.05$ , \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$ .

### Predictors of change in psychological well-being

Finally, we examined in a longitudinal analysis whether changes in perception of risk and seriousness were associated with changes in the psychological outcomes. Table 2 demonstrates that increases in perception of the 2-year risk of wheelchair dependence were accompanied by significant increases in intrusion, avoidance, anxiety and depression. Also, an increase in perceived 10-year risk was accompanied by significant increases in intrusion and depression. With regard to the seriousness of wheelchair dependence, a change in perceived seriousness of the 2-year, 10-year and lifetime prognosis was significantly associated with avoidance and anxiety at follow-up. Changes in EDSS were not significantly associated with changes in the psychological outcomes (all  $p > 0.05$ ).

### Discussion

The early period after diagnosis is a stressful period for MS patients and their partners. We have previously reported that patients and their partners had high levels of disease-related distress and higher levels of anxiety than people from the general population (Chapter 4). In the present paper, it was demonstrated that both in patients and partners levels of disease-related distress, measured by the intrusion



**Table 2** Predictors of change in psychological outcomes: the role of perceived risk and seriousness of wheelchair dependence in patients

	Δ Intrusion	Δ Avoidance	Δ Anxiety	Δ Depression
<b>Short-term prognosis</b>				
Δ Perceived 2-year risk	0.80 [0.31, 1.29] **	0.55 [0.00, 1.11]*	0.41 [0.17, 0.66] ***	0.21 [0.01, 0.41]*
Δ Perceived 2-year seriousness	0.30 [-0.21, 0.82]	0.74 [0.14, 1.34] *	0.49 [0.23, 0.74] ***	0.09 [-0.12, 0.30]
<b>Medium-term prognosis</b>				
Δ Perceived 10-year risk	0.52 [0.04, 1.00] *	0.29 [-0.23, 0.81]	0.22 [-0.01, 0.45]	0.30 [0.12, 0.47] **
Δ Perceived 10-year seriousness	0.32 [-0.22, 0.85]	0.73 [0.14, 1.32] *	0.37 [0.11, 0.62] **	-0.06 [-0.26, 0.14]
<b>Long-term prognosis</b>				
Δ Perceived lifetime risk	0.31 [-0.15, 0.77]	-0.24 [-0.74, 0.27]	0.14 [-0.09, 0.37]	0.10 [-0.08, 0.28]
Δ Perceived lifetime seriousness	0.19 [-0.25, 0.62]	0.67 [0.19, 1.15] **	0.29 [0.07, 0.50] **	-0.07 [-0.24, 0.10]

B (95% CI) is presented per 10 points increase in perception of risk and seriousness. Analyses are adjusted for disability status, age, sex, time since diagnosis, time since first symptoms. \*  $p < 0.05$ , \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$ .

and avoidance of MS-related thoughts and feelings, decreased significantly during the 2-year follow-up of this study. As an illustration, these changes are comparable to that found in a one-year follow-up of individuals who were informed about their genetic predisposition of Huntington's Disease.<sup>[12]</sup> These results indicate that the high levels of disease-specific distress at baseline may have reflected early stages of patients' coping processes. Despite the substantial decrease in distress, levels of anxiety did not significantly decrease. Also at follow-up, patients and partners were more anxious than controls from the general population.<sup>[13]</sup> Of the patients and partners with clinical relevant levels of anxiety (scores  $\geq 8.0$ ) at baseline, 55% and 62% still had these high levels at 2-year follow-up. These findings are in line with those of others who have demonstrated high levels of anxiety in later phases of MS.<sup>[14-17]</sup> We add that the psychological burden also persisted in the first years after diagnosis in at least a subgroup of patients and partners. Screening for symptoms of anxiety using the 7-items HADS Anxiety scale may be a short and effective strategy to identify patients who need psychological support.

Depression is a frequent symptom of MS.<sup>[17-19]</sup> Nevertheless, we previously demonstrated that levels of depression were not increased compared to general population controls (Chapter 4). The present results showed no significant increase

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in depression during the 2-year follow-up of this study. Symptoms of depression were more frequent among patients with higher disability. Moreover, higher anxiety scores at the first time points were not associated with higher depression at the final visit. These findings combined suggest that depression is a feature of later stages of the disease, rather than the result of enduring stress.<sup>[20]</sup>

The main topic of this paper concerned the analyses of the relationship between perception of prognostic risk and emotional well-being in the follow-up data. The present findings confirmed the association between perceived 2-year risk and anxiety, depression and disease-related distress. In addition, perceived 10-year risk was significantly related to all indicators of psychological well-being during follow-up. Compared to the baseline analyses (Chapter 7), the regression coefficients of the perceived 2-year risk were lower at follow-up than at baseline, whereas those of the perceived 10-year risk were higher. One may argue that this is a result of successful coping: patients may be better informed about their disease and may be more confident that their disease will not severely progress within two years. As a result, these short-term expectations may have become less stressful.

One of the most important findings of this longitudinal analysis was that a change in the perception of the 2-year risk of wheelchair dependence was significantly associated with change in anxiety, depression, intrusion and avoidance. The association could not be explained by changes in disability status as measured by the EDSS. These associations suggest a causal relationship between perceived short-term risks and psychological well-being. However, the direction of this relationship may be subject to debate. It can be argued that a somber mood leads to more pessimistic expectations of future wheelchair dependence. In that case, however, one would also expect these influences on perceived 10-year and lifetime risk, but this was not supported by the findings of this study. Therefore, we argue that our data support the view that perception of the short-term risk of wheelchair dependence determines psychological well-being. This short-term risk may be particularly important because it implies a major disruption in the life of patients. When patients believe that this threat is more likely to occur, they may as a consequence feel more anxious and distressed.

The association between perceived seriousness and psychological outcomes in this follow-up study confirmed our previous findings in the baseline analyses: perceived seriousness was consistently related to intrusion, avoidance and anxiety, but not to depression. The fact that perceived seriousness was not consistently associated with anxiety in the baseline analyses was likely due to a lack of statistical power. Our longitudinal analysis of the change in perception of seriousness showed a significant association to change in avoidance and anxiety

consistently in all analyses. Like perception of the short-term risk, also seriousness reflects the perceived threat of wheelchair dependence, and for that reason may be related to anxiety and distress.

In conclusion, also the longitudinal studies demonstrated a significant relationship of perceived risk and seriousness with psychological well-being that could not be explained by changes in disability status. Taken in mind that patients overestimated their short- and medium-term risks (Chapter 6), these findings underscore the importance of further research on the communication of uncertain information to patients aiming to reassure patients about their short-term prognosis.

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