A diagnosis of MS can create havoc and confusion in many aspects of your life. It is normal to experience a roller coaster of emotions including fear, shock, frustration, sadness, anger, and the feeling that “this isn’t happening to me”. Perhaps diagnosis brings relief - finally there is an explanation for the symptoms you’ve been experiencing. The diagnosis of MS is unsettling for both you and your family. You may feel isolated from family and close friends, despite their good intentions to support you. Your family will also struggle with coming to terms with the diagnosis. Naturally, you are all concerned about the future and the impact that MS will have on your lives. It is important to know that you can successfully move through these difficult emotions, adjust to the changes and resume the pursuit of your goals.

Multiple sclerosis (MS) is a chronic neurological disease, affecting young individuals in the prime of their lives. The quote above illustrates the far-reaching impact of the disease on the lives of patients and their families. It shows that in the early phase, the burden of MS is characterized not by physical limitations but rather by psychological distress. Since the course of MS is highly variable and unpredictable, the uncertainty about the disease progression is a key problem for patients and their families. In the absence of clinical information about the course of disease, personal expectations about disease progression, or, perception of prognostic risks, will play a major role in the psychological well-being. Despite
the vast literature on the psychological burden of MS, we know nothing about perceptions of prognostic risk of patients and their relatives.

This thesis is motivated by our lack of knowledge of perceptions of prognostic risk in MS patients and by the view that these perceptions may be potentially modifiable determinants of psychological well-being. The three main questions targeted are: (1) How do patients and their partners perceive prognostic risks? (2) How do these perceptions relate to psychological well-being? (3) What are the determinants of perception of prognostic risks? These questions are addressed from a quantitative angle in cross-sectional and longitudinal studies in patients recently diagnosed with MS. To come to a better understanding of how patients come to their perceptions, also a qualitative study in which patients explained their perception of risk and seriousness was included. In this chapter, the current status of our knowledge of MS and its psychosocial consequences is reviewed.

Clinical aspects of multiple sclerosis
Pathology and epidemiology

Multiple sclerosis (MS) is a chronic disease of the central nervous system (CNS). The disease is characterized by inflammations of the myelin sheath – the insulation of the nerves. These inflammations disrupt transmission of neural information and thereby cause loss of bodily functions. Inflammations come and go, but they can leave damaged nerves, neurons and axons. This damage is considered important in the development of irreversible disability.[5] The pathogenesis of MS is unknown, but there is strong evidence that the disease is caused by the interaction of multiple genes and environmental factors.[5]

The prevalence of MS in Western countries is estimated to be about 1 in 1000,[8] with an incidence of 2-6 per 100,000 person years.[10] For the Netherlands, this means that approximately 16,000 people suffer from MS and about 600 are newly diagnosed with the disease each year. MS generally affects young adults between 20 and 40 years of age[12] and is more frequent among women than men.[10]

Clinical features and diagnosis

MS is characterized by a wide variety of symptoms, including fatigue, sensory disturbances, optic neuritis, diplopia, limb weakness, cognitive impairment, spasticity, sexual dysfunction, clumsiness, bladder and bowel problems.[10] The severity of these symptoms ranges from mild to severely disabling.

The diagnosis of MS is primarily based on clinical and paraclinical evidence of typical CNS lesions disseminated in time and place.[12,16,17] This evidence is
formulated in a set of diagnostic criteria – known as the Poser criteria[16] – that have been the gold standard for almost two decades. Based on these criteria patients with definite and probable MS can be distinguished. The advances in MRI diagnostics and CSF technology and the emerging possibilities of early treatment have recently induced an update of the Poser criteria, known as the McDonald criteria.[20] Through the extensive use of MRI as a diagnostic tool these new criteria allow for a definite diagnosis of MS within only a few months after the first presentation of suspected symptoms. This may be particular of benefit to those patients and neurologists who would opt for treatment in the earliest phase of the disease. First findings on the clinical application of these criteria have been promising.[21]

Despite the higher accuracy of diagnosis, the benefits of the new McDonald criteria are still subject to discussion. Argument against the use of these criteria is the higher risk of misdiagnosis due to the reliance on MRI findings that are not properly validated prospectively.[22] Further, in the new criteria there is a decreased role for clinical history and dissemination of lesions and events in time. This may lead to a diagnosis and treatment of patients with mild benign forms of MS who would not have developed further symptoms for years anyway.[17]

The present debate on the timing of diagnosis builds upon earlier discussions on whether to disclose the diagnosis at the presentation of first symptoms.[23-28] This debate is for a large part determined by the (lack of) clinical knowledge of the course of disease, the (lack of) possibilities of treatment in an early phase, and the anticipated burden for patients of knowing (or not knowing) the diagnosis. It is not known whether patients themselves would prefer an earlier diagnosis.

Clinical course and prognosis

The course of disease is diverse, ranging from a benign course with minimal disability to a rapid progressive course leading to significant disability or death within a relatively short time after disease onset.[1] The most frequent courses of symptoms are illustrated in Figure 1. In approximately 10-15% of the patients, the disease has a course that is progressive from onset (Figure 1a).[35] In the majority of patients (80-85%) the disease presents with a relapsing-remitting form (Figure 1b), in which the presence (relapse) and absence (remission) of signs and symptoms alternate.[15,10,29] A relapse of symptoms typically evolves over a couple of days, stabilizes and then often improves, spontaneously or in response to medication, within weeks. This recovery of function can be complete or partial, i.e., leaving some degree of symptoms. A next relapse may occur, within weeks, months or years. The relapsing-remitting course can develop into progressive clinical
disability, with or without superimposed relapses and remissions (Figure 1c).\textsuperscript{[1,2]}
Finally, when patients have a relapsing-remitting course with long phases of remission and have not reached a score of 3.0 on the Expanded Disability Status Scale (EDSS) in ten years, the course is referred to as benign (Figure 1d).\textsuperscript{[30]} The distinction between the courses is not always clear: patients can gradually progress to more severe forms, but not vice versa. It is important to note that a reliable diagnosis of benign MS can only be made in retrospect, since also patients who initially met these criteria may develop more severe disability later in life.\textsuperscript{[30]}

For individual MS patients prognosis is largely unpredictable. Prognostic studies have aimed to define risks of EDSS endpoints and to identify factors that predict a benign or progressive course of disease. Based on epidemiological data (Figure 2), it is estimated that within ten years after the onset of disease 30\% of the patients will require aids to walk about 20-100 meters, as indicated by a score of 6.0 on the Disability Status Scale (DSS).\textsuperscript{[2]} The lifetime risk of wheelchair dependence without being able to walk a few steps (DSS = 8.0) is about 50\%.\textsuperscript{[2]}

**Figure 1** Possible courses of MS
A. Primary progressive MS; B. Relapsing-remitting MS; C. Secondary progressive MS, D. Benign MS (adapted from Lublin\textsuperscript{[1]}). The dashed lines in Figure B-D demonstrate that the same disease history (two relapses – left to the line) can lead to a diverse course.
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Factors that predict a more progressive course include a high relapse rate in the early years of disease, motor or cerebellar signs at onset, older age at onset, incomplete remission after first relapses, early disability, male sex, short interval between initial and second attack and high lesion load detected by early MRI of the brain.[31-34] Yet, the predictive value of these prognostic factors is limited.[30]

Treatment
At present, there is no therapy that can halt the accumulation of disability,[10] but several treatment strategies that have a favorable effect on the natural course of disease have been developed. The main options are corticosteroids for the treatment of acute exacerbations and immunomodulatory drugs for the long-term slowdown of disease progression.[29] Corticosteroids are often used to treat clinically significant relapses in order to speed up recovery, and prevent permanent damage of the nerves. At present there is no consensus about the optimal form, dose, route (oral or injection) or duration of corticosteroid therapy.[10] Immunomodulatory drugs, such as interferon β, aim to reduce the frequency and severity of relapses and to prevent or postpone the onset of the progressive phase of disease.[29]

The optimal treatment of patients after a first clinical episode of possible MS remains uncertain. Two recent trials indicate that early interferon treatment may

Figure 2 Actuarial analysis of disability from onset in a population of 1100 MS patients[21]

DSS = Disability Status Scale, which is the precursor of the Expanded Disability Status Scale (EDSS) used in this study. The EDSS distinguishes within one step of the DSS, e.g. EDSS scores of 6.0 and 6.5 are identical with a DSS value of 6.[30]
delay the development of a second relapse. These findings may influence patients’ and physicians’ decisions towards an early start of interferon therapy. In contrast, the treatment-related side effects, inconvenience, costs, and lack of evidence of an important long-term benefit of interferon will deter others from treatment early in the disease course. In addition, the optimal dose and duration of interferon treatment and the possible teratogenic effects on the developing fetus in pregnant patients are unknown.

In summary, the clinical expression of MS is highly variable in type, duration, intensity and consequences of symptoms. The course of disease is unpredictable and, at present, insufficiently controllable by medication. The increasing functional limitations and the prognostic uncertainty may have a significant influence on psychological well-being and quality of life of patients and their families. These consequences are reviewed in the next section.

**Psychological aspects of multiple sclerosis**

**Diagnostic and prognostic uncertainty**

As a consequence of the unpredictable and uncontrollable course of MS, uncertainty is a predominant feature of MS with major effects on psychological well-being. Patients with MS merely have to wait and see what consequences will happen to them. Uncertainty has been rated the second most stressful aspect of MS by patients, following fatigue but preceding the inability to walk.

For many patients the burden of uncertainty starts with a long period of vague unexplained symptoms before diagnosis. Symptoms are not always recognized as early signs of MS by patients themselves or by their general practitioners. For some patients, a prolonged diagnostic period may occur even when referred to a neurologist because they do not meet the criteria for definite MS at their initial visit and only learn about MS when a second or later episode occurs. The burden of uncertainty in the phase prior to diagnosis has only been studied retrospectively in comparison to the uncertainty after diagnosis. To date, three studies have examined the impact of the diagnosis of MS on illness uncertainty in patients with MS. In two studies, patients reported significantly lower uncertainty and distress over physical symptoms after diagnosis than before, whereas in another study the decrease in uncertainty, anxiety and worries was only moderate. As expected, learning that the diagnosis was MS significantly reduced uncertainty about the diagnosis, but did not reduce uncertainty about the future course of disease. Several studies in advanced phases of the disease demonstrated that increased feelings of uncertainty sustained after diagnosis. In patients with
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relapsing-remitting MS, exacerbations heightened patients’ feelings of uncertainty which in turn increased their symptoms of depression. Other studies have also demonstrated that perceived uncertainty was an important determinant of depression, also after adjustment for disability status.

Health-related quality of life

Health-related quality of life is a multi-dimensional concept that refers to the patients’ evaluation of their physical, mental and social functioning. Many studies have demonstrated that patients with multiple sclerosis (MS) report poorer quality of life (QoL) than persons from the general population. A major impact of the disease was found for both the physical health and mental health dimensions of QoL. In patients with MS, QoL is for a large part determined by the presence of physical limitations. Higher disability status, as assessed by the EDSS is primarily associated with poorer QoL of physical health, whereas only a few studies also reported a negative effect on mental health. Other factors that have been found as determinants of poorer QoL in patients with MS include depression, anxiety and fatigue.

Studies on QoL in MS have generally been conducted in patients who were ill for a long period: the average duration of illness of the studies conducted to date was longer than eight years. QoL in advanced stages of MS may for a large part be determined by the progression of disease resulting in more disability. In contrast, in the early period after diagnosis most patients face relatively good health and their need for care and assistance in daily activities is limited. QoL of patients may then be more affected by the burden of the diagnosis, rather than the presence of physical symptoms. To date, no studies have addressed QoL of patients in the early phase of disease specifically. This is an important period from a psychological perspective as in this period patients will be coping with the diagnosis of MS.

Depression and anxiety

Depression is a common feature in MS. Depression is more prevalent in MS patients than in healthy controls. Although some studies reported a higher frequency of depression in patients with more physical limitations, others failed to replicate this finding. The origin of depression is not clear. Several studies have found that symptoms of depression were strongly correlated to MRI lesions. These findings suggest that brain lesions play a causative role in the pathogenesis of depression. Arguing against this hypothesis is that others found no relation between MRI abnormalities and depression, or found that depression
mainly resulted from feelings of uncertainty.\[^{[44]}\] Also, one can argue that MRI lesions correlate to disability status, which may consequently influence the mood of patients. These findings suggest that to some extend depressive symptoms may also have a psychological origin.\[^{[58]}\]

Patients with MS also demonstrate high levels of anxiety.\[^{[59,63,64,68]}\] In contrast to depression, anxiety is thought to be of psychological origin – as a result of the accumulation of stressful events.\[^{[59,63]}\] So far, studies of anxiety and depression have been conducted in patients with advanced stages of disease; the mean duration of disease in the aforementioned studies was longer than eight years.\[^{[59,62,64,68]}\] The prevalence of anxiety and depression in earlier phases has not been studied. This early period may be crucial as high levels of anxiety and depression in patients may hamper the process of coping with the diagnosis. The success of coping may consequently determine whether psychosocial problems sustain.

**Psychological burden for partners**

Compared to other chronic diseases, the burden of MS for partners and caregivers is not extensively studied.\[^{[69]}\] Only a few studies have addressed the consequences on quality of life and emotional well-being of partners.\[^{[56,70,72]}\] These studies found that partners of patients with more physical limitations had higher levels of anxiety and depression, lower mood and poorer quality of life.\[^{[56,70,72]}\] QoL of partners was poorer compared to persons from the general population.\[^{[56]}\] Perceived illness uncertainty was associated with poorer emotional well-being among partners.\[^{[72]}\] In addition, partners also experienced considerable problems in social relationships and work.\[^{[70,71,73]}\]

In summary, the uncontrollable and unpredictable nature of the disease implies that patients have little opportunity to anticipate or prevent future disease progression. The prognostic uncertainty plays a crucial role in psychological well-being of patients with MS and their partners. It is an important determinant of depression and anxiety and may consequently lower QoL. In the absence of unambiguous clinical information, patients’ expectations about their future course of disease – whether realistic or not – may play a crucial role in their decisions about treatment, family planning, relationships, career and housing. Expectations can be regarded as a psychological strategy to reduce feelings of (prognostic) uncertainty\[^{[74]}\] and may therefore influence psychological well-being. For example, patients who expect that their disease will progress within a short time may be more anxious and distressed than patients who expect that the severity of their condition will remain unchanged. In the next part, we will discuss relevant
literature on perception of prognostic risk, which is an alternative way to study expectations about particular prognostic outcomes.

**Perception of prognostic risk**

*What is risk perception?*

Risk is defined as the probability of an adverse event to happen within a certain period of time.\(^{[76]}\) The subjective judgment of individuals about the height of the risk is referred to as perception of risk. Within the context of chronic diseases, examples of adverse events are disease progression, functional disability, handicap, side-effects of treatment, and mortality. It is obvious that the evaluation whether an event is adverse is highly subjective. For that reason, perception of seriousness of an outcome is often measured together with perception of risk. Perceived risk and seriousness of adverse health outcomes are considered important determinants of health-related behavior such as treatment uptake and compliance. For that reason, perception of the risk and seriousness have developed into key concepts in many health behavior theories.\(^{[77,78]}\)

The first study of risk perception in a medical context dates from 1975 and reports about determinants of participation in a genetic screening program.\(^{[80]}\) In that study, persons who considered themselves at higher risk of being a mutation carrier of Tay-Sachs disease (perceived susceptibility) and those who perceived the impact of learning about the carrier status as being low (perceived seriousness) were more likely to participate in the screening program. To date, risk perception has primarily been studied with regard to the risk of disease in healthy individuals, particularly among those at high risk of a specific disease. A large number of studies have addressed perception of disease risk in relation to behavior change and preventive strategies. Examples include the risk of HIV/AIDS in relation to safe sex, the risk of cardiovascular disease in relation to diet, exercise and smoking, the risk of cancer in relation to smoking, sun-bathing and screening for disease, and the risk of congenital anomalies (e.g. Down syndrome or spina bifida) in offspring in relation to prenatal testing.\(^{[81-86]}\) Perception of these risks and in particular their impact on psychosocial well-being may essentially differ from so-called ‘embodied’ risks\(^{[87]}\) that are not easily preventable, such as genetic and prognostic risks. To date, no studies have investigated the impact of perception of prognostic risk on psychological well-being. For that reason, the selection of determinants of perceived risk and psychological consequences in this study will mainly be based on previous research in the area of genetic (embodied) risks. In the remaining part of this chapter, we will review these and previous findings on expectations of future consequences in MS and other chronic disorders.
Studies on perception of genetic risk
Perception of genetic risk has been studied extensively in persons at high risk of hereditary diseases such as Huntington’s disease, prostate cancer, breast cancer and ovarian cancer. These studies have focused on various topics including the accuracy of risk perception compared to actual risks, the impact of risk perception on psychological well-being and the determinants of perceived risk. With regard to the accuracy, it has been demonstrated that perception of risk is often inaccurate: high-risk individuals were found to overestimate or underestimate their risks of disease. High perception of risk was associated with increased worry, disease-related distress, anxiety and depression in some studies, but not in others. Studies on determinants of risk perception have demonstrated that higher perception or overestimation of risk was associated with higher actual risk, higher number of affected relatives, closer family relation to the patient with the hereditary disorder, higher severity of illness of the affected relative, younger age, lower education and prior disease experience (e.g. biopsies or benign breast disease). Findings on the importance of these determinants differed between studies: some did not find a significant association between risk perception and previous disease experience, the number of affected first-degree relatives, age and education.

When we translate these findings to perception of prognostic risk of patients with MS, we may expect that higher perception of risk may also have a significant impact on psychological well-being of patients. Also, we expect patients’ beliefs about their illness and personality factors to influence perceptions of risk. Patients may have expectations about the course of disease that may not be evidently anticipated given their present health condition, i.e. they may over- or underestimate their risks of complications.

Studies on perception of prognostic risk and expectations about prognosis
A major difference in the perception of genetic and prognostic risks is that prognostic risks are faced by individuals who may already experience symptoms of the disease. These symptoms may be interpreted as signs of favorable or unfavorable prognosis and are for that reason potentially important determinants of perception of risk of patients and partners. There has been limited research on perception of prognostic risk or expectations about prognosis. Table 1 shows an overview of studies on expectations of specific health outcomes and general health status in patients with chronic diseases. The majority of these studies were conducted in relation to decisions about surgery or pharmacological treatment. These studies demonstrate that patients tend to overestimate their
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Table 1 Overview of studies on expectations of prognosis in chronic diseases

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<td><strong>Descriptive studies on expectations</strong></td>
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<td>Cancer (during palliative radiotherapy)</td>
<td>Cure of disease and disease duration</td>
<td>Overestimation of the benefits of radiotherapy</td>
<td>Chow et al., 2001 [4]; Doyle et al., 2001 [6]</td>
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<td>TIA and stroke patients</td>
<td>Risk of stroke, risk of surgery and benefit of surgery</td>
<td>Overestimation of the risks and the benefits of surgery (carotid endarterectomy)</td>
<td>Lloyd et al., 2001 [7]</td>
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<tr>
<td>Diabetes</td>
<td>Risk of blindness, end-stage renal disease and lower-leg amputation</td>
<td>Overestimation of the prognostic risks and benefits of treatment effects</td>
<td>Meltzer et al., 2000 [9]</td>
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<tr>
<td><strong>Studies of expectations in relation to health outcomes</strong></td>
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<tr>
<td>Arthroplasty patients (before and after total hip revision)</td>
<td>Future pain and walking ability</td>
<td>Pre-operative unrealistic optimistic expectations contributed to greater post-operative dissatisfaction</td>
<td>Eisler et al., 2002 [11]</td>
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<tr>
<td>Asthma</td>
<td>Future health status</td>
<td>A priori expectations of cure from asthma were associated with poorer QoL at follow-up.</td>
<td>Mancuso et al., 2001 [13]</td>
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<tr>
<td>Epilepsy (before and after surgery)</td>
<td>Frequency of seizures</td>
<td>More realistic a priori expectations were related to higher satisfaction with post-operative functioning.</td>
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<td>HIV/AIDS</td>
<td>Risk of complications if treatment is not taken</td>
<td>Higher perceptions of risk were related to stronger treatment adherence.</td>
<td>Gao et al., 2000 [15]</td>
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<td>Multiple sclerosis</td>
<td>Risk of recurrent attacks and improvement in health status</td>
<td>Unrealistic optimistic expectations of improvement in health status were related to higher risk to discontinue therapy in 6 months</td>
<td>Mohr et al., 1996 [18]</td>
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<td>Rheumatoid arthritis</td>
<td>Health status within the next years</td>
<td>Pessimistic expectations were significantly correlated with poorer clinical and self-perceived health status, but not with neuroticism</td>
<td>Radanov et al., 1997 [19]</td>
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prognostic risks, [7] and are too optimistic about the possibilities for treatment. [4,6,7] Furthermore, patients who had unrealistic a priori expectations were more likely to discontinue treatment [15,18] and had poorer QoL. [13] None of the previous studies addressed expectations about prognosis in partners of chronically ill patients.

Despite the high levels of uncertainty, patients’ expectations about future disease status in MS have not been studied extensively. Only one previous study on expectations about prognosis has been conducted in MS. Mohr et al.
investigated patients’ expectations about the effectiveness of treatment, and found that 57% of the patients who started interferon β treatment had unrealistic expectations about the risk of recurrent attacks and 34% about the improvement in health status. Patients who had unrealistic positive expectations about the benefits of treatment were more likely to discontinue treatment within the first six months. The only other study in MS that relates to expectations of future disease was conducted by Fournier et al. They demonstrated that MS patients who generally hold a positive outlook on life reported less symptoms of depression. However, this study did not provide insight whether these patients also had favorable expectations about their prognosis.

In summary, the studies on expectations about prognosis in chronic diseases conducted so far demonstrate that being too optimistic or too pessimistic may both negatively affect psychological well-being: being too optimistic may lead to later disappointment, whereas being too pessimistic may be accompanied by increased worry. To date, there are no studies that investigated what MS patients expect with regard to their future course of disease and how these expectations relate to psychological well-being.

**Scope of this thesis**

This study aims to get insight in the expectations of prognosis of patients recently diagnosed with MS and their partners. Of all possible consequences of MS, we focus on the risk of future wheelchair dependence. This prognostic outcome was selected for several reasons: (1) it is the best-known consequence of disease, so it is unlikely that patients will be confronted with new information; (2) it is a frequent consequence with a lifetime risk of wheelchair dependence of 70-80%[2]; (3) we expect that the majority of patients will consider this a serious consequence of their disease; (4) wheelchair dependence can be clearly defined following descriptions of wheelchair dependence of the EDSS; (5) by following these descriptions, perceptions of patients and partners can be compared with data from epidemiological studies that have used this scale as an outcome measure.

An overview of the study design, patient population and the instruments is presented in Chapter 2. In Chapter 3, as an indication of the burden of uncertainty before diagnosis, the preference with regard to the timing of diagnosis of patients is described and related to the duration of the diagnostic work-up. Chapter 4 presents the psychological well-being and quality of life of patients and their partners in the early phase after diagnosis. Where possible, these data are compared with that of general population controls. Next, Chapter 5 discusses the influence of anxiety and
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depression on the relationship between disability status and quality of life. In Chapter 6, the expectations of risk and seriousness of future wheelchair dependence of patients and partners are described. Chapter 7 addresses the question whether perception of risk and seriousness of wheelchair dependence relate to higher levels of anxiety, depression and distress. In Chapter 8 to 10, the factors associated with perception of risk and seriousness are investigated. The role of illness beliefs and personality characteristics are described in Chapter 8 and 9, respectively. Chapter 10 reports on the results of the qualitative study in which patients explained their perception of risk and seriousness.

In the last part of the thesis, confirmation of the findings of the cross-sectional analyses on perception of risk and seriousness is sought in follow-up assessments. Using follow-up measurements, we examined whether changes in determinants found to be of importance in the cross-sectional analyses in Chapter 6 to 9 were associated with changes in perception of risk and seriousness (Chapter 11), and whether changes in perception of risk and seriousness were associated with changes in anxiety, depression and disease-related distress (Chapter 12). The findings of this study are summarized and discussed in Chapter 13.

References

CHAPTER 1


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Strecher VJ, Kreuter MW, Kohrin SC. Do cigarette smokers have unrealistic perceptions of their heart attack, cancer, and stroke risks? J Behav Med 1995; 18:45-54.


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