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Chapter 1

General introduction

GENERAL INTRODUCTION

A patient

Mrs. Petersen, 59 years old (BMI 30), has suffered from painful joints for the past three years. About two years ago, she first presented her worries about these complaints to her general practitioner (GP). Until then, she had been healthy apart from well-controlled diabetes since 1997. The pain was mainly affecting both knees, her left shoulder and her both hands. The GP could not find a somatic explanation for her symptoms after physical examination and laboratory tests. They tried several pain medications, but the pain symptoms remained. At that time she was working half the hours she used to because of the pain. She told the GP that she felt like she was failing in her responsibilities at work. The GP felt frustrated, not being able to help enough to make her feel better. After a few months during one of the consultations, she told the GP that she had lost her appetite and also had lost weight. Thinking back over the last couple of months the GP realized that Mrs. Petersen had changed from being a cheerful woman to a very timid person. When inquiring about depressive symptoms, indeed she claimed to be suffering from very low mood, little interest in things, not being able to make decisions and severe problems sleeping. The GP diagnosed her with a depressive disorder and referred her to a psychologist. Luckily, the psychologist's treatment helped her to regain joy in life. But unfortunately, although slightly less severe, her pain symptoms persisted and she was still worried about her pains. She was referred to a rheumatologist who did not find an explanation for her pain symptoms. Since then she has visited a physiotherapist numerous times, which has given her little and only temporary relief. Just recently she stopped playing tennis, which was her favourite hobby. Now, she has made an appointment with the GP, because the GP's practice nurse is currently unable to help her control the diabetes and advised her to visit the GP. The GP, now well acquainted with her, sees her walk in with a slow gait and when they shake hands he notices a sad facial expression...

The problems faced

This patient could be listed in any Dutch general practice and just like Mrs. Petersen many patients face both mental and physical health issues. Unfortunately, depressive and anxiety disorders are not recognized by general practitioners (GPs) in approximately half of the cases, which could be due to regarding depressive or anxiety symptoms as part of a somatic condition¹⁻⁷. One of the aims of this thesis is therefore to study how well general practitioners recognize depressive and anxiety disorders in patients with physical health problems. Many cross-sectional studies have shown that the prevalence of depressive and anxiety disorders is increased in patients with several physical health problems⁸⁻¹⁵. The comorbidity of physical health problems with depression and anxiety is associated with increased disability, decreased quality of life and reduced treatment effects compared to patients with either physical or mental health problems¹⁶⁻²⁰. However, less is known about which specific

physical health problems are risk indicators of incidence and prognosis of depressive and anxiety disorders. For Mrs. Petersen and her GP it would be interesting to know whether her diabetes and pain symptoms affect her mood problems, is she for instance at risk of a poorer depression course? And could it be that Mrs Petersen became depressed partly due to diabetes? To her painful joints or perhaps to both? Also, when Mrs. Petersen walked in during the last consultation she showed symptoms of depression recurrence, could this be related to her physical ill health? Our research will provide information about which specific physical health problems are associated with incidence and course of depressive and anxiety disorders. A more in-depth understanding of the temporal relationship may shed light on possible treatment options. In this Chapter, background information on issues relevant for this thesis will be given, finishing with a thesis outline.

Depressive and/or anxiety disorders

In daily practice depressive and/or anxiety disorders are highly prevalent. Lifetime prevalences of depressive disorders and anxiety disorders in Dutch society are around 20%²¹⁻²³. The impact of depressive and anxiety disorders on public health is substantial, with reduced social and work-related functioning, decrements in quality of life and major societal costs²⁴⁻²⁸. This large impact on individuals and society is probably largely due to both depressive and anxiety disorders often running unfavourable courses over lifespan with recurrent or chronic episodes. For depressive disorders it is estimated that 30-50% of individuals have recurrent episodes and up to 30% suffer from chronic course^{29,30}. Anxiety disorders often have an even less favourable course with longer durations³¹⁻³³. Comorbidity rates of depressive and anxiety disorder range from 30-60%³⁴⁻³⁷ and these disorders may share pathophysiological underpinnings. Many previous epidemiological studies have focused on either depressive or anxiety disorder. Depressive disorders have received much more attention to date, but the number of studies on anxiety are increasing⁸. Since these disorders so often arise in the same person, we will focus on the associations between physical health and depressive, anxiety disorders and the combination of both in this thesis.

In the studies reported in this thesis, depressive disorders include major depressive disorder and dysthymic disorder according to the fourth edition of the Diagnostic and Statistical Manual of mental disorder (DSM IV)³⁸. Major depressive disorder is characterised by depressed mood and/or loss of interest or pleasure in life activities for at least 2 weeks which is accompanied by symptoms such as changes in sleep, and unintentional changes in weight, agitation or psychomotor retardation, feelings of guilt, lack of energy, indecisiveness and recurring thoughts of death. Dysthymic disorder is characterized by the same symptoms as major depressive disorder which are persistently present over a time period of at least two years, but are less severe. DSM IV anxiety disorders studied in this thesis comprise the most common anxiety disorders: situational (social phobia, panic disorder with and without agoraphobia) and generalized anxiety disorder³⁸. Social phobia is a marked and persistent fear of one or more social or performance situations in which

the person fears that he or she will act in a way that will be humiliating or embarrassing. Panic disorder is characterized by recurrent unexpected panic attacks, which may be accompanied by agoraphobia. Agoraphobia involves an intense fear of being alone in public places, especially in situations from which escape might be difficult or embarrassing, or where help is not readily available. Generalized anxiety disorder encompasses feelings of anxiety and excessive worry about everyday situations for at least six months.

Physical health

Next to mental health, physical health can have a large impact on wellbeing. Research among Dutch citizens has shown that 'being healthy' always ranks the top 5 of what people find important, close to being with a partner, having a family and being able to provide³⁹. We defined physical health problems in two ways. We used pain as a subjective measure of physical health, and chronic somatic diseases as a more objective indicator.

Pain

The International Association for the Study of Pain (IASP) defined pain in 1979 as: "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage"^{40;41}. Pain is highly prevalent, with a point prevalence of around 20% for chronic pain^{10;16}. Pain is known to have harmful effects on patient-perceived health status and everyday day activities (i.e. decreased work productivity, inability to sleep, no longer able to attend social functions). Also, societal costs are also tremendously affected by pain, through higher healthcare utilization and reduced number of work days^{10;16;42}.

Studies on pain often focus on a single pain location. Chronic pain has traditionally been defined by duration, however, studies have shown that duration alone is not as predictive for clinically significant pain in the future as measures regarding the severity of pain⁴²⁻⁴⁴. To examine pain in relation to depressive and anxiety disorders in this dissertation, pain was defined in numerous ways: location(s), duration and severity.

Chronic somatic diseases

Chronic somatic diseases -particularly non-communicable- including cardiovascular diseases, diabetes, chronic respiratory conditions and cancer, are now -like depression and anxiety- among the main causes of disability, and also death in western countries⁴⁵⁻⁴⁷. Survival with these chronic diseases has increased due to improved standards of living, better hygiene and healthcare facilities - with continuously expanding and improving diagnostics and treatments -. The rise in the prevalence and burden of these diseases over the last century is due to changes in lifestyle and aging⁴⁵⁻⁴⁸. Chronic diseases pose a burden on daily activities, can lead to disturbances in mood and have a large impact on society⁴⁸.

Kriegsman et al.⁴⁹ showed that participants' self-reports of common somatic diseases were overall rather reliable when compared to information obtained from their general practitioners. This thesis therefore relies on face-to-face interview data about common chronic somatic diseases. In order to assess the somatic diseases most 'objectively', we considered somatic disease only to be present if the participant stated that the disease was being treated by a healthcare professional or when medication was being used. To group the chronic somatic diseases, seven categories were distinguished; cardiometabolic, pulmonary, endocrine, neurological, musculoskeletal, digestive disorders or cancer.

Recognition of depression and anxiety by general practitioners (GP)

In the Netherlands every individual is registered with a GP, who serves as 'gatekeeper' of the health care system. The Dutch GP Society (Nederlands Huisartsen Genootschap) has defined the GP's role in 1959: "To deliver continuous, integrated and personal care to patients". The GP is therefore in the unique opportunity to diagnose and manage both physical and mental health problems. Primary care patients suffering from pain and chronic somatic diseases often also have a depressive or anxiety disorder⁵⁰⁻⁵². Research on recognition of depressive and anxiety disorders shows that GPs recognize these disorders in 20-70% of cases¹⁻⁷. The finding that GP recognition is not optimal, could be due to the patients' preference not to reveal such symptoms, lack of time (usually ten minutes per consultation), a somatic focus during the consultation or reasons the GP may have not to label the patient as depressed or anxious. Factors that seem to facilitate depression and anxiety recognition are the severity of depressive and anxiety symptoms and previous episodes of depression and anxiety^{6;53;54}. Not consulting the GP for (mental) health problems is associated with lower recognition^{6;54}. Since patients who have physical health problems next to their depression or anxiety may be at increased risk of worse depression and anxiety and also of reduced quality of life^{8;9;18;55;56}, it is particularly interesting to know whether physical health problems affect recognition. Whether pain symptoms and chronic somatic diseases are associated with GP recognition of depression or anxiety has not been studied in detail. So far, results have been conflicting, with studies finding no influence on recognition and others reporting lower or higher recognition rates^{1;2;6;54;57-61}. Studies specifically focusing on pain symptoms and particular diseases have not yet been performed. In this thesis we study the associations between specific physical health problems (pain and somatic diseases) and GP recognition of depression and anxiety, taking into account other factors that may play a role in the association such as severity of psychiatric symptoms and number of GP visits.

Comorbidity of physical health problems and depressive and anxiety disorders

High comorbidity rates of depressive and anxiety disorders with physical ill health have been reported in cross-sectional and to a lesser extent longitudinal studies^{8;9;62-66}. The alarming

consequences of the comorbidity of depressive and anxiety disorders with both pain and somatic diseases are worse treatment outcomes, reduced social and work-related quality of life, major societal costs and increased numbers of suicide death compared to having only physical or mental health problems^{16;64;67-69}. For health care providers such as GPs, who are often facing patients with multiple diseases, it is of particular interest to know whether certain pain symptoms or specific diseases could be associated with depressive and anxiety disorder incidence and course. This may enable them to recognize affective problems early and to be able to intervene early on when facing individuals with particular physical health problems. GPs could also provide patients with more specific information about the expected course when a patient with a particular disease develops a depressive or anxiety disorder. Pathways underlying physical and mental comorbidity are very complex, with for instance dysregulation of the autonomic nervous system, of the hypothalamic-pituitary-adrenal axis and of inflammatory processes^{50;70-76}. A more in-depth insight into which physical health problems are associated with incidence and prognosis of depression and anxiety may guide researchers to focus on specific new hypotheses regarding possible underlying pathways. The epidemiologic knowledge on the link between physical health problems and the incidence and course of depressive and anxiety disorders could be improved. Answers as to why some people recover quickly from a depressive or anxiety disorder while others suffer from these disorders chronically may be obtained from longitudinal studies using a cohort with participants who are (prone to be) depressed and/or anxious, since the course of these disorders can then be studied in detail. So far, the longitudinal studies on physical and mental health comorbidity, often used different settings and differed in methodologies. Most studies that have longitudinally studied physical and mental health problems have focused on depressive disorder only, anxiety has been studied to a lesser extent.

Pain

There are more longitudinal studies examining depression or anxiety in pain patients than studies on pain in depressed or anxious patients^{8;9}. Of these studies, some have been performed amongst tertiary care pain clinic patients which are the worst affected patients and are probably not representative of pain patients in general^{8;9}. Evidence for the impact of pain on depressive or anxiety course was also obtained indirectly from clinical trials studying treatments for depressive and anxiety disorders^{20;77-79}. Many studies that have focused on longitudinal associations between pain and depression and anxiety have focused on depressive and anxiety symptoms and not on depressive and anxiety disorders⁹, particularly for the role of pain in depression and anxiety incidence⁸⁰. Symptom overlap between depressive and anxiety symptoms (also covering 'subthreshold' states) may show greater overlap and therefore overestimate the associations. Also, there is a lack of longitudinal information on how pain is experienced in depressed and anxious individuals compared to healthy controls.

Chronic somatic diseases

Results from studies indicate that having chronic somatic disease(s) in general is associated with worse course of depression and anxiety^{30;34;55;81}. Less studies have focused on several specific diseases and have found conflicting results. For instance diabetes was associated with worse course in one study but not in another^{55;56}. Most studies focus on specific disease populations, as such studies -most often still cross-sectional- have found that the incidence and course of depression is worse in for instance diabetes patients and that major depression is associated with more complications of diabetes⁸²⁻⁸⁴. However, many diseases have not been studied in such detail and an overall picture of which particular chronic somatic diseases impact on depression and anxiety course is lacking.

This thesis will contribute to the longitudinal knowledge regarding pain characteristics, specific chronic somatic diseases and depressive and anxiety disorders. The role of the depression and anxiety course on pain symptoms over time will be examined and compared to pain symptoms in individuals without depressive and anxiety disorder. Once a more in-depth understanding of the role of particular physical health problems on depression and anxiety incidence and prognosis is elucidated, then studying the possible underlying biological mechanisms, and developing prevention and treatment strategies can be focused on these specific comorbidities with depressive and/or anxiety disorders.

The Netherlands Study of Depression and Anxiety

All the studies in this dissertation are based on data from the Netherlands Study of Depression and Anxiety (NESDA). NESDA is an ongoing longitudinal cohort study designed to examine the long-term course and consequences of depressive and anxiety disorders in different health care settings⁸⁵. A total of 2,981 adults (18-65 years) were recruited from the general population (19%), primary care (54%) and secondary mental health care organizations (27%). Across recruitment settings, uniform exclusion criteria were used: 1) a primary clinical diagnosis of a psychotic disorder, obsessive compulsive disorder, bipolar disorder, or severe addiction disorder and 2) not being fluent in Dutch. During the assessments which took place every two years - including written questionnaires, face-to-face interviews, a medical examination, cognitive computer tasks and collection of blood/saliva/hair - extensive information was gathered about depressive and anxiety disorders, demographic, psychosocial, clinical, biological and genetic determinants. Specially trained clinical research staff conducted the assessments. The baseline assessments took place between 2004-2007. Of the 2,981 participants, 22% were healthy controls, 21% had a prior history of depression and/or anxiety and 57% had a current depressive and/or anxiety disorder. For this dissertation we used the face-to-face interview data (demographics, depressive and anxiety disorders, chronic somatic diseases, pain and medication), written questionnaire data (depressive and anxiety symptoms) and Electronic Medical Record (EMR) data (from the general

practitioners of the primary care participants) from baseline, 2- and 4- year follow-up. At the 2- and 4-year follow-up assessments respectively, 2,596 (87.1%) and 2,402 (80.6%) individuals responded.

Aims and outline of this thesis

The main objectives of this thesis are:

1. To examine whether physical health problems - specific chronic somatic diseases and particular pain symptoms – are associated with GP recognition of depressive and anxiety disorders (*Chapter 2*).
2. To enhance our understanding of the longitudinal associations between pain, chronic somatic diseases and the presence (*Chapter 3*), the onset (*Chapter 4*) and the course (*Chapters 5, 6, 7*) of depressive and anxiety disorders.
3. To examine how changes in depressive and anxiety symptoms and disorders affect changes in pain over time (*Chapter 8*).

The findings reported in this thesis may contribute to the understanding of how mental and physical comorbidity are intertwined longitudinally, and in the future these insights may help to understand course types, and perhaps tailor preventative measures and treatment for patients with such comorbidity (like Mrs Petersen).

In *Chapter 2*, we examine whether physical health problems are associated with recognition of depressive and anxiety disorders by general practitioners and we investigate whether these associations were mediated by number of GP visits and the severity of depressive and anxiety symptoms.

In *Chapter 3*, we examine cross-sectional associations between migraine, other pain locations and depressive and anxiety disorders. We also study whether there is a specific link between migraine and depressive and anxiety disorder, or whether the association of pain with depressive and anxiety disorders is independent of the anatomical site of the pain.

In *Chapter 4*, we focus on the associations between different pain characteristics and the onset of depressive and anxiety disorders.

In *Chapter 5*, we subsequently focus on the associations between pain characteristics and depressive and anxiety disorder course over two years and we examine the associations between pain and comorbid depression and anxiety versus depression or anxiety alone. In both *Chapters 4 and 5* we have examined the role of severity of depressive and anxiety symptoms as possible mediators of the associations between pain and depressive and anxiety disorders.

In *Chapter 6*, we study the associations between several chronic somatic diseases (i.e. diabetes, COPD) and the 2-year course of depressive and anxiety disorders.

In *Chapter 7*, we look at whether several chronic somatic diseases and pain are associated with the recurrence of depressive and anxiety disorders over a total of four years, also taking into account the role of subthreshold depressive and anxiety symptomatology.

In *Chapter 8*, we concentrate on the associations between changes in depressive and anxiety symptomatology and disorders and changes in pain over the course of four years. We focus on whether pain course is different in chronic or temporary states of depression and anxiety versus healthy controls.

Finally, in *Chapter 9* we discuss the main findings, the methodological aspects and clinical implications of the studies included in this thesis and we present suggestions for future research.

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