Cover Page

Universiteit Leiden

The handle http://hdl.handle.net/1887/40073 holds various files of this Leiden University dissertation.

Author: Schat, A.
Title: Clinical epidemiology of commonly occurring anxiety disorders : insights into the phenomenology and course of anxiety disorders from the Leiden Routine Outcome Monitoring Study
Issue Date: 2016-06-08

Clinical epidemiology of commonly occurring anxiety disorders

Insights into the phenomenology and course of anxiety disorders from the Leiden Routine Outcome Monitoring Study

Anke Schat

Clinical epidemiology of commonly occurring anxiety disorders

Insights on the phenomenology and course of anxiety disorders from the Leiden Routine Outcome Monitoring Study

Table of contents

Chapter 1

General introduction and thesis outline

1.1 Epidemiology of commonly occurring anxiety disorders

Anxiety disorders are characterised by strong feelings of fear and distress that are often accompanied by physical sensations. They incur significant suffering and affect the individual's level of functioning. Anxiety disorders are the most frequently occurring psychiatric disorders, with an estimated 12-month prevalence of 12.0% in the European adult general population (Wittchen et al., 2011), and 10.1% in the Netherlands (de Graaf et al., 2012). Anxiety disorders occur across all ages and are far more prevalent in women than in men: for women, lifetime prevalence estimates range from 16.3% (Wittchen et al., 2011) to 23.4% (de Graaf et al., 2012), while for men lifetime prevalence estimates range from 7.8% (Wittchen et al., 2011) to 15.9% (de Graaf et al., 2012). The Diagnostic Statistical Manual, fourth edition, text revision[1] (DSM-IV-TR, American Psychiatric Association, 2000) defines several subtypes of anxiety disorders: panic disorder with or without agoraphobia (PD/A), agoraphobia without panic (AP), social phobia (SP), generalised anxiety disorder (GAD), post-traumatic stress disorder, obsessive compulsive disorder, specific phobia, acute stress disorder, anxiety disorder due to medical condition, substance-induced anxiety disorder, and anxiety disorder not otherwise specified. Following a common approach (Penninx et al., 2008; Bruce et al., 2005), this thesis focuses on PD/A, AP, SP, and GAD. These four disorders commonly result in referral to mental health care (Bijl & Ravelli, 2000), they share many features, and differ with regard to aetiology, expression, and clinical course from the other anxiety disorders (Friedman et al., 2011; Stein et al., 2010; Lebeau et al., 2010).

PD/A is characterised by repeated episodes of intense fear, which are accompanied by physical symptoms (for example increased heart rate, sweating, trembling, shortness of breath, chest pain, nausea, faintness, paraesthesia, or hot or cold rushes), feelings of derealisation, fear of losing control or of dying. In addition to worry about recurrence of the attacks and possible (physical) consequences of the attacks, there are behavioural changes in response to the attacks. In PD/A, panic attacks can occur with or without symptoms of AP. In SP, a strong and constant fear of social situations or situations in which one is subject to judgement by others is central. The places or situations that incur fear are avoided, as when the individual is exposed to them he or she fears this leads to extreme anxiety and possibly panic attacks. Individuals with GAD experience prolonged and constant uncontrollable fear and/or worry about everyday life. This fear is accompanied by restlessness, tiredness, concentration problems, irritability, increased muscle tension, or sleep difficulties. For the general population, 12-month prevalence estimates for PD/A range between 2.3% (Wittchen et

---

[1] In 2013 DSM-IV-TR was replaced by DSM-5, this led to a number of changes which are described in box 1.1.

Box 1.1 Changes in DSM-5 anxiety disorder

In 2013 DSM-IV-TR was replaced by DSM-5. This led to a number of changes in the anxiety disorder category. Obsessive compulsive disorder is no longer categorised under anxiety disorders but has instead been moved to the chapter obsessive compulsive and related disorders. Post-traumatic stress disorder and acute stress disorder are no longer categorised under anxiety disorders but have been moved to trauma- and stress related disorders. It is no longer necessary for an individual to recognise their fear is unreasonable or extreme to meet diagnostic criteria for social anxiety disorder (social phobia) or specific phobia. Instead, it must be recognised that the fear is disproportional in relation to the actual threat. For all age groups minimal duration of symptoms is set at six months. Panic attacks can be noted as a specification in any DSM-5 disorder. The diagnoses of panic disorder and agoraphobia are no longer connected, DSM-5 simply contains panic disorder and agoraphobia as separate diagnoses each with its own criteria. The specification generalised has been removed from social anxiety and stage fright has been added. Separation anxiety and selective mutism have been added (American Psychiatric Association, 2000).

al., 2011) and 1.2 (de Graaf et al., 2012). For AP prevalence estimates range between 2.0% (Wittchen et al., 2011) and 0.4% (de Graaf et al., 2012). For SP they range between 2.0% (Wittchen et al., 2011) and 3.8% (de Graaf et al., 2012), and finally, for GAD, prevalence estimates range between 1.5% (Wittchen et al., 2011) and 1.7% (de Graaf et al., 2012). Figure 1.1 shows the 12-month prevalence of PD/A, AP, SP, and GAD in the European adult general population, specified by gender and age group.

Anxiety disorders generally have an onset in adolescence or early adulthood (Baldwin et al., 2010). Although for different anxiety disorders, typical ages of onset have been described, these onsets tend to overlap, and have broad ranges: PD/A and AP often have adolescent- through mid-adult onset (Beesdo et al., 2009; Kessler et al., 2007; Thyer et al., 1985; Craske, 1999). SP typically has a childhood- or adolescent onset (Beesdo et al., 2009; Kessler et al., 2007; Thyer et al., 1985; Craske, 1999; Scheibe & Albus, 1992). Finally, for GAD, adolescent and early adult (Beesdo et al., 2009; Scheibe & Albus, 1992), as well as mid- (Kessler et al., 2007; Thyer et al., 1985), and late-adult onsets are reported (Craske, 1999). In addition to this early onset, anxiety disorders frequently have a chronic course. This was demonstrated by a general population study in The Netherlands, in which 47.1% of those with PD/A, AP, SP and/or GAD, and 51.7% of those with comorbid anxiety and depression, met diagnostic criteria at 7-year follow-up (Rhebergen et al., 2011). In addition, 46.5% of those with anxiety disorder, and 43.3% of those with comorbid anxiety and depression at baseline had not been free of anxiety symptoms at any point during follow-up (Rhebergen et al., 2011). On top of anxiety disorders having an early onset and a chronic course, individuals with anxiety disorders often meet diagnostic criteria for multiple anxiety disorders (inter-anxiety or homotypic comorbidity;

Beesdo et al. 2009). For example, individuals with SP are 3.8 times more likely to experience lifetime GAD and 4.8 times more likely to have PD/A than those without SP; individuals with PD/A are even 12.3 times more likely to have lifetime GAD than those who do not have PD/A (Michael et al., 2007). In addition, anxiety disorders are often comorbid with other mental disorders, such as mood-, somatoform-, alcohol abuse-, or substance abuse disorders (heterotypic comorbidity; Michael et al., 2007). Lifetime comorbidity rates range between 81% in SP to 92% in PD (Michael et al., 2007). In a general population study on comorbid anxiety and mood disorders, it was found that mood disorders often arose secondary (de Graaf et al., 2012). As such, anxiety disorders have been suggested to predispose towards mood disorders. Overall, anxiety disorders have detrimental consequences at an individual level. They are associated with severe impairment of quality of life. In 2010, anxiety disorders were the sixth leading global cause of disability in terms of years of life lived with disability (Baxter et al., 2014). In addition, although anxiety disorders are not regarded as a direct underlying cause of death according to the International Classification of Diseases and Related Health Problems (ICD), a study of the global burden of anxiety disorders concluded that 7% of all suicide mortality could be attributed to anxiety disorders (Baxter et al., 2014). A general population study showed that 60.6% of those who reported suicidal ideation had one or more anxiety disorders (Kessler et al., 2005). Among those who had attempted to commit suicide, the percentage of respondents meeting diagnostic criteria for anxiety disorders was even higher, at 70.4% (Kessler et al., 2005). These numbers signify that suicidality in anxiety is an important topic that must not be overlooked. Finally, consequences of anxiety disorders can be expressed at a societal level. Taking into account direct healthcare- (e.g. treatment), indirect healthcare- (e.g. social work), and indirect costs (e.g. productivity loss due to work absence), the financial impact of anxiety disorders was estimated at €74.4 billion for Europe in 2010 (Gustavsson et al., 2011). In the Netherlands for 2003 (based on health care consumption in 1997), the average annual excess costs of PD/A were estimated at €185 million, costs of AP were estimated at €78 million, costs of SP were estimated at €88 million, and costs for GAD were estimated at €11 million (Penninx et al., 2008). This shows that anxiety disorders have a large economic impact. Table 1.1 shows healthcare use ratios for individuals meeting diagnostic criteria of PD/A, AP, SP, and GAD relative to individuals without an anxiety disorder in The Netherlands.

Figure 1.1 12-Month prevalence of panic disorder with or without agoraphobia, agoraphobia without panic disorder, social phobia, and generalised anxiety disorder.
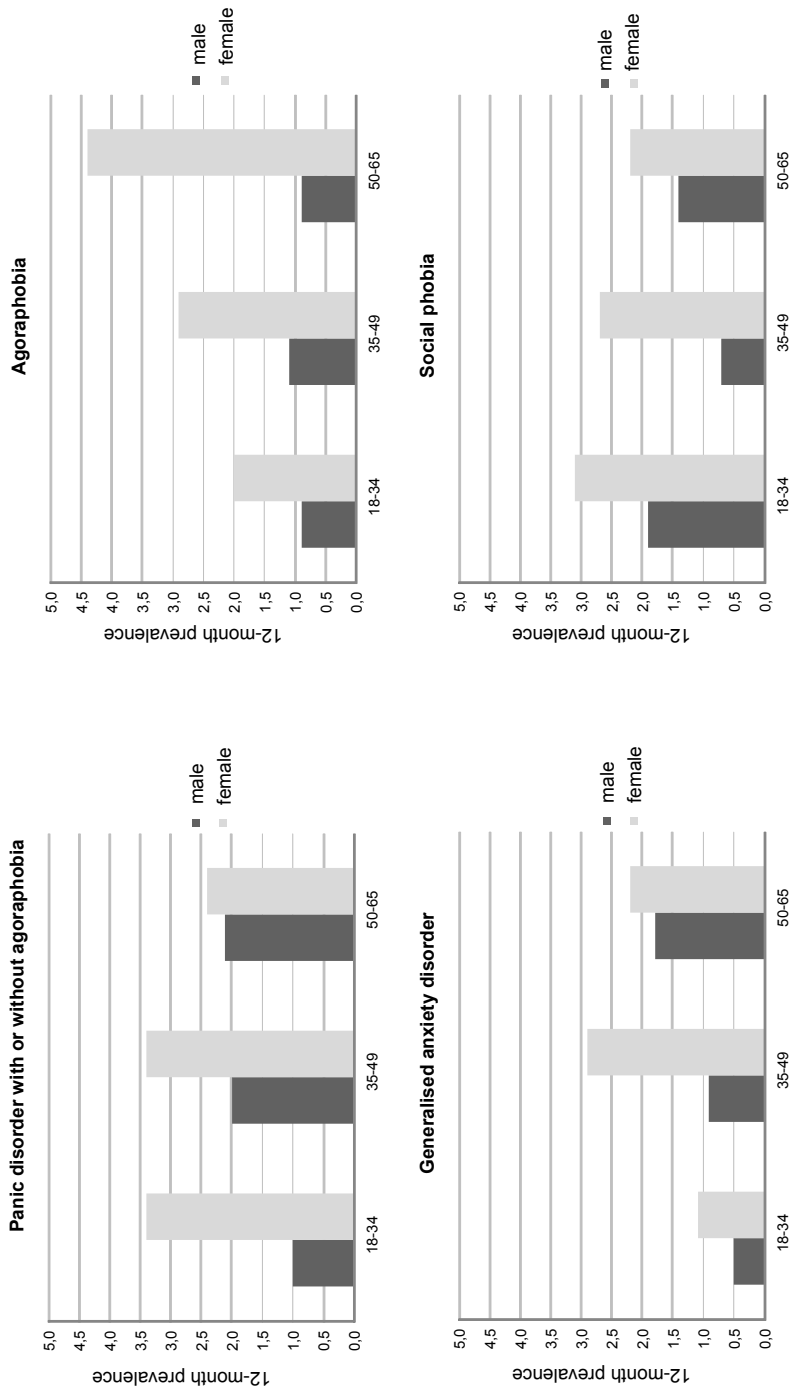
1

Table 1.1 12-month DSM-III-R anxiety diagnoses as predictors for care use in the past 12 months

	Primary care		Mental health care		Informal care		Any type of care	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
PD/A	4.35	2.70-7.01	3.63	2.33-5.65	1.57	NS	5.03	3.26-7.77
AP	3.34	2.00-5.56	2.61	1.30-5.26	1.93	NS	1.65	1.16-2.33
SP	1.37	NS	1.19	NS	1.49	NS	1.65	1.16-2.33
GAD	4.23	2.14-8.38	3.34	1.61-6.91	2.65	1.40-5.00	4.83	2.40-9.72
No disorder	1.00 (ref.)		1.00 (ref.)		1.00 (ref.)		1.00 (ref.)	

Source: based on Bijl, R.V. & Ravelli, A. (2000) Psychiatric morbidity, service use, and the need for care in the general population: Results of The Netherlands Mental Health Survey and Incidence Study. American Journal of Public Health, 19(4) 602-607. Odds Ratio's for health care utilisation are given for panic disorder with or without agoraphobia, agoraphobia without panic, social phobia and generalised anxiety disorder relative to no DSM-III-R disorder. PD/A denotes panic disorder with or without agoraphobia, AP denotes agoraphobia without panic, SP denotes social phobia, GAD denotes generalised anxiety disorder, OR denotes Odds Ratio, 95% CI denotes 95% confidence interval, NS denotes not specified, ref. denotes reference category.

1.2 The need for clinical epidemiological studies of commonly occurring anxiety disorders

In summary, anxiety disorders have a high prevalence, an early onset and chronic course, high risk for comorbidity and other adverse outcomes, and severe impact on quality of life as well as an economic impact. Taken together, this stresses the need for research on anxiety disorders that will help improve treatment through the identification of patients who are at risk for higher severity, complications, or chronicity. However, although anxiety disorders have been studied extensively, the majority of studies were randomised clinical trials (RCT's), or general population epidemiological studies. Although RCT's are well suited for studying the comparative effectiveness of new treatment options and have high internal validity, trials are often expensive, unpractical, have short term follow-up periods, demand strict protocol adherence and, have low external validity (Black, 1996; van der Lem et al., 2011; Rothwell, 2005; Vandenbroucke, 2008; Rochon et al., 2005). This entails that results from RCT's may have limited relevance for clinical practice, as populations and circumstances differ significantly. General population studies on the other hand, have few exclusion criteria. However, generalizability of findings from general population studies to clinical settings may be equally debatable (Kessler, 2007). It was estimated that in Europe, only 26.1% of those in the general population who met diagnostic criteria for any anxiety disorder received some type of formal healthcare (Wittchen et al., 2011). In The Netherlands, 31.9% of those in the general population who met diagnostic criteria for an anxiety disorder consulted primary care, 18.4%

used ambulatory mental healthcare, and 1.6% used residential mental healthcare (Bijl & Ravelli, 2000). This demonstrates that the group of anxiety disorder patients receiving mental healthcare represents only a proportion of the anxiety disorder subjects in the general population. The large group of patients not receiving help warrants studies of precursors of disorders, unmet treatment need and development of untreated disorders, a goal for which general population epidemiological studies are uniquely suited. However, when it comes to the study of factors that may be relevant tor treatment, it is likely that findings from studies in the general population may not be readily generalizable to patients in clinical practice, as these patients represent only a subset of the subjects with anxiety disorders in the general population.

Although studies with a clinical epidemiological approach, such as the Harvard Brown Anxiety Research Programme (HARP; Bruce et al., 2005), and the Netherlands Epidemiological Study of Anxiety and Depression (NESDA; Penninx et al., 2008) do exist, the samples included in these studies and those seen in everyday clinical practice may still differ to some extent (Kessler, 2007). First of all, patients who agree to take part and stay enrolled in a long-term ongoing study are likely to be more motivated and compliant than the average patient seen in clinical practice. Second, patients included in the HARP study were recruited from tertiary care facilities, which implies severity in these patients was higher than in general mental healthcare (Kessler, 2007). Conversely, NESDA patients were for a large part recruited in the general population and in primary care, implying lower severity than in general mental healthcare. Therefore:

> Clinical epidemiological studies are needed to study the predictors of individual differences in treatment response. This type of work would ideally involve investigating baseline (i.e. as of the onset of treatment) predictors of course of illness in broadly representative clinical samples (Kessler, 2007, p10).

1.3 Central aims of this thesis

In summary, anxiety disorders are highly prevalent, have a detrimental course, a high disease burden, and come with substantial societal costs. There is a strong need for clinical epidemiological studies in a naturalistic setting to describe commonly occurring anxiety disorders in individuals who present in clinical practice. The aim of this thesis is to describe the phenomenology and course of anxiety disorders in a naturalistic outpatient setting. We will outline patient characteristics and evaluate their direct clinical significance and their relevance to clinical course. Findings will be more likely to be generalizable to clinical practice, and will help clinicians identify patients who may have special needs or who are at risk for adverse outcome.

1.4 Routine Outcome Monitoring as an instrument in this thesis

At Rivierduinen, a Dutch mental healthcare provider in the greater Leiden area and at the department of psychiatry of the Leiden University Medical Centre (LUMC), patients complete an extensive battery of self-report and observer-rated measures at intake, and repeatedly during treatment as part of standard care. This procedure is known as Routine Outcome Monitoring (ROM). A more detailed description of ROM in Leiden can be found in box 1.2 and in De Beurs et al. (2011). In Rivierduinen and the department of psychiatry of the LUMC, ROM was implemented as part of standard care for patients who presented with mood, anxiety, or somatoform disorders in 2004. The primary goal of ROM is to improve care by informing clinicians and patients on diagnosis, symptomatology, and progression at intake and during the course of treatment. Although participation in ROM is voluntary, inclusion was shown to be high: in a random sample an estimated 80% of all patients was assessed at intake (De Beurs et al., 2011; van Noorden et al., 2011; Zitman, 2012). In ROM both generic and disorder-specific questionnaires are administered by trained psychiatric nurses and through supervised computerized self-report, which prevents missing data within questionnaires. Data collection covers measures of social demographics, psychiatric diagnosis, generic symptom severity, disorder-specific symptom severity, and generic health. Taking into account the setting, the extensiveness of the data collection, and the high inclusion, ROM presents a unique opportunity to undertake clinical epidemiological research in a naturalistic setting. To this end, ROM data have been anonymised and their use in scientific research was approved by the Ethical Review Board at the LUMC.

Box 1.2 ROM in the Leiden University Medical Centre and Rivierduinen

In spring 2002, the regional mental healthcare provider Rivierduinen (an institute serving a region with more than 1 million inhabitants) and the Department of Psychiatry of the Leiden University Medical Centre (LUMC) started collaboration for routine assessment of Diagnostic Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR) diagnoses as well as symptom severity, wellbeing, and generic health status at intake and follow-up. This project is known as Routine Outcome Monitoring (ROM). Initially, ROM was restricted to patients who were referred for treatment of mood, anxiety, and/or somatoform (MAS) disorders. These patients form a relatively homogenous group with substantial mutual comorbidity (Kessler et al., 1996) who mainly receive outpatient care. To be eligible, patients must have sufficient mastery of the Dutch language, and have to be able to complete self-report questionnaires. Patients who are considered (by their clinician) to be too ill to complete questionnaires or refuse assessment, are excluded from ROM.

Patients are assessed by psychiatric research nurses who have been extensively trained and supervised. Assessments are scheduled at intake, at three- to four-month intervals during follow-

Box 1.2 ROM in the Leiden University Medical Centre and Rivierduinen (continued)

up, at the start of a new treatment step, and at the end of treatment. During the first session, a standardised diagnostic interview (the Mini-International Neuropsychiatric Interview-plus, MINI-plus; Sheehan et al., 1998) is administered to determine DSM-IV-TR axis-I diagnoses. In addition, socio-demographic characteristics are assessed and maladaptive personality traits are identified with the Dimensional Assessment of Personality Pathology Short Form (DAPP-SF; Livesley & Jackson, 2006). At baseline and at follow-up, a number of self-report as well as observer-rated generic and disorders specific symptom severity scales are administered in order to monitor change in symptom reduction, wellbeing, and general functioning (Sperry et al., 1996). All instruments are commonly used in treatment-outcome research and have good psychometric properties as demonstrated by national and international publications. An overview of instruments used is available at lumc.nl/psychiatry/rom-instruments. To date, treatment information has not been documented in ROM.

Results are summarised in a report which is discussed with the patient by the clinician and which is used to evaluate treatment. In addition, data are anonymised and used for scientific research. As data collection is integrated in standard care and data are anonymised, patients are not required to provide informed consent. The use of the anonymised data for scientific purposes has been approved by the Medical Ethical Committee of the LUMC.

Source: Based on Van Noorden, 2012, On real-world patients and real-world outcomes: The Leiden Routine Outcome Monitoring Study in patients with mood, anxiety and somatoform disorders; p22. With permission from the author.

1.5 Outline of this thesis

In this thesis, several studies that were undertaken to describe the phenomenology of common anxiety disorders in clinical practice are discussed. **Chapter two** describes the age of onset of commonly occurring anxiety disorders (PD/A, AP, SP, and GAD). While generally thought to be clinically relevant (e.g. associated with higher severity or more comorbidity), definitions of early onset of these disorders vary. Therefore, we used cluster analysis to define early onset based on frequency distributions of ages of onset for PD/A, AP, SP, and GAD sampled in the general population (Netherlands Mental health Survey and Incidence Study-2; NEMESIS-2).[2] To test the hypothesis that early onset was associated with higher severity, these cut-offs for early onset were then used to compare psychiatric comorbidity and general wellbeing among those with early- versus late onset anxiety disorders, both in the general population and in an outpatient sample (ROM). **Chapter three** focuses on the characteristics of adult outpatients with anxiety disorders in three different age groups (18-25; 26-45; 46-65). In this explorative

---

[2] In chapter two, in addition to data collected with ROM, data collected in The Netherlands Mental health Survey and Incidence Study-2 have been used. This study is described in box 1.3.

study, a comparison between age groups was made with regard to a number of social demographic factors: gender, education level, employment, and living situation. In addition, comparisons with regard to diagnostic characteristics were made to determine if differences with regard to anxiety diagnoses, comorbid substance abuse or dependence, comorbid alcohol abuse or dependence, and comorbid dysthymic or major depressive disorder existed. Finally, the three age groups were compared with regard to anxiety symptom profile, general psychiatric symptom profile, and generic health status. In **chapter four**, prognostic factors in the course of anxiety disorders were identified. We used up to 2 years of naturalistic follow-up data to explore what baseline patient characteristics were associated with response to treatment. In **chapter five** we sought to evaluate prognostic factors in the course of suicidal ideation in anxious and/or depressed outpatients. Up to 2 years of naturalistic follow-up data were analysed to simultaneously evaluate a broad set of prognostic factors that were previously associated with remission of suicidal ideation. **Chapter six** expands on measurement scales for anxiety severity, by comparing self-report and observer-rated anxiety severity instruments. We described the overall level of concordance between both types of measures in a sample of outpatients with anxiety disorders. Subsequently, patients were categorized as concordant (agreement across both types of scales) or discordant (disagreement between both types of scales), and compared with regard to social demographic, clinical, and functional characteristics in order to identify correlates of concordance. Finally, in **chapter seven**, results described in the previous chapters are summarised. General relevance to literature and clinical implications will be discussed. Strengths and limitations of the study and of using clinical data in research will be considered, and finally directions for future research will be addressed.

Box 1.3 The Netherlands Mental Health and Incidence Study-2

The Netherlands Mental health Survey and Incidence Study-2 (NEMESIS-2) is a large epidemiologic survey in the Dutch general population ages 18-64. The first wave ran between November 2007 and July 2009, the response percentage was 65% and the sample adequately represented the Dutch population (de Graaf et al., 2012). In this study, 6646 respondents with sufficient command of the Dutch language were included through a multistage random sampling procedure, sampling one respondent per household by selecting the person with the most recent birthday. Structured interviews screening for psychiatric disorders were conducted during house visits by trained- and supervised lay-interviewers. Respondents provided written informed consent, and the study design was approved by the METIGG, a national mental healthcare ethics committee in The Netherlands. A more detailed description of the NEMESIS-2 design can be found in De Graaf et al. (2010).

Source: Based on De Graaf, R. et al., (2010) The Netherlands Mental health Survey and Incidence Study-2 (NEMESIS-2): design and methods. International Journal Of Methods in Psychiatric Research, 19(3):125-141.

Reference List

American Psychiatric Association (2000). Diagnostic and Statistical Manual of Mental Disorders, Fouth Edition, Text Revision (DSM-IV-TR). Washington DC: American Psychiatric Association.

Baldwin, D. S., Allgulander, C., Altamura, A. C., Angst, J., Bandelow, B., den Boer, J. et al. (2010). Manifesto for a European Anxiety Disorders Research Network. European Neuropsychopharmacology, 20, 426-432.

Baxter, A. J., Vos, T., Scott, K. M., Ferrari, A. J., & Whiteford, H. A. (2014). The global burden of anxiety disorders in 2010. Psychological Medicine, 44, 2363-2374.

Beesdo, K., Knappe, S., & Pine, D. S. (2009a). Anxiety and Anxiety Disorders in Children and Adolescents: Developmental Issues and Implications for DSM-V. Psychiatric Clinics of North America, 32, 483-+.

Bijl, R. V. & Ravelli, A. (2000). Psychiatric morbidity, service use, and need for care in the general population: results of The Netherlands Mental Health Survey and Incidence Study. Am.J.Public Health, 90, 602-607.

Black, N. (1996). Why we need observational studies to evaluate the effectiveness of health care. BMJ, 312, 1215-1218.

Bruce, S. E., Yonkers, K. A., Otto, M. W., Eisen, J. L., Weisberg, R. B., Pagano, M. et al. (2005). Influence of psychiatric comorbidity on recovery and recurrence in generalised anxiety disorder, social phobia, and panic disorder: A 12-year prospective study. American Journal of Psychiatry, 162, 1179-1187.

Craske, M. G. (1999). Anxiety disorders psychological approaches to theory and treatment. Oxford: Westview Press.

De Beurs, E., den Hollander-Gijsman, M. E., van Rood, Y. R., van der Wee, N. J. A., Giltay, E. J., van Noorden, M. S. et al. (2011). Routine Outcome Monitoring in the Netherlands: Practical Experiences with a Web-Based Strategy for the Assessment of Treatment Outcome in Clinical Practice. Clinical Psychology & Psychotherapy, 18, 1-12.

De Graaf R., ten Have M., van Gool C., & van Dorsselaer S. (2012). Prevalence of mental disorders and trends from 1996 to 2009. Results from the Netherlands Mental Health Survey and Incidence Study-2. Soc.Psychiatry Psychiatr Epidemiol., 47, 203-213.

Friedman, M. J., Resick, P. A., Bryant, R. A., Strain, J., Horowitz, M., & Spiegel, D. (2011). Classification of Trauma and Stressor-Related Disorders in Dsm-5. Depression and Anxiety, 28, 737-749.

Gustavsson, A., Svensson, M., Jacobi, F., Allgulander, C., Alonso, J., Beghi, E. et al. (2011). Cost of disorders of the brain in Europe 2010. European Neuropsychopharmacology, 21, 718-779.

Kessler, R. C. (2007). Psychiatric epidemiology: challenges and opportunities. Int.Rev.Psychiatry, 19, 509-521.

Kessler, R. C., Amminger, G. P., Aguilar-Gaxiola, S., Alonso, J., Lee, S., & Ustun, T. B. (2007). Age of onset of mental disorders: a review of recent literature. Current Opinion in Psychiatry, 20, 359-364.

Kessler, R. C., Berglund, P., Borges, G., Nock, M., & Wang, P. S. (2005). Trends in suicide ideation, plans, gestures, and attempts in the United States, 1990-1992 to 2001-2003. JAMA, 293, 2487-2495.

Kessler, R. C., Nelson, C. B., McGonagle, K. A., Liu, J., Swartz, M., & Blazer, D. G. (1996). Comorbidity of DSM-III-R major depressive disorder in the general population: results from the US National Comorbidity Survey. Br.J.Psychiatry Suppl, 17-30.

Lebeau, R. T., Glenn, D., Liao, B., Wittchen, H. U., Beesdo-Baum, K., Ollendick, T. et al. (2010). Specific Phobia: A Review of Dsm-Iv Specific Phobia and Preliminary Recommendations for Dsm-V. Depression and Anxiety, 27, 148-167.

Livesley, W. J. & Jackson, D. N. (2006). Manual for the dimensional assessment of personality problems - basic questionnaire. Port Huron, Michigan: Sigma.

Michael, T., Zetsche, U., & Margraf, J. (2007). Epidemiology of anxiety disorders. Psychiatry, 6, 135-170.

Penninx, B. W. J. H., Beekman, A. T. F., Smit, J. H., Zitman, F. G., Nolen, W. A., Spinhoven, P. et al. (2008a). The Netherlands Study of Depression and Anxiety (NESDA): rationale, objectives and methods. International Journal of Methods in Psychiatric Research, 17, 121-140.

Rhebergen, D., Batelaan, N. M., de Graaf, R., Nolen, W. A., Spijker, J., Beekman, A. T. et al. (2011). The 7-year course of depression and anxiety in the general population. Acta Psychiatr Scand., 123, 297-306.

Rochon, P. A., Gurwitz, J. H., Sykora, K., Mamdani, M., Streiner, D. L., Garfinkel, S. et al. (2005). Reader's guide to critical appraisal of cohort studies: 1. Role and design. BMJ, 330, 895-897.

Rothwell, P. M. (2005). Treating Individuals 1 - External validity of randomised controlled trials: "To whom do the results of this trial apply?. Lancet, 365, 82-93.

Scheibe, G. & Albus, M. (1992). Age at Onset, Precipitating Events, Sex Distribution, and Cooccurrence of Anxiety Disorders. Psychopathology, 25, 11-18.

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E. et al. (1998). The Mini-International Neuropsychiatric Interview (MINI): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. Journal of Clinical Psychiatry, 59, 22-33.

Sperry, L., Brill, P. L., Howard, K. I., & Grissom, G. R. (1996). Treatment outcomes in psychotherapy and psychiatric interventions. Philadelphia, PA: Brunner/Mazel.

Stein, D. J., Fineberg, N. A., Bienvenu, O. J., Denys, D., Lochner, C., Nestadt, G. et al. (2010). Should OCD be Classified As An Anxiety Disorder in DSM-V? Depression and Anxiety, 27, 495-506.

Thyer, B. A., Parrish, R. T., Curtis, G. C., Nesse, R. M., & Cameron, O. G. (1985). Ages of Onset of DSM-III Anxiety Disorders. Comprehensive Psychiatry, 26, 113-122.

van der Lem, R., van der Wee, N. J. A., van Veen, T., & Zitman, F. G. (2011). The generalizability of antidepressant efficacy trials to routine psychiatric out-patient practice. Psychological Medicine, 41, 1353-1363.

van Noorden, M. S., Minkenberg, S. E., Giltay, E. J., den Hollander-Gijsman, M. E., van Rood, Y. R., van der Wee, N. J. et al. (2011). Pre-adult versus adult onset major depressive disorder in a naturalistic patient sample: the Leiden Routine Outcome Monitoring Study. Psychological Medicine, 41, 1407-1417.

Vandenbroucke, J. P. (2008). Observational research, randomised trials, and two views of medical science. PLoS Med., 5, e67.

Wittchen, H. U., Jacobi, F., Rehm, J., Gustavsson, A., Svensson, M., Jonsson, B. et al. (2011). The size and burden of mental disorders and other disorders of the brain in Europe 2010. European Neuropsychopharmacology, 21, 655-679.

Zitman, F. G. (2012). [ROM in mood, anxiety and somatoform disorders: a promising technique with pleasing results]. Tijdschr.Psychiatr., 54, 173-177.

Chapter 2

A cluster analysis of early onset in common anxiety disorders

Abstract

Early onset is regarded as an important characteristic of anxiety disorders, associated with higher severity. However, previous findings diverge, as definitions of early onset vary and are often unsubstantiated. We objectively defined early onset in social phobia, panic disorder (with or without agoraphobia), agoraphobia (without panic), and generalised anxiety disorder, using cluster analysis with data gathered in the general population. Resulting cut-off ages for early onset were ≤22 for social phobia, ≤31 for panic disorder, ≤21 for agoraphobia, and ≤27 for generalised anxiety disorder. Comparison of psychiatric comorbidity and general wellbeing between subjects with early and late onset in the general population and an outpatient cohort, demonstrated that among outpatients anxiety comorbidity was more common in early onset agoraphobia, but also that anxiety- as well as mood comorbidity were more common in late onset social phobia. Our results encourage future studies into correlates of early onset of psychiatric disorders.

2.1. Introduction

Age of onset (AOO) is seen as an important clinical characteristic of psychiatric disorders (Kessler et al., 2007). Anxiety disorders form a class of disorders that, overall, are known to typically emerge early in life. Social phobia (SP) often has an onset in childhood or adolescence (Beesdo et al., 2009; Kessler et al., 2007; Thyer et al., 1985; Craske, 1999; Scheibe & Albus, 1992). In panic disorder (with or without agoraphobia; PD), as well as agoraphobia (without panic; AP), onset usually occurs during adolescence through mid-adulthood (Beesdo et al., 2009; Kessler et al., 2007; Thyer et al., 1985; Craske, 1999). Finally, for generalised anxiety disorder (GAD), adolescent-/early adult- (Beesdo et al., 2009; Scheibe & Albus, 1992), as well as mid adult- (Kessler et al., 2007; Thyer et al., 1985), and late adult onset are common (Craske, 1999). Anxiety disorders that have an early onset are thought to represent a subtype that is generally thought to be more severe. Early onset has been associated with higher symptom severity in SP (Van Ameringen et al., 2004), PD (Segui et al., 2000; Tibi et al., 2013), and GAD (Le Roux et al., 2005). In addition, more psychiatric comorbidity was found in early onset PD (Goodwin et al., 2001; Goldstein et al., 1997; Ramsawh et al., 2011; Segui et al., 1999; Tibi et al., 2013) and GAD (Le Roux et al., 2005; Campbell et al., 2003). Finally early onset was associated with more suicidality in PD (Iketani et al., 2004). It must be noted though, that these findings have been contradicted by studies reporting no association between early onset and symptom severity, comorbidity, or suicidality (Segui et al., 2000; Iketani et al., 2004; Segui et al., 1999; Le Roux et al., 2005).

These contradictory findings regarding correlates of early onset might be attributed to variations in definitions of early onset that were used in previous studies (Tibi et al., 2013). AOO has for example been approached as a continuous variable in SP (Van Ameringen et al., 2004), GAD (Campbell et al., 2003), and PD (Goodwin et al., 2001); but also through unsubstantiated cut-off ages, covering a wide age-range covering 9 (Van Ameringen et al., 2004) and 20 (Ramsawh et al., 2011) in SP; 18 (Segui et al., 1999), 20 (Goldstein et al., 1997; Ramsawh et al., 2011), 25 (Iketani et al., 2004), and 60 (Segui et al., 2000) in PD; and 20 (Ramsawh et al., 2011) and 50 (Le Roux et al., 2005) in GAD. The use of an objectively determined cut-off to define early onset could benefit the comparability of findings, as well as their translation to clinical practice. One method that has been suggested to empirically define age cut-offs for early- and late onset in various psychiatric disorders is model based clustering (Albert et al., 2015; Anholt et al., 2014; Bauer et al., 2010; Bellivier et al., 2001; Delorme et al., 2005; Hamshere et al., 2009; Ortiz et al., 2011; Panariello et al., 2010; Tibi et al., 2013; Tibi et al., 2015; Tozzi et al., 2011; Zhu et al., 2012). If early onset anxiety is a naturally occurring subtype within anxiety disorders, the distribution of age of onset of this subtype will be Gaussian (Delorme et al., 2005). Therefore, if we would describe the total AOO frequency

distribution of each disorder, separate normal distributions should be discernable. Description of the distinct normal distributions that can be detected in the AOO frequency distribution will allow the identification of early onset. Cut-points of the distributions can then be used to determine cut-offs for early onset. Cluster analysis can be used to define the number of distinct normal distributions, or clusters, that best fits the AOO frequency distribution. With regard to anxiety disorders, application of cluster analysis in previous studies has resulted in cut-offs of 27 years for PD (Tibi et al., 2013) and AP (Tibi et al., 2015). In these studies, both carried out in a sample containing a mix of treated as well as untreated subjects, early onset PD was associated with higher prevalence of AP and childhood trauma (Tibi et al., 2013). Early onset AP was associated with first-degree family history of anxiety disorders (Tibi et al., 2015). To date, to our knowledge, no attempt has been made to describe early onset of SP and GAD using cluster analysis.

In the present study we applied cluster analysis to age of onset data that were gathered in a large general population study to estimate early onset cut-offs for PD, AP, SP, and GAD. Subsequently, we compared psychiatric comorbidity as well as general wellbeing in subjects with early- and late onset PD, AP, SP, and GAD. In order to identify the relevance of early onset for clinical practice, the comparison of psychiatric comorbidity and wellbeing between early- and late onset anxiety was repeated in an outpatient sample. Based on previous studies (Van Ameringen et al., 2004; Campbell et al., 2003; Goodwin et al., 2001; Goldstein et al., 1997; Iketani et al., 2004; Le Roux et al., 2005; Ramsawh et al., 2011; Segui et al., 1999; Segui et al., 2000; Tibi et al., 2013; Tibi et al., 2015), we hypothesized that early onset would be associated with more psychiatric comorbidity and less wellbeing.

2.2. Materials and methods

2.2.1 Participants

AOO frequency data were collected in The Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2), a large epidemiologic survey in the Dutch general population ages 18-64. The first wave ran between November 2007 and July 2009. Structured interviews were conducted during house visits by trained- and supervised lay-interviewers. The response percentage was 65% and the sample adequately represented the Dutch population (de Graaf et al., 2010). Respondents provided written informed consent, and the study design was approved by the METIGG, a national mental healthcare ethics committee in The Netherlands. A more detailed description of the NEMESIS-2 design can be found in De Graaf et al. (2010). Although the NEMESIS-2 sample reflected the Dutch population well, younger subjects were

slightly under-represented; therefore, NEMESIS-2 data were weighted in analyses (de Graaf et al., 2010).

For the comparison of psychiatric comorbidity and general wellbeing between subjects with early- and late onset anxiety, in addition to the NEMESIS-2 general population sample, we used clinical data from the Leiden Routine Outcome Monitoring (ROM) Study. The Leiden ROM Study is a naturalistic study among outpatients at Rivierduinen, a regional mental healthcare provider, and at the department of psychiatry of the Leiden University Medical Centre in The Netherlands. Both centres treat patients who have been referred by their general practitioner for specialized treatment of mood-, somatoform- or anxiety disorders. As part of routine clinical practice, all patients between ages 18 and 65 were administered an extensive battery of diagnostic and psychometric measures by trained research nurses or through supervised computerized self-report. This procedure is known as ROM and is described in more detail by De Beurs et al. (2011). Inclusion during the study period January 2004 and September 2012 was estimated at 80% (van Noorden et al., 2011; Zitman, 2012). Data were anonymised and the ethical review board at the Leiden University Medical Centre approved their use in scientific research.

2.2.2 Measures

In the NEMESIS-2 sample, diagnostic information was collected using the Composite International Diagnostic Interview 3.0 (CIDI-3.0; Kessler & Ustun, 2004). The CIDI-3.0 has good validity (Haro et al., 2006). studies of earlier versions of the CIDI demonstrated good reliability with inter-rater reliabilities above 0.94 for anxiety disorders (Wittchen et al., 1991) and test-retest reliability above 0.57 for all anxiety disorders except GAD (κ=0.41) (Semler et al., 1987). In ROM, diagnostic information was collected with the MINI International Neuropsychiatric Interview-Plus (MINI-Plus; Sheehan et al., 1998; van Vliet et al., 2000). The MINI-Plus also has good psychometric properties, with inter-rater reliability between 0.88 and 1.00; test-retest reliability between 0.76 and 0.93; and adequate validity compared to the CIDI-1.0 (Lecrubier et al., 1997). The CIDI-3.0 and MINI-Plus were used to ascertain current (12-month) and lifetime Diagnostic Statistical Manual fourth edition (DSM-IV; NEMESIS-2) and DSM-IV-text revision (DSM-IV-TR; ROM) anxiety disorders (including post-traumatic stress disorder, specific phobia, and obsessive compulsive disorder), comorbid depressive and dysthymic disorders, and alcohol- and drug abuse and dependence. As in both samples all diagnostic information was collected through diagnostic screening instruments, no distinctions between primary and secondary diagnoses could be made.

In both the CIDI-3.0 and the MINI-Plus, AOO of anxiety disorders was assessed. In the MINI-plus, after confirming (past or present) diagnosis, the patient was asked: "How old were

you when you first experienced these symptoms?" In the CIDI-3.0, after confirming (past or present) diagnosis, the subject was asked: "Can you remember your exact age the very first time you experienced these symptoms?" If the subject did not provide an exact age, he/she was asked to provide an estimate. If the answer remained inconclusive, the subject was asked whether this occurred before the first year of school (AOO=4), before puberty (AOO=12) or not before puberty (AOO=13). For subjects who could not provide an AOO or stated that the disorder had always been present, AOO was considered missing.

In both samples general wellbeing was examined using the subscale general health perception of the Dutch version of the Short Form-36 (SF-36; Aaronson et al., 1998), a 36-item self-report survey. Measurement scales vary, ranging from yes/no to answers on a 3-, 5- or 6-point Likert-scale. Raw scores are linearly converted to 0-100 subscales, with higher scores representing higher levels of wellbeing. The SF-36 general health perception scale has moderate to good psychometric properties (Cronbach's alphas between 0.76 and 0.78 (Aaronson et al., 1998)). To facilitate interpretation, we used reference cut-off values for the general population (Schulte-van Maaren et al., 2012), with scores below the cut-off of 45 indicating poor functioning, and scores above the cut-off being in the normal range.

2.2.3 Statistical analyses

We applied 'mclust module version 5.0.2 for R: normal mixture modelling for model-based clustering, classification and density estimation' (Fraley & Raftery, 2002; Fraley et al., 2012) to the AOO data of NEMESIS-2 subjects with lifetime SP, PD, AP, and/or GAD. Mclust assumes that data represent a mixture of normal distributions without making prior assumptions regarding their size, number, or shape (Fraley & Raftery, 2002). Selection of the optimal number of clusters was based on the Bayesian Information Criteria (BIC). Group-membership and cut-off age were determined by calculating individual posterior probabilities of belonging to the resulting clusters.

For each disorder, the resulting cut-off for early onset was then used to compare subjects with early- and late onset current PD, AP, SP, and/or GAD with regard to psychiatric comorbidity (multiple anxiety disorders, depressive/dysthymic disorder, alcohol abuse or -dependence, drug abuse or -dependence), and general wellbeing (SF-36 general health subscale). These comparisons were made in the general population (NEMESIS-2) as well as the clinical (ROM) sample. For each disorder, the early onset cut-off was used as a lower limit for inclusion of subjects. Associations with early onset were analysed with multivariable logistic regression, adjusting for confounding by age and gender. Categorical data are presented as number (percentage), continuous variables are presented as mean (M; ±standard deviation; SD), odds ratios (OR) with 95% confidence intervals (CI) are provided. All tests were two-tailed

with p<0.05 denoting statistical significance, and corrected for multiple testing using Bonferroni adjustment. We used R version 3.2.2 (R foundation for Statistical Computing) and SPSS 20.0 (IBM Corp., Armonk, NY, USA).

2.3 Results

2.3.1 Cut-off for early onset in general population lifetime anxiety disorders

A total of 618 participants in the NEMESIS-2 study met diagnostic criteria for lifetime SP. For 3 participants no AOO could be established, therefore they were excluded. Mean age of the lifetime SP sample was 40.27 and 58.2% was female. A total of 251 subjects had lifetime PD, their mean age was 43.67 (SD=11.53) and 62.4% were female; 59 subjects met criteria for lifetime AP, one participant was unable to report an AOO and therefore had to be excluded. The average age in the lifetime AP sample was 44.37 years (SD=10.81) and 76.5% were female. Finally, 298 subjects met criteria for lifetime GAD, for 3 subjects no AOO could be established so they had to be excluded. The mean age in the lifetime GAD sample was 41.43 (SD=12.80) and 59.0% was female.

For SP, according to the BIC, model based cluster analysis yielded a best fitting model of two normally distributed clusters with equal variance. Based on the posterior probabilities, the early onset group ranged from AOO=4 to 22 (M=11.07; SD=4.28; n=575) and the late onset cluster ranged from AOO=23 to 58 (M=33.35; SD=8.48; n=40). Cluster analysis of the PD AOO data yielded a best fit with two normally distributed clusters with equal variance, with the early onset group ranging from AOO=4 to 31 (M=19.21; SD=7.05; n=174). Late onset ranged from AOO=32 to 61 (M=40.85; SD=7.12; n=77). The AP AOO distribution was best described by two normally distributed clusters with equal variance. The early onset group ranged from AOO=4 to 21 (M=14.01; SD=5.26; n=36); the late onset group ranged from AOO=23 to 49 (M=34.18, SD=7.54; n=22). Finally, the GAD AOO distribution was best described by three clusters with equal variances. The early onset cluster ranged from AOO=4 to 27 (M=15.95; SD=5.63; n=176), late onset could be divided in two groups: an intermediate group ranging from AOO=28 through 43 (M=34.42; SD=4.33; n=88) and a late onset group ranging from AOO=45 to 61 (M=50.84; SD=4.17; n=32). The results of the cluster analysis are shown in table 2.1 and figure 2.1.

Table 2.1 Classification of early onset in DSM-IV social phobia, panic disorder with or without agoraphobia, agoraphobia without panic, and generalised anxiety disorder

	No. clusters	Log likelihood	BIC	Cut-off for early onset	Early onset		Late onset	
					n	Mean AOO(±SD)	n	Mean AOO (±SD)
Lifetime SP (n=615)	1	-424.8398	-4327.266					
	2	-397.0027	-4057.627	22	575	11.07 (4.28)	40	33.35 (8.48)
	3	-2016.052	-4070.479					
Lifetime PD (n=251)	1	-200.5739	-2075.300					
	2	-198.7438	-2073.651	31	174	19.21 (7.05)	77	40.85 (7.12)
	3	-197.7456	-2076.267					
Lifetime AP (n=58)	1	-78.38744	-550.9114					
	2	-76.27216	-537.2767	21	36	14.01 (5.26)	22	34.18 (7.54)
	3	-76.12158	-545.4261					
Lifetime GAD (n=295)	2	-235.9144	-2420.752					
	3	-233.1117	-2414.178	27	175	15.95 (5.63)	110	38.79 (8.45)
	4	-233.0287	-2424.901					

DSM-IV denotes Diagnostic Statistical Manual fourth edition; AOO denotes age of onset; SD denotes standard deviation; BIC denotes Bayesian Information Criterion; SP denotes social phobia; PD denotes panic disorder (with or without agoraphobia); AP denotes agoraphobia (without panic); GAD denotes generalised anxiety disorder; classification of early- and late onset is based on the results of cluster analysis using the mclust module version 5.0.2 for R.

Figure 2.1 Distribution and classification of age of onset of DSM-IV social phobia (A), panic disorder with or without agoraphobia (B), agoraphobia without panic (C), and generalised anxiety disorder (D).
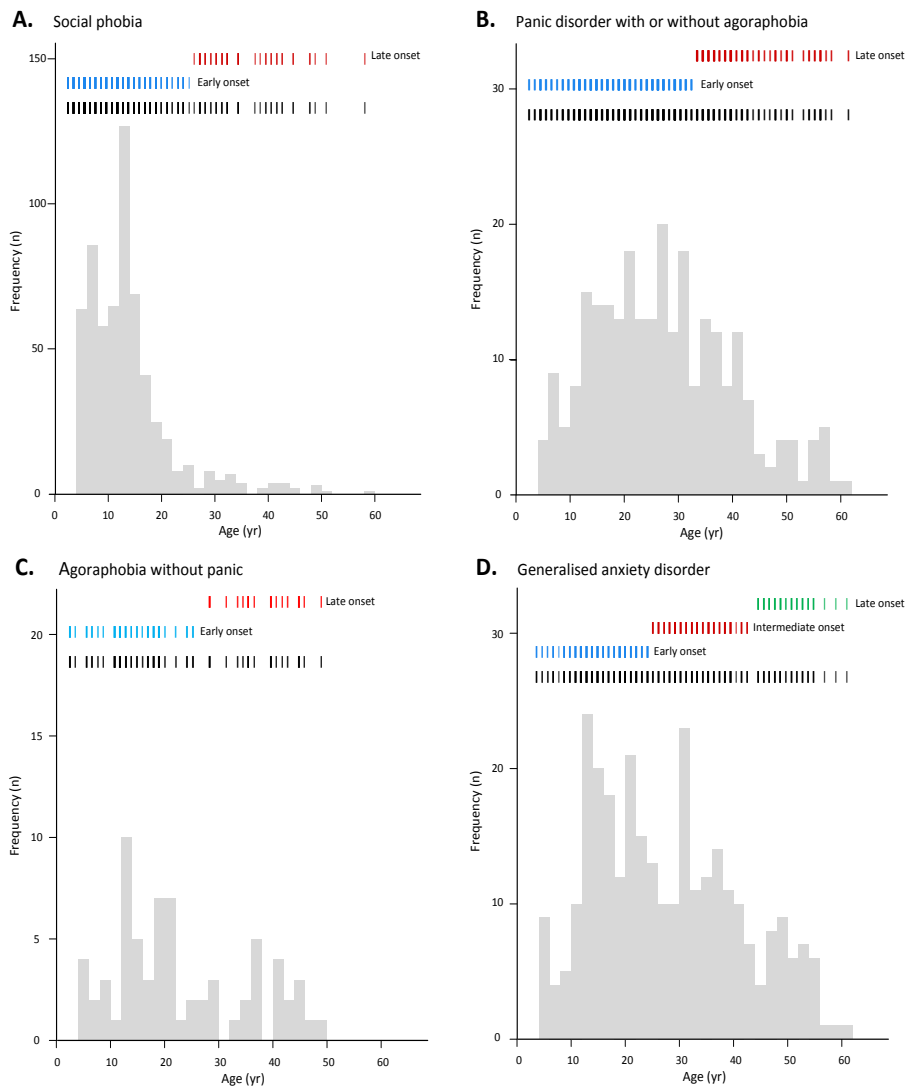
DSM-IV denotes Diagnostic Statistical Manual fourth edition; Classification of early- and late onset is based on the results of cluster analysis using the mclust module version 5.0.2 for R.

Table 2.2 Associations with early onset of anxiety disorder in general population subjects (NEMESIS-2) with DSM-IV social phobia, panic disorder with or without agoraphobia, agoraphobia without panic, or generalised anxiety disorder

	Early onset	Late onset	OR (95% CI)	p-value
Social phobia (n= 220)	*n=209 (95.0%)*	*n=11 (5.0%)*	*cut-off for early onset =22*	
Age (years) Mean (SD)	40.69 (10.51)	48.66 (9.88)		
Male gender n (%)	99 (47.5%)	5 (40.7%)		
Depressive/dysthymic	58 (27.8%)	5 (45.4%)	N.A.	N.A.
Alcohol abuse/dependence	29 (13.7%)	1 (10.2%)	N.A.	N.A.
Drug abuse/dependence	39 (18.8%)	2 (21.6%)	N.A.	N.A.
> 1 anxiety disorder	74 (35.7%)	6 (55.8%)	N.A.	N.A.
SF-36 general health below cut-off n (%)	56 (26.8%)	6 (49.7%)	N.A.	N.A.
Panic disorder (n=65)	*n=29 (44.6%)*	*n=36 (55.4%)*	*cut-off for early onset =31*	
Age (years) Mean (SD)	45.46 (7.53)	48.27 (8.68)		
Male gender n (%)	12 (40.6%)	21 (58.4%)		
Depressive/dysthymic	11 (38.2%)	9 (23.8%)	1.61 (0.53-4.93)	0.40
Alcohol abuse/dependence	4 (13.4%)	1 (3.8%)	5.02 (0.61-41.39)	0.13
Drug abuse/dependence	5 (18.4%)	2 (5.8%)	3.76 (0.66-21.37)	0.14
> 1 anxiety disorder	9 (31.3%)	6 (17.7%)	2.05 (0.62-6.81)	0.51
SF-36 general health below cut-off n (%)	11 (38.6%)	9 (24.2%)	0.45 (0.14-1.40)	0.17
Agoraphobia without panic (n= 25)	*n= 18 (72.0%)*	*n= 7 (28%)*	*cut-off for early onset =21*	
Age (years) Mean (SD)	43.32 (8.29)	45.60 (10.50)		
Male gender n (%)	5 (30.2%)	1 (13.5%)		
Depressive/dysthymic	8 (46.5%)	5 (69.8%)	N.A.	N.A.
Alcohol abuse/dependence	2 (10.4%)	0	N.A.	N.A.
Drug abuse/dependence	2 (10.4%)	0	N.A.	N.A.
> 1 anxiety disorder	14 (79.1%)	5 (68.2%)	N.A.	N.A.
SF-36 general health below cut-off n (%)	4 (53.5%)	9 (48.1%)	N.A.	N.A.

Generalised anxiety disorder (n=85)	n=47 (55.3%)	n=38 (44.7%)		cut-off for early onset =27
Age (years) Mean (SD)	43.11 (11.00)	48.03 (9.00)		
Male gender n (%)	18 (38.4%)	11 (28.1%)		
Depressive/dysthymic	21 (44.7%)	16 (41.1%)	1.00 (0.41-2.47)	1.00
Alcohol abuse/dependence	5 (10.8%)	1 (2.2%)	4.76 (0.43-52.78)	0.20
Drug abuse/dependence	8 (16.5%)	2 (4.1%)	4.67 (0.75-29.06)	0.09
> 1 anxiety disorder	17 (37.0%)	6 (16.1%)	3.27 (1.11-9.67)	0.03
SF-36 general health below cut-off n (%)	21 (44.8%)	21 (54.4%)	1.33 (0.55-3.24)	0.53

*Odds Ratios (OR) are presented with 95% confidence interval (CI) and p-value obtained in logistic regression analysis adjusted for age and gender with early onset as the higher coded category; NEMESIS-2 denotes Netherlands Mental Health Survey and Incidence Study-2; DSM-IV denotes Diagnostic Statistical Manual fourth edition; AOO denotes age of onset; SD denotes standard deviation; SF-36 denotes short form 36; SF-36 reference value cut-offs are based on 95th percentile scores in the general population reference group from the NormQuest study (Schulte-van Maaren et al. 2012); N.A. indicates a reliable assessment was not attainable because of low cell count; * indicates significant difference post-hoc with Bonferroni correction for multiple testing.*

Table 2.3 Associations with early onset of anxiety disorder in outpatients (ROM) with DSM-IV-TR social phobia, panic disorder with or without agoraphobia, agoraphobia without panic, or generalised anxiety disorder

	Early onset	Late onset	OR (95% CI)	p-value
Social phobia (n=1080)	*n=841 (77.9%)*	*n=239 (22.1%)*	*cut-off for early onset =22*	
Age (years) Mean (SD)	35.46 (10.60)	41.14 (9.57)		
Male gender n (%)	375 (44.6%)	125 (52.3%)		
Depressive/dysthymic	408 (48.5%)	142 (59.2%)	0.72 (0.53-0.97)	0.03
Alcohol abuse/dependence	67 (8.0%)	24 (10.0%)	0.92 (0.55-1.53)	0.74
Drug abuse/dependence	51 (6.1%)	16 (6.7%)	0.77 (0.42-1.40)	0.39
> 1 anxiety disorder	275 (32.7%)	109 (45.6%)	0.61 (0.45-0.83)	.001*
SF-36 general health below cut-off n (%)	344 (40.9%)	124 (51.9%)	0.69 (0.52-0.93)	0.02
Panic disorder (n= 877)	*n=439 (50.1%)*	*n=438 (49.9%)*	*cut-off for early onset =31*	
Age (years) Mean (SD)	40.51 (8.24)	45.66 (7.71)		
Male gender n (%)	188 (42.8%)	160 (36.5%)		
Depressive/dysthymic	206 (46.9%)	258 (58.9%)	0.71 (0.54-0.95)	0.02
Alcohol abuse/dependence	35 (8.0%)	28 (6.4%)	1.25 (0.73-2.18)	0.41
Drug abuse/dependence	16 (3.6%)	12 (2.7%)	1.46 (0.64-3.35)	0.37
> 1 anxiety disorder	96 (21.9%)	74 (16.9%)	1.37 (0.96-1.96)	0.08
SF-36 general health below cut-off n (%)	227 (51.7%)	211 (48.2%)	1.16 (0.88-1.54)	0.27
Agoraphobia without panic (n= 871)	*n=303 (34.8%)*	*n=568 (65.2%)*	*cut-off for early onset =21*	
Age (years) Mean (SD)	36.9 (11.73)	42.64 (10.23)		
Male gender n (%)	94 (31.0%)	188 (33.1%)		
Depressive/dysthymic	129 (42.6%)	319 (56.2%)	0.59 (0.44-0.79)	<.001*
Alcohol abuse/dependence	26 (8.6%)	38 (6.7%)	1.36 (0.79-2.33)	0.27
Drug abuse/dependence	28 (9.2%)	23 (4.0%)	1.05 (1.13-3.71)	0.02
> 1 anxiety disorder	114 (37.6%)	127 (22.4%)	2.04 (1.49-2.78)	<.001*
SF-36 general health below cut-off n (%)	147 (48.5%)	305 (53.75)	0.83 (0.62-1.11)	0.21

Generalised anxiety disorder (n=656)	n=391 (59.6%)	n=265 (40.4%)	cut-off for early onset =27
Age (years) Mean (SD)	40.49 (9.97)	45.78 (9.11)	
Male gender n (%)	149 (38.1%)	133 (50.2%)	
Depressive/dysthymic	196 (50.1%)	135 (50.9%)	1.10 (0.79-1.52) 0.58
Alcohol abuse/dependence	28 (7.2%)	15 (5.7%)	1.51 (0.77-2.95) 0.23
Drug abuse/dependence	13 (3.3%)	6 (2.3%)	1.55 (0.56-4.31) 0.40
> 1 anxiety disorder	143 (36.6%)	70 (26.4%)	1.47 (1.03-2.08) 0.03
SF-36 general health below cut-off n (%)	168 (43.0%)	122 (46.0%)	0.90 (0.65-1.25) 0.53

*Odds Ratios (OR) are presented with 95% confidence interval (CI) and p-value obtained in logistic regression analysis adjusted for age and gender with early onset as the higher coded category; ROM denotes Routine Outcome Monitoring; DSM-IV-TR denotes Diagnostic Statistical Manual fourth edition, text revision; AOO denotes age of onset; SD denotes standard deviation; SF-36 denotes short form 36; SF-36 reference value cut-offs are based on 95th percentile scores in the general population reference group from the NormQuest study (Schulte-van Maaren et al., 2012); * indicates significant difference post-hoc with Bonferroni correction for multiple testing.*

2.3.2 Application of cut-offs for early onset in current anxiety samples

2.3.2.1 General population current anxiety sample

In order to test the hypothesis that early onset of anxiety disorders was associated with psychiatric comorbidity and wellbeing, we applied the cut-offs for early onset to subjects with current anxiety disorders in the general population (NEMESIS-2) as well as in an outpatient setting (ROM). After application of the early onset cut-offs as a lower limit for inclusion, the general population SP sample consisted of 220 subjects, 209 of whom could be categorised as having early onset, and 11 as having late onset SP. The current PD general population sample consisted of 65 subjects, 29 had early onset and 36 had late onset PD. The general population current AP sample consisted of 25 subjects, 18 of whom had early onset, whereas 7 had late onset. Finally, the general population GAD sample consisted of 85 subjects, 47 with early onset, and 38 with late onset. Age, gender, psychiatric comorbidity, and general wellbeing scores of the general population current anxiety sample are shown in table 2.2. Due to the small sample sizes no test results could be calculated for the SP and AP samples. In PD and GAD no significant associations emerged.

2.3.2.1 Outpatient current anxiety sample

Application of the cut-off for early onset SP in the outpatient sample resulted in a sample of 1080 outpatients, 841 of whom had early onset and 239 had late onset. The current PD sample consisted of 877 patients, 439 of whom had early onset and 438 had late onset. The current AP sample consisted of 871 subjects, 303 could be classified as having early onset, and 568 had late onset AP. A total of 656 outpatients met diagnostic criteria for GAD, 391 had early onset and 265 had late onset. Associations between early onset and psychiatric comorbidity and wellbeing in the outpatient sample are shown in table 2.3. Among those with early onset SP, anxiety comorbidity was less common (32.7%) than in patients with late onset SP (59.2%; OR= 0.61; 95% CI=0.45-0.83; p=0.001). In AP, patients with early onset significantly less often had comorbid depressive or dysthymic disorder (42.6%) than patients with late onset (56.2%; OR=0.59; 95% CI=0.44-0.79; p<0.001). In addition, patients with early onset AP were more likely to have anxiety disorder comorbidity (37.6%) than those with late onset AP (22.4%; OR=2.04; 95% CI=1.49-2.78; p<0.001). In PD and GAD no significant associations between early onset psychiatric comorbidity or general wellbeing emerged.

2.4 Discussion

To our knowledge, this has been the first study to empirically define early onset in SP and GAD. In addition, we have attempted to replicate previously found cut-offs in PD and AP (Tibi et al., 2013; Tibi et al., 2015). We found that the AOO distribution of SP, PD, and AP has a bimodal fit. The cut-off age for SP was 22 (with early onset when AOO≤22; and late onset when AOO>22). The cut-off for PD was 31 (with early onset when AOO≤31; and late onset when AOO> 31), and the cut cut-off for AP was 21 (with early onset when AOO≤21; and late onset when AOO>21). The distribution of AOO in GAD was best described by three clusters with a cut-off for early onset at 27 (with early onset when AOO≤27; and late onset when AOO>27). Few associations between early onset and psychiatric comorbidity and general wellbeing emerged: we found anxiety comorbidity was more common in late onset SP, more depressive comorbidity in late onset AP, and more anxiety comorbidity in early onset AP. These associations only emerged in the outpatient samples and not in the general population samples, although this may be attributable to the small sizes of the current anxiety general population samples. Previous reports of higher prevalence of psychiatric comorbidity in PD (Goodwin et al., 2001; Goldstein et al., 1997; Ramsawh et al., 2011; Segui et al., 1999; Tibi et al., 2013), and GAD (Campbell et al., 2003; Le Roux et al., 2005) were not confirmed.

When comparing the cut-offs found in this study for SP and GAD with the (unsubstantiated) cut-offs that were used to distinguish early onset and late onset SP and GAD in previous studies, it appears that some were comparable (20 in SP (Ramsawh et al., 2011)), but others differed markedly (9 in SP (Van Ameringen et al., 2004), and 20 (Ramsawh et al., 2011) and 50 (Le Roux et al., 2005) in GAD). Our cut-off for early onset AP at 21 differs from the cut-off of 27 that was found previously in a similar study (Tibi et al., 2015). This is not surprising however, as Tibi et al. (2015) studied agoraphobia with or without panic, whereas our study focused on agoraphobia without panic disorder. The difference in the resulting cut-offs suggests that AP without PD may have an earlier onset than the comorbid state. Early onset PD was previously defined using cluster analysis at 27 (Tibi et al., 2013), our cut-off at 31 is somewhat later. However, it is clear that based on our and Tibi's (Tibi et al., 2013) results, the cut-off for early onset PD most likely lies around the late twenties/early thirties. This implies that previously used cut-offs of 18 (Segui et al., 1999), 20 (Goldstein et al., 1997; Ramsawh et al., 2011), and 60 (Segui et al., 2000), are likely to have been inappropriate for distinguishing early- and late onset PD.

Possibly, the difference between our cut off for early onset PD (31) and that found by Tibi et al. (27) (Tibi et al., 2013) stems from methodological differences. In the previous study AOO data were assessed in a sample that was gathered in the general population, primary care, and mental healthcare facilities (Penninx et al., 2008), whereas in the present study AOO

frequency data were gathered in a general population sample. This may be relevant, as in the sample used by Tibi et al. (Tibi et al., 2013; Tibi et al., 2015), subjects who sought help (in primary care or mental healthcare) were overrepresented relative to the general population. This help-seeking behaviour might be taken as an indication of higher severity or more impaired wellbeing, as it has been estimated that only 26.1% of those in the general population who meet diagnostic criteria for anxiety disorders actually seek help (Wittchen & Jacobi, 2005) As onset has been suggested to be associated with severity of the disorder, using a sample that over represents more severe cases, might distort the AOO distribution and the resulting cut-off. Our application of cluster analysis to data gathered in the general population might therefore have yielded different results. Another consideration is the use of current versus lifetime diagnoses. In the present study, the AOO frequency data of lifetime disorders were used, conversely, the studies by Tibi et al. (Tibi et al., 2013; Tibi et al., 2015) used AOO data of current cases. Including only those who currently meet diagnostic criteria for an anxiety disorder may also have implications for the distribution of AOO that is sampled. When including only current diagnoses, the sample will consist of younger as well as older subjects who have just experienced their first onset anxiety disorder, and of older subjects who have experienced early onset of an anxiety disorder that has become chronic or recurrent. However, as anxiety disorders can and do remit across the lifespan (Beesdo et al., 2009), the current anxiety sample will not contain the onsets of older subjects who had an early onset anxiety disorder that has remitted. Thus, sampling only current cases may negate part of the AOO distribution and, as such, influence the cut-off resulting from cluster analysis of that distribution. Consequently, our sampling the onset of lifetime anxiety disorders may have yielded different results. Further studies using cluster analysis are needed to replicate these findings.

Late onset SP was atypical in both our general population and our clinical sample. The finding of higher prevalence of anxiety comorbidity among outpatients with late onset SP, as well as the higher prevalence of mood disorders among those with late onset AP, could be hypothesized to reflect secondary onsets of these disorders. The late onset SP cases may have initially developed another disorder, to which the development of a social phobia came secondary. Although late onset AP was more common in our clinical sample, the higher prevalence of depression amongst late onset agoraphobics might similarly reflect elevated avoidance in chronic depression, leading to a secondary onset of AP in chronic depression. However, as our data are cross sectional and no information on primary or secondary diagnoses was available, these interpretations remain speculative. While findings of more psychiatric comorbidity in early onset PD and GAD, which had repeatedly been reported (Campbell et al., 2003; Goldstein et al., 1997; Goodwin et al., 2001; Le Roux et al., 2005; Ramsawh et al., 2011; Segui et al., 1999; Tibi et al., 2013) did not emerge, we did find more

anxiety comorbidity in early onset AP. Possibly, this erratic pattern of findings regarding comorbidity in early onset across studies, with repeated but not consistent reports of more comorbidity in early onset in various disorders, reflects a general element of chronicity in earlier onset cases. Perhaps the early onset cases are more likely to suffer from multiple disorders as a consequence of longer disease duration (Tibi et al., 2013). This would imply early onset as a subtype might be of less significance than disease duration (defined as total period of time during which the disorder was present). Unfortunately we did not have information on disease duration; therefore disease duration could not be included in analyses.

In addition to using general population data and lifetime diagnoses, our study is the first to describe cluster analysis of AOO data in SP and GAD. Further strong points are the use of a general population- as well as an outpatient sample when comparing psychiatric comorbidity and general wellbeing between those with early and late onset anxiety disorders. Our study does however also have some potential limitations. The size of the general population current anxiety disorder samples was small, especially for SP and AP. This did not allow for statistical analyses regarding psychiatric comorbidity and general wellbeing. In addition, as the primary aim of our study was the definition of early onset, a relatively small number of patient characteristics was incorporated (psychiatric comorbidity and general wellbeing) future studies could use the cut-offs for early onset to further explore associations between patient characteristics and early onset to replicate previous associations with suicidality, childhood trauma, and family history of anxiety disorders. A methodological consideration that could be noted is the fact that the current age of our cluster analysis sample (18-65) may have influenced the AOO frequency distribution: while all subjects would have had the chance to have experienced an AOO of 18, only those who had reached the age of 65 had been at risk for an AOO of 65. This may have skewed the AOO frequency distributions towards an overrepresentation of younger AOO's. Using lifetime anxiety data from a large older cohort might have yielded different results. Furthermore, the AOO of anxiety disorders was assessed retrospectively, which may have led to inaccurate reports (Simon & Vonkorff, 1995). However, this limitation holds for all previous studies using cluster analysis to determine a cut-off for early onset (Albert et al., 2015; Anholt et al., 2014; Bauer et al., 2010; Bellivier et al., 2001; Delorme et al., 2005; Hamshere et al., 2009; Ortiz et al., 2011; Panariello et al., 2010; Tibi et al., 2013; Tibi et al., 2015; Tozzi et al., 2011; Zhu et al., 2012). Retrospectively reported AOO has also been the norm in studies describing correlates of AOO in anxiety disorders (Goldstein et al., 1997; Goodwin et al., 2001; Iketani et al., 2004; Le Roux et al., 2005; Ramsawh et al., 2011; Segui et al., 1999; Segui et al., 2000; Van Ameringen et al., 2004) and studies describing AOO-distributions (Beesdo et al., 2009; Kessler et al., 2007; Scheibe & Albus, 1992; Thyer et al., 1985). However, a study by Kessler and Ustun (2004) on age of onset in psychiatric disorders did apply an adapted methodology, by asking a series of more elaborate questions geared

towards triggering autobiographical memory in order to improve accuracy (Knauper et al., 1999). Future studies could be improved through the use of this methodology. Finally, and perhaps most importantly, like many studies on the topic of AOO in anxiety disorders, our study did not take into account that anxiety disorders are often comorbid with other anxiety disorders and with other psychiatric disorders. It has been demonstrated that while anxiety disorders can occur in isolation, they can also be preceded by other anxiety disorders (broad homotypic continuity) and by other psychiatric disorders such as externalising disorders (heterotypic continuity; Beesdo et al., 2009). In this light, it might be thought valuable to study the onset of psychiatric morbidity in general over the lifespan of the individual, rather than classifying the onset of an isolated disorder as early or late.

2.5. Conclusion

In conclusion, we have empirically defined early onset of SP (AOO≤22), PD (AOO ≤31), AP (AOO ≤21), and GAD (AOO ≤27). Future studies of early onset in anxiety disorders should use empirically defined age cut-offs to further explore associations with early onset (Anholt et al., 2014; Tibi et al., 2013), and take into account psychiatric history. Although we found some evidence of higher prevalence of anxiety comorbidity in early onset AP, and late onset SP, as well as more mood comorbidity in late onset AP, in general, with regard to the four commonly occurring anxiety disorders in this study, our results did not show more psychiatric comorbidity or less wellbeing in early onset.

2.6. Acknowledgements

Reference List

Albert, U., Manchia, M., Tortorella, A., Volpe, U., Rosso, G., Carpiniello, B. et al. (2015). Admixture analysis of age at symptom onset and age at disorder onset in a large sample of patients with obsessive-compulsive disorder. Journal of affective disorders, 187, 188-196.

Aaronson, N. K., Muller, M., Cohen, P. D. A., Essink-Bot, M. L., Fekkes, M., Sanderman, R. et al. (1998). Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. Journal of Clinical Epidemiology, 51, 1055-1068.

Anholt, G. E., Aderka, I. M., van Balkom, A. J. L. M., Smit, J. H., Schruers, K., van der Wee, N. J. A. et al. (2014). Age of onset in obsessive-compulsive disorder: admixture analysis with a large sample. Psychological Medicine, 44, 185-194.

Bauer, M., Glenn, T., Rasgon, N., Marsh, W., Sagduyu, K., Munoz, R. et al. (2010). Association between age of onset and mood in bipolar disorder: Comparison of subgroups identified by cluster analysis and clinical observation. Journal of Psychiatric Research, 44, 1170-1175.

Beesdo, K., Knappe, S., & Pine, D. S. (2009). Anxiety and Anxiety Disorders in Children and Adolescents: Developmental Issues and Implications for DSM-V. Psychiatric Clinics of North America, 32, 483-524.

Bellivier, F., Golmard, J. L., Henry, C., Leboyer, M., & Schurhoff, F. (2001). Admixture analysis of age at onset in bipolar I affective disorder. Archives of General Psychiatry, 58, 510-512.

Campbell, L. A., Brown, N. A., & Grisham, J. R. (2003). The relevance of age of onset to the psychopathology of generalised anxiety disorder. Behavior Therapy, 34, 31-48.

Craske, M. G. (1999). Anxiety disorders psychological approaches to theory and treatment. Oxford: Westview Press.

de Graaf, R., ten Have, M., & van Dorsselaer, S. (2010). The Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2): design and methods. International Journal of Methods in Psychiatric Research, 19, 125-141.

Delorme, R., Golmard, J. L., Chabane, N., Millet, B., Krebs, M. O., Mouren-Simeoni, M. C. et al. (2005). Admixture analysis of age at onset in obsessive-compulsive disorder. Psychological Medicine, 35, 237-243.

Fraley, C., Raftery, A. E., Murphy, T. B., & Scrucca L. (2012). Mclust Version 4 for R: Normal Mixture Modeling for Model-Based Clustering, Classification, and Density Estimation Technical Report No. 597, Department of Statistics, University of Washington.

Fraley C. & Raftery A. E. (2002). Model-based Clustering, Discriminant Analysis and Density Estimation. Journal of the American Statistical Association, 97, 611-631.

Goldstein, R. B., Wickramaratne, P. J., Horwath, E., & Weissman, M. M. (1997). Familial aggregation and phenomenology of 'early'-onset (at or before age 20 years) panic disorder. Archives of General Psychiatry, 54, 271-278.

Goodwin, R., Lipsitz, J. D., Chapman, T. F., Mannuzza, S., & Fyer, A. J. (2001). Obsessive-compulsive disorder and separation anxiety co-morbidity in early onset panic disorder. Psychological Medicine, 31, 1307-1310.

Hamshere, M. L., Gordon-Smith, K., Forty, L., Jones, L., Caesar, S., Fraser, C. et al. (2009). Age-at-onset in bipolar-I disorder: Mixture analysis of 1369 cases identifies three distinct clinical sub-groups. Journal of Affective Disorders, 116, 23-29.

Haro, J. M., Arbabzadeh-Bouchez, S., Brugha, T. S., De Girolamo, G., Guyer, M. E., Jin, R. et al. (2006). Concordance of the composite international diagnostic interview version 3.0 (CIDI 3.0) with standardized clinical assessments in the WHO World Mental Health Surveys. International Journal of Methods in Psychiatric Research, 15, 167-180.

Iketani, T., Kiriike, N., Stein, M. B., Nagao, K., Minamikawa, N., Shidao, A. et al. (2004). Patterns of axis II comorbidity in early-onset versus late-onset panic disorder in Japan. Comprehensive Psychiatry, 45, 114-120.

Kessler, R. C., Amminger, G. P., Aguilar-Gaxiola, S., Alonso, J., Lee, S., & Ustun, T. B. (2007). Age of onset of mental disorders: a review of recent literature. Current Opinion in Psychiatry, 20, 359-364.

Kessler, R. C. & Ustun, T. B. (2004). The World Mental Health (WMH) Survey Initiative version of the World Health Organization (WHO) Composite International Diagnostic Interview (CIDI). International Journal of Methods in Psychiatric Research, 13, 93-121.

Knauper, B., Cannel, C. F., Schwarz, N., Bruce, M. L., & Kessler, R. C. (1999). Improving accuracy of major depression age-of-onset reports in the US National Comorbidity Survey. International Journal of Methods in Psychiatric Research, 8, 39-48.

Le Roux, H., Gatz, M., & Wetherell, J. L. (2005). Age at onset of generalised anxiety disorder in older adults. American Journal of Geriatric Psychiatry, 13, 23-30.

Lecrubier, Y., Sheehan, D. V., Weiller, E., Amorim, P., Bonora, I., Sheehan, K. H. et al. (1997). The Mini International Neuropsychiatric Interview (MINI). A short diagnostic structured interview: Reliability and validity according to the CIDI. European Psychiatry, 12, 224-231.

Ortiz, A., Bradler, K., Slaney, C., Garnham, J., Ruzickova, M., O'Donovan, C. et al. (2011). An admixture analysis of the age at index episodes in bipolar disorder. Psychiatry Research, 188, 34-39.

Panariello, F., O'Driscoll, L., de Souza, R. P., Tiwari, A., Manchia, M., Kennedy, J. et al. (2010). Age at onset in Canadian Schizophrenia patients: Admixture analysis. Schizophrenia Research, 122, 278-279.

Penninx, B. W. J. H., Beekman, A. T. F., Smit, J. H., Zitman, F. G., Nolen, W. A., Spinhoven, P. et al. (2008). The Netherlands Study of Depression and Anxiety (NESDA): rationale, objectives and methods. International Journal of Methods in Psychiatric Research, 17, 121-140.

Ramsawh, H. J., Weisberg, R. B., Dyck, I., Stout, R., & Keller, M. B. (2011). Age of onset, clinical characteristics, and 15-year course of anxiety disorders in a prospective, longitudinal, observational study. Journal of Affective Disorders, 132, 260-264.

Scheibe, G. & Albus, M. (1992). Age at Onset, Precipitating Events, Sex Distribution, and Cooccurrence of Anxiety Disorders. Psychopathology, 25, 11-18.

Schulte-van Maaren, Y. W. M., Carlier, I. V. E., Zitman, F. G., van Hemert, A. M., de Waal, M. W. M., van Noorden, M. S. et al. (2012). Reference values for generic instruments used in routine outcome monitoring: the leiden routine outcome monitoring study. Bmc Psychiatry, 12.

Segui, J., Marquez, M., Garcia, L., Canet, J., Salvador-Carulla, L., & Ortiz, M. (1999). Differential clinical features of early-onset panic disorder. Journal of Affective Disorders, 54, 109-117.

Segui, J., Salvador-Carulla, L., Marquez, M., Garcia, L., Canet, J., & Ortiz, M. (2000). Differential clinical features of late-onset panic disorder. Journal of Affective Disorders, 57, 115-124.

Semler, G., Wittchen, H. U., Joschke, K., Zaudig, M., Vongeiso, T., Kaiser, S. et al. (1987). Test-Retest Reliability of A Standardized Psychiatric Interview (Dis/Cidi). European Archives of Psychiatry and Clinical Neuroscience, 236, 214-222.

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E. et al. (1998). The Mini-International Neuropsychiatric Interview (MINI): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. Journal of Clinical Psychiatry, 59, 22-33.

Simon, G. E. & Vonkorff, M. (1995). Recall of Psychiatric History in Cross-Sectional Surveys - Implications for Epidemiologic Research. Epidemiological Reviews, 17, 221-227.

Thyer, B. A., Parrish, R. T., Curtis, G. C., Nesse, R. M., & Cameron, O. G. (1985). Ages of Onset of Dsm-III Anxiety Disorders. Comprehensive Psychiatry, 26, 113-122.

Tibi, L., van Oppen, P., Aderka, I. M., van Balkom, A. J. L. M., Batelaan, N. M., Spinhoven, P. et al. (2013). Examining determinants of early and late age at onset in panic disorder: An admixture analysis. Journal of Psychiatric Research, 47, 1870-1875.

Tibi, L., van Oppen, P., Aderka, I. M., van Balkom, A. J. L. M., Batelaan, N. M., Spinhoven, P. et al. (2015). An admixture analysis of age of onset in agoraphobia. Journal of affective disorders, 180, 112-115.

Tozzi, F., Manchia, M., Galwey, N. W., Severino, G., Del Zompo, M., Day, R. et al. (2011). Admixture analysis of age at onset in bipolar disorder. Psychiatry Research, 185, 27-32.

Van Ameringen, M., Oakman, J., Mancini, C., Pipe, B., & Chung, H. (2004). Predictors of response in generalised social phobia: Effect of age of onset. Journal of Clinical Psychopharmacology, 24, 42-48.

van Noorden, M. S., Minkenberg, S. E., Giltay, E. J., den Hollander-Gijsman, M. E., van Rood, Y. R., van der Wee, N. J. et al. (2011). Pre-adult versus adult onset major depressive disorder in a naturalistic patient sample: the Leiden Routine Outcome Monitoring Study. Psychological Medicine, 41, 1407-1417.

van Vliet, I. M., Leroy, H., & van Megen, H. J. G. M. (2000). MINI internationaal neuropsychiatrisch interview nederlandse versie 5.0.0. (5 ed.) Utrecht.

Wittchen, H. U. & Jacobi, F. (2005). Size and burden of mental disorders in Europe - a critical review and appraisal of 27 studies. European Neuropsychopharmacology, 15, 357-376.

Wittchen, H. U., Robins, L. N., Cottler, L. B., Sartorius, N., Burke, J. D., & Regier, D. (1991). Cross-Cultural Feasibility, Reliability and Sources of Variance of the Composite International Diagnostic Interview (Cidi). British Journal of Psychiatry, 159, 645-653.

Zhu, T. N., De Luca, V., Gallaugher, L. A., Woldeyohannes, H. O., Soczynska, J. K., Szymkowicz, S. et al. (2012). Admixture analysis of age at onset in major depressive disorder. General Hospital Psychiatry, 34, 686-691.

Zitman, F. G. (2012). [ROM in mood, anxiety and somatoform disorders: a promising technique with pleasing results]. Tijdschr.Psychiatr., 54, 173-177.

Chapter 3

Age related characteristics of outpatients with anxiety disorders: The Leiden Routine Outcome Monitoring Study

Abstract

It has been hypothesised that clinically important differences between adults with anxiety disorders in different age groups exist. However, to date, large scale epidemiological studies comparing adults in different age groups and using standardised instruments are scarce. We analysed data from 1950 outpatients who were diagnosed with DSM-IV-TR panic disorder (with or without agoraphobia), agoraphobia (without panic), social phobia, and /or generalised anxiety disorder. Patients were divided in three age groups: young adult (18-25; n=435), mid-adult (26-40; n=788), and older adult (41-65; n=727). The three age groups were compared with regard to social demographic characteristics, diagnostic characteristics, anxiety symptom profile, general psychiatric symptom profile, and generic health status. Overall, patients had an average age of 36.48 years (standard deviation 11.71), 62.8% were female. A number of differences between the three age groups emerged: older patients were more often male, unemployed, living with a partner, and had lower education levels. With regard to clinical characteristics, older patients were more often diagnosed with agoraphobia and comorbid depression, younger patients were more likely to have social phobia. Anxiety symptom profiles of older patients showed more aches and pains, inner tension, and sleep problems, whereas younger patient had higher levels of hostility. The general psychiatric symptom profiles of younger patients showed elevated scores on measures of interpersonal sensitivity and hostility. With regard to generic health status, older patients experienced lower levels of physical functioning and vitality, while they had more physical problems, role limitations due to emotional problems, and pain. Our findings show that clinically relevant differences exist between younger and older adult outpatients with anxiety disorders. Clinicians should take these findings into account, as insight in these differences may help clinicians to better recognise the needs of patients and adapt prevention and treatment accordingly.

3.1 Introduction

Adult psychiatry is generally regarded as a uniform concept, with homogenous treatment protocols and guidelines. However, between an 18-year old and a 60-year old patient who are diagnosed with an anxiety disorder, numerous differences may exist. Age related differences in the adult population may for example be incidental to changes in physical health associated with aging. In addition, social demographic cohort differences, such as lower education levels and related competitive disadvantages in the labour market among older subjects, could impact emotionality (Schieman et al., 2001). More generally speaking, adulthood can be divided in several life phases (Wong et al., 2015). During early adulthood (ages 18-25), achieving social, psychological and financial independence are central. Mid-adulthood (ages 26-40), is generally marked by growing responsibilities that come with career development and family planning. During late adulthood (ages 41-65), interests generally shift to social responsibility, caregiving duties, helping the next generation, and adjusting to approaching retirement and post-work identity (Wong et al., 2015). Together, these physical changes, cohort differences, and life phases may impact the symptomatology and presentation of anxiety disorders, which in turn, may require different diagnostic and therapeutic approaches from health care professionals (Schneider et al., 2004; Husain et al., 2005).

Numerous studies have focussed on differences between child/adolescent or geriatric subjects with anxiety disorders relative to the adult population. In general, child and adolescent, as well as adult subjects with anxiety disorders were more likely to present with irritability symptoms than geriatric subjects (Lenze & Wetherell, 2011). Furthermore, among geriatric subjects (ages 65 and over), panic was less prevalent than among adults (ages 18-65), and worry content shifted from work related to health related (Wolitzky-Taylor et al., 2010). Similarly, the content of social fear in adults (ages 18-59) centred on speaking in public and catastrophizing on social situations, whereas geriatric subjects (ages 60-94) feared a greater number of situations (Gretarsdottir et al., 2004). Finally, fatigue and cognitive dysfunction, like memory complaints and concentration difficulties were more prominent geriatric patients (Lenze & Wetherell, 2011).

To date, however, the phenomenology of anxiety across the adult life span has not been studied. Comparisons of adult subjects according to age have been made in depression. As anxiety and depression are often comorbid, and have been suggested to share many features (Barlow et al., 1986), these findings might hold relevance to anxiety disorders. In depression, older patients (older than 50) had more general medical comorbidities, more insomnia, and less irritability than younger adult patients (Husain et al., 2005). Also, older patients had less negative views of themselves as well as their future (Husain et al., 2005), while in younger depressed adults (younger than 45), suicidal ideation, suicide attempts,

irritability, anhedonia, and persistence of symptoms between episodes were more frequent (Wilkowska-Chmielewska et al., 2013). Finally, older subjects were less likely to be diagnosed with comorbid generalised anxiety disorder (GAD), social phobia/social anxiety disorder (SP), panic disorder, or drug abuse (Husain et al., 2005).

In the present study, age related differences between adult outpatients diagnosed with a set of frequently occurring anxiety disorders were explored in order to identify clinically relevant correlates of age. We focused on outpatients diagnosed with DSM-IV-TR panic disorder (with or without agoraphobia; PD), agoraphobia (without panic; AP), SP, and GAD. We compared data on a broad set of social demographic, clinical and functional characteristics. Several hypotheses could be formulated: we expected older patients to have lower education levels, to more often live with a partner, and to be employed less often. Based on comparisons between child- and adolescent and geriatric subjects with adults (Lenze & Wetherell, 2011) as well as findings in depression (Husain et al., 2005), we expected more irritability in younger patients, and more health related worry in older patients. In addition, we expected older patients to have more physical complaints, more sleep problems, less vitality and more pain. However, no hypotheses were specified regarding clinical characteristics and symptomatology. In order to fully explore associations with age, we therefore examined age related differences allowing for non-linear associations, as well as linear associations. This study is the first to examine age related differences among adults with anxiety disorders. Findings may help clinicians to better adapt treatment to the needs of individual patients.

3.2 Method

3.2.1 Routine Outcome Monitoring

As part of routine practice at the facilities involved in this study, all patients completed an extensive battery of self-report and observer-rated measures at intake. This procedure is known as Routine Outcome Monitoring (ROM), and is described in more detail by De Beurs et al. (2011). Both generic and disorder-specific questionnaires were administered by trained psychiatric nurses and through supervised computerized self-report which prevented missing data within questionnaires. Although participation in ROM is voluntary, inclusion is high with an estimated 80% of all patients being assessed at intake. (van Noorden et al., 2011; Zitman, 2012) Although the primary goal of ROM is to inform both clinicians and patients, data were anonymised and their use in scientific research was approved by the Ethical Review Board at the Leiden University Medical Centre (LUMC).

3.2.2 Patients and procedure

Subjects were outpatients who had been referred for treatment by their general practitioner to Rivierduinen, a regional mental healthcare provider, or the psychiatry department of the LUMC between January 2004 and October 2010. Inclusion criteria held that patients must be between ages 18 and 65, have adequate command of the Dutch language and meet DSM-IV-TR diagnostic criteria for one or more of the following disorders: PD, AP, SP or GAD; with moderate to severe anxiety. Moderate to severe anxiety severity was assessed using a self-report as well as an observational measure: the Dutch versions of the Brief Symptom Inventory-12 item version (BSI-12; Roy-Byrne et al., 2010), a self-report anxiety measure derived from the BSI (De Beurs & Zitman, 2006; Derogatis & Melisaratos, 1983), and the observer-rated Brief Anxiety Scale (BAS; Tyrer et al., 1984), (see measures section). Moderate to severe baseline severity was defined as ≥10.38 on the BAS (Tyrer et al., 1984; Schat et al., 2013), equalling the average BAS score in a group of general practice patients diagnosed with anxiety disorders (Tyrer et al., 1984), and ≥6 on the BSI-12 (Schat et al., 2013), with scores <6 signifying no- to mild anxiety (Roy-Byrne et al., 2010). Missing data resulting from the incidental failure to administer complete questionnaires and from large time intervals (more than 21 days) between administration of questionnaires served as exclusion criteria.

3.2.3 Measures

In addition to patients' age and gender, education level (low: primary-lower secondary versus high: higher secondary-university), living situation (with versus without partner), and employment status (full- or part-time employed versus unemployed) were assessed. The Dutch version of the MINI International Neuropsychiatric Interview-Plus (MINI-Plus; Sheehan et al., 1998; Van Vliet & De Beurs, 2007) was used to collect diagnostic information. The MINI-Plus has good psychometric properties (Lecrubier et al., 1997), and was used to determine the presence of DSM-IV-TR anxiety disorders, comorbid depressive or dysthymic disorders, alcohol abuse or -dependence and drug abuse or -dependence. The number of comorbid anxiety disorders (including comorbid specific phobia) was dichotomized into "single anxiety disorder" versus "multiple anxiety disorders." Anxiety symptoms were assessed using the BAS (Tyrer et al., 1984). The BAS is a 10-item observer-rated scale, derived from the abbreviated Comprehensive Psychopathological Rating Scale (CPRS; Åsberg et al., 1978; Goekoop et al., 1992). The total score equals the sum-score of all 10 items on a 7-point Likert scale (0-6; range 0-60). The BAS assesses the main components of all anxiety disorders, covering psychological and somatic components, a higher score corresponds to more severe anxiety. The BSI (De Beurs & Zitman, 2006; Derogatis & Melisaratos, 1983) was used to assess a general psychiatric

symptom profile. The BSI is a self-report measure consisting of 53 items on a 5-point Likert scale (0-4; range 0-48). A total of 9 subscales (somatisation, obsessive compulsive symptoms, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, psychoticism) can be obtained by averaging the corresponding items. Generic health status was examined using the Dutch version of the Short Form-36 (SF-36; Ware & Sherbourne, 1992; Aaronson et al., 1998), a 36-item self-report survey screening eight domains of general health: physical functioning, social functioning, role limitations due to physical health problems, role limitations due to emotional problems, general mental health perception, vitality, bodily pain, and general health perception. Measurement scales vary per subscale, ranging from yes/no to answers on a 3-, 5- or 6-point Likert scale. All raw scores are linearly converted to 0-100 subscales, with higher scores representing higher levels of functioning or wellbeing. However, to facilitate comparability to other measures, SF-36 scores were inverted so that higher scores reflect poorer generic health.

3.2.4 Statistical analyses

Categorical characteristics are presented as number (percentage), continuous variables are presented as mean (M) (± standard deviation (SD)). Comparisons between included and excluded patients were made using χ^2 for categorical, and independent samples t-tests for continuous variables. Based on previous studies, patients were divided into 3 cohorts: age 18-25; 26-40 and 41-65 (van Noorden et al., 2011; Regier et al., 1990; Somers et al., 2006; Robins et al., 1984). Age groups were compared with regard to demographic variables, diagnostic variables, anxiety symptom profile (BAS), general psychiatric symptom profile (BSI), and generic health status (SF-36). Comparisons between the three age groups were made using χ^2 or ANOVA for categorical and continuous variables respectively, with pair-wise post-hoc comparisons. For overall comparisons Cramer's V or Eta squared were calculated, for pair-wise post-hoc comparisons, phi and Cohen's d were computed. To test whether associations fitted a linear shape, in addition, all variables were examined in linear regression. Significance level was set at $p<0.05$; Bonferroni correction for multiple testing was applied. Data were analysed using SPSS version 20.0 (IBM Corp., Armonk, NY, USA).

### 3.3 Results

3.3.1 Sample characteristics

Between January 2004 and October 2010, a total of 2214 patients met DSM-IV-TR diagnostic criteria for PD, AP, SP, and GAD with at least moderate severity. 264 patients (11.9%) had to be

excluded, as they had missing data, or a large time gap (more than 21 days) existed between completion of distinct questionnaires. The latter criterion was set to guarantee that all assessments had taken place at intake. Therefore, 1950 patients (88.1%) were included for analyses. Figure 3.1 shows a flowchart of inclusion and exclusion. Although differences between included and excluded patients with regard to BAS item 'aches and pains,' BSI subscales 'cognitive distortion,' 'hostility,' and 'phobic anxiety,' and SF-36 subscale 'bodily pain' were significant at $p<0.05$ after Bonferroni correction, these differences were very small, with eta squares ranging from 0.001 to 0.01 (results not shown). Of the total sample, 62.8% was female, mean age was 36.48. A total of 816 patients (42%) was diagnosed with PD, 433 (22%) patients with AP, 586 patients (30%) with SP, and 440 patients (23%) with GAD. Patients were divided according to age in early adult (age 18-25; n=435), mid-adult (age 26-40; n=788) and late adult (age 41-65; n=727).

Figure 3.1 Flowchart of inclusion
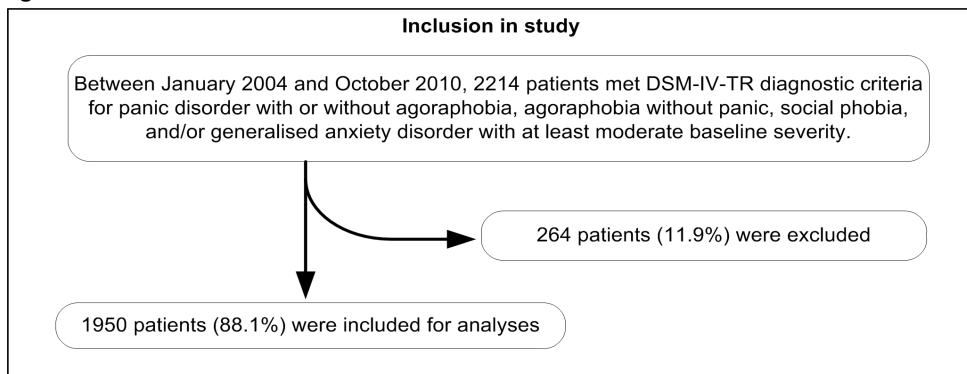
DSM-IV-TR denotes Diagnostic Statistical Manual-fourth edition, text revision

3.3.2 Differences between age groups

3.3.2.1 Social demographic and clinical characteristics

Social demographic and clinical comparisons across the three age groups with pairwise post-hoc analyses with Bonferroni correction as well as results for regression analyses are summarised in table 3.1. Significant associations with age emerged for gender, employment, education level, living situation, and comorbid depression. The percentage of men increased with age (28.0% in the early adult group, 36.5% in the mid-adult, and 43.3% in the late adult group). The percentage of patients with a part-time or fulltime job decreased with age (46.6% in the early adult group, 47.0% in the mid-adult group, and 37.7% in the late adult group), as did the number of patients with a high education level (65.5% in the early adult group, 60.8% in

did the number of patients with a high education level (65.5% in the early adult group, 60.8% in the mid-adult group, and 47.9% in the late adult group). Older patients were more likely to live with a partner than younger patients (22.3% in the early adult group, 58.1% in the mid-adult group, and 64.4% in the late adult group).Younger patients were less likely to have a comorbid depressive disorder (48.5% in the early adult group, 51.6% in the mid-adult group, and 60.8% in the late adult group). The distribution of the four included DSM-IV-TR anxiety diagnoses (PD, AP, SP, and GAD) across the three age groups is shown in figure 3.2. AP was more prevalent with increasing age (17.2%) in the early adult group, 18.8% in the mid-adult group, and 28.9% in the late adult group). The number of patients with SP on the other hand decreased with age (39.8% in the early adult group, 30.7% in the mid-adult group, and 23.5% in the late adult group).

3.3.2.2 Anxiety symptoms

Comparisons of anxiety symptoms across the three age groups with pairwise post-hoc analyses with Bonferroni correction, as well as results for regression analyses are shown in table 3.2. Significant differences between the three age groups emerged on the items aches and pains, inner tension, and reduced sleep. Complaints of aches and pains increased with age (early adult group M=1.93, SD=1.37; mid-adult group M=2.09, SD=1.45; late adult group M=2.29, SD=1.52), as did levels of inner tension (early adult group M=3.03, SD=1.00; mid-adult group M=3.15, SD=1.01; late adult group M=3.29, SD=1.00), and sleep problems (early adult group M=1.81, SD=1.59; mid-adult group M=2.22, SD=1.68; late adult group M=2.43, SD=1.74). Although group-wise comparisons were not statistically significant, regression analyses showed a decrease in hostility scores with age.

3.3.2.3 General psychiatric symptoms

Table 3.3 shows comparisons of general psychiatric symptoms across the three age groups with pairwise post-hoc analyses with Bonferroni correction, as well as results for regression analyses. With regard to psychiatric symptoms, significant differences between the three age groups emerged on measures of interpersonal sensitivity, hostility, and on observed depression. Levels of interpersonal sensitivity decreased with age (early adult group M=2.06, SD=1.08; mid-adult group M=1.94, SD=0.94; late adult group M=1.73, SD=1.06), as did levels of self-reported hostility (early adult group M=1.18, SD=8.30; mid-adult group M=1.12, SD=0.92; late adult group M=0.95, SD=0.85). Observed depression scores on the other hand, increased with age (early adult group M=18.69, SD=8.30; mid-adult group M=20.38, SD=8.31; late adult group M=21.82, SD=8.54).

Figure 3.2 Anxiety diagnoses per age group in 1950 outpatients diagnosed with DSM-IV-TR anxiety disorders (panic disorder with or without agoraphobia, agoraphobia without panic, social phobia and/or generalised anxiety disorder).
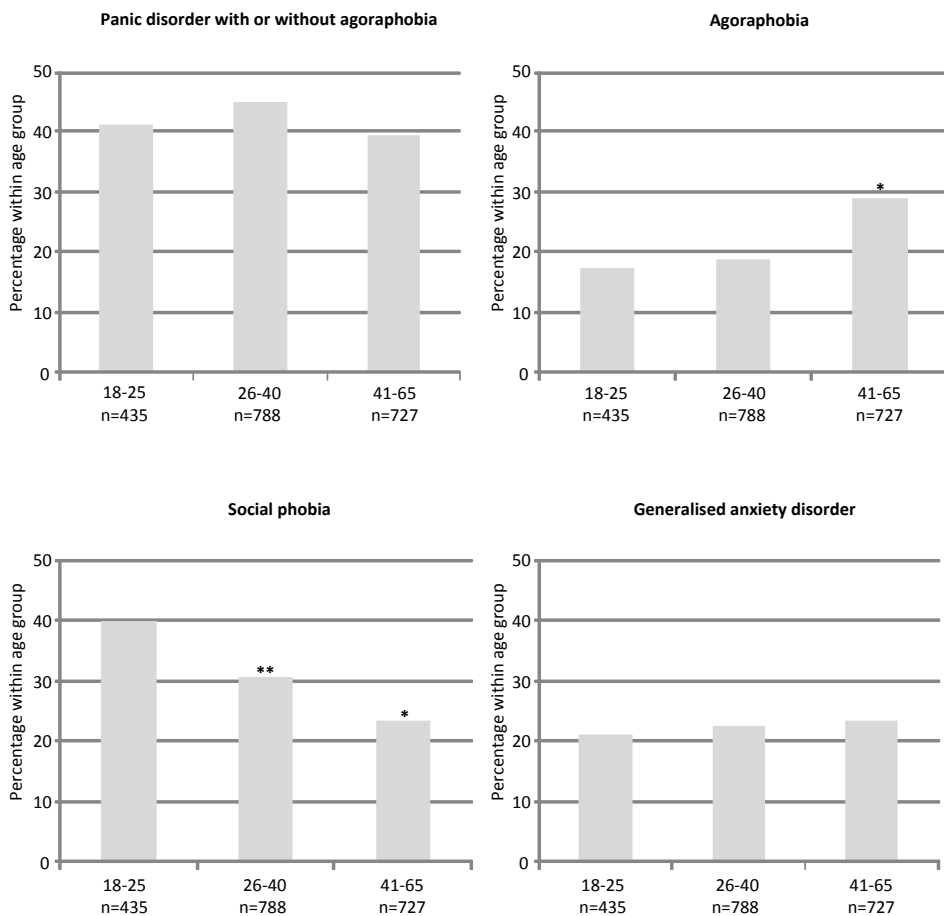
DSM-IV-TR denotes Diagnostic Statistical Manual-fourth edition, text revision; *denotes significantly different from early adult (18-25; n=435) and mid-adult (26-40; n=788) post-hoc with Bonferroni correction for multiple testing; **denotes significantly different from early adult (18-25; n=435) and late adult (41-65; n=727) post-hoc with Bonferroni correction for multiple testing.

3.3.2.4 Generic health status

Comparisons across the three age groups with regard to generic health status with pairwise post-hoc analyses with Bonferroni correction, as well as results for regression analyses are summarised in table 3.4. Significant differences emerged between the three age groups with regard to physical functioning, role limitations due to physical problems, role limitations due to emotional problems, vitality, and bodily pain. Physical functioning deteriorated with age (early adult group M=20.05, SD=20.42; mid-adult group M=23.93, SD=22.05; late adult group M=30.77, SD=24.40). Physical problems increased with age (early adult group M=56.78, SD=39.36; mid-adult group M=64.78, SD=38.48; late adult group M=71.70, SD=36.83), as did the level of role limitations due to emotional problems (early adult group M=70.88, SD=34.54; mid-adult group M=80.16, SD=30.43; late adult group M=78.4, SD=32.07). Levels of vitality decreased with age (early adult group M=64.54, SD=15.45; mid-adult group M=67.26, SD=15.93; late adult group M=68.65, SD=16.43), while the level of bodily pain increased with age (early adult group M=32.77, SD=24.38; mid-adult group M=36.71, SD=27.15; late adult group M=39.95, SD=28.22).

3.4 Discussion

We identified a number of differences between the three age-groups of outpatients with anxiety disorders. Older patients were more often male, although in all three age groups the majority of patients was female. Older patients were less often employed, less likely to have high education levels, but more likely to live with a partner. With regard to clinical characteristics, the percentage of patients diagnosed with SP decreased with age, whereas older patients were more likely to be diagnosed with AP as well as comorbid depression. With regard to the anxiety symptom profile, older patients scored higher on aches and pains and inner tension. In addition, sleep problems became more likely with increasing age and hostility scores decreased with age. Looking at the general psychiatric symptom profile, reported interpersonal sensitivity and hostility were higher in younger patients, whereas observed depression scores were higher in older patients. With regard to generic health status, a number of differences emerged: physical functioning and levels of vitality declined with age. The level of physical problems, pain, and role limitations due to emotional problems increased with age.

A number of our findings fits hypotheses. The finding that older patients more often lived with a partner and were less often employed is not surprising, as both early retirement and difficulty finding a new job after losing one's job are more likely with increasing age. The finding that older patients had lower education levels is also in line with expectations, as it fits

general demographics (Lutz & KC, 2011). The findings of more aches and pains, more bodily pain, a decline in physical functioning and vitality, more role-limitations due to physical problems, as well as reduced sleep in older patients also fit the process of aging in the general population (Aaronson et al., 1998). However, although physical decline is expected in aging, the detection of signs of significantly lower physical functioning in the mid-adult group compared to the early adult group might be thought of as surprising. Subtle subjective signs of physical deterioration may emerge among 26-40 year olds. Possibly our results reflect the overall finding that people with anxiety disorders are generally at an elevated risk for a number of physical conditions (Sareen et al., 2005), a risk that further increases with age (Scott et al., 2008). In addition, a previous study demonstrated that anxiety amplified the effect of age on physical disability (Brenes et al., 2008) Therefore, perhaps physical decline moves at a faster pace in outpatients with anxiety disorders than in the general population, resulting in earlier emergence of signs of physical deterioration. However, a direct comparison with general population subjects is warranted to gain further insight on this matter.

The shift in the male to female ratio towards a more equal distribution with increasing age, was previously reported in the general population, where the percentage of women meeting diagnostic criteria for anxiety disorders dropped markedly after the age of 45 (Regier et al., 1990), although in our clinical sample this shift occurred earlier. With regard to anxiety diagnoses, we found a decrease in prevalence of SP with age, which has been reported previously in the general population (Somers et al., 2006). AP on the other hand was more prevalent in the late adult group. This confirms findings in the general population of higher prevalence of AP in older (55+) compared to younger (15-54) subjects (Cairney et al., 2008), although prevalence of AP has also been found to be stable or even decline across age groups (Somers et al., 2006). In our sample a structured diagnostic interview was used that screened for various psychiatric disorders; however, primary diagnosis was unknown. It could be hypothesised that the increased prevalence of AP in the older adult group is a secondary diagnosis that follows from increased avoidance associated with the elevated prevalence of either physical complaints or depression among older patients.

Across all age groups, mood-disorder comorbidity was common, but it was highest in the late adult group. However, the increased prevalence of physical complaints with age (i.e. reduced vitality, sleep problems and aches and pains) may have increased the probability of meeting diagnostic criteria for depression, and therefore the increased prevalence in our older adult group could be an artefact. This is supported by the fact that the older patients did not report higher levels of depression on the self-report scale (BSI). On the other hand however, observed depression severity (MADRS) was elevated in the older group. Therefore, it may also be that the older adult group was in fact more depressed, and was adequately diagnosed as such, as anxiety disorders have been hypothesised to lead to comorbid depression (Angst &

Vollrath, 1991). Possibly, when confronted with a self-report questionnaire, the older adult group attributed their psychiatric symptoms to general medical problems or to the process of aging (Knauper & Wittchen, 1994), and as such did not report a high depression score. Fitting the observation of more mood comorbidity in the late adult group, older patients also scored higher on measures of inner tension and role limitations due to emotional problems. The higher level of role limitations due to emotional problems with increasing age indicates that older patients feel more limited in their daily functioning as a result of their emotional problems. As age groups did not differ in their levels of anxiety severity per se, this may reflect different (perceptions of) tasks set in daily life, for example in caregiving tasks or in work situations. Both younger groups reported more interpersonal sensitivity and hostility. Although feelings of hostility and interpersonal sensitivity could be thought to be reflective of cortical immaturity, as brain development has been demonstrated to continue into early adulthood (Uhlhaas et al., 2009). However, this thought is contradicted by the fact that the mid-adult group also demonstrated higher levels of hostility than the late adult group. Alternatively, feelings of hostility and interpersonal sensitivity may emerge from the demands that are typically made of the younger age groups which may have a stronger social component, for example in achieving independence, possible student life, dating, and career development. In addition, increased interpersonal sensitivity fits our findings of higher prevalence of social phobia in the younger age groups although feelings of hostility do not. Interestingly, younger patients' hostility scores, which were measured through a subscale on the self-report BSI, as well as an item on the observer-rated BAS, were elevated only on the self-report measure, perhaps the single item of the BAS lacked sensitivity to detect the variation in hostility.

Our study has several strengths. To our knowledge, it is the first study to report on age related characteristics of anxiety disorders across the adult life span (i.e. ages 18-65). Furthermore, as we examined outpatients, using data from a large, representative naturalistic sample, we ensured applicability to clinical practice. The inclusion of a broad set of patient characteristics, covering social demographics, diagnostic characteristics, anxiety- and general psychiatric symptom profiles, as well as generic health status, further strengthens our study. However, several limitations need to be acknowledged. As our study was explorative in nature, we used unsubstantiated cut-offs to define the age groups. Although our cut-offs have been used previously (van Noorden et al., 2011; Regier et al., 1990; Somers et al., 2006; Robins et al., 1984), alternative cut-offs may better fit the research question. In addition, no information on primary diagnosis or physical comorbidity was available in our sample. Furthermore, it must be noted that although differences between groups were significant after correction for multiple testing, effect sizes indicated that the differences were generally small. This does not imply that differences between groups are not clinically important, but it does warrant moderation when interpreting the data. As differences were small, our results could be interpreted as

support for the uniform approach of the group of 18 through 65 year-old in terms of diagnostic protocols. In addition, we studied an outpatient group, therefore, our results should be interpreted accordingly, they may not generalise to anxiety disorders as seen in the general population.

In conclusion, our study has convincingly demonstrated that significant differences exist between different age groups in outpatients with anxiety disorders with regard to social demographic and clinical characteristics, symptomatology, and generic health status. Older patients were more often male, unemployed, living with a partner, and had lower education levels. With regard to clinical characteristics, older patients were more often diagnosed with agoraphobia and comorbid depression, younger patients were more likely to have social phobia. Anxiety symptom profiles of older patients showed more aches and pains, inner tension, and sleep problems, whereas younger patient had higher levels of hostility. The general psychiatric symptom profiles of younger patients showed elevated scores on measures of interpersonal sensitivity and hostility. With regard to generic health status, older patients experienced lower levels of physical functioning and vitality, while they had more physical problems, role limitations due to emotional problems, and pain. Although a number of these differences fit expectations related to development across the adult lifespan, they are relevant and clinicians should be aware of these differences as they relate to needs of patients and demands made of them. The finding of increased observed but not self-reported depression in the older adult group merits special attention in clinical practice as well as in future research. It is important to be aware of increased chances of agoraphobia and mood comorbidity in older adults, as both have been associated with negative outcome (Angst & Vollrath, 1991; Schat et al., 2013). As expected, younger adults seem less burdened by physical complaints, but have more feelings of hostility and interpersonal sensitivity, possibly reflecting strong social demands that are made of them. Older adults less often have a job, but more often live with a partner, a possible source of support in dealing with anxiety. Finally, the older groups report more sleep problems and feel more limited in their functioning as a result of emotional problems. Clinicians should be aware of these differences, and where possible take them into account when providing treatment.

Table 3.1 Social demographic and clinical categorical patient characteristics per age group in 1950 outpatients diagnosed with DSM-IV-TR anxiety disorders (panic disorder with or without agoraphobia, agoraphobia without panic, social phobia and/or generalised anxiety disorder).

Number (%)	Early adult (E) 18-25 (n=435)	Mid adult (M) 26-40 (n=788)	Late adult (L) 41-65 (n=727)	Categorical comparison overall		phi post-hoc			Linear comparison	
				Cramer's V	p	E-M	E-L	M-L	B (95%CI)	p
Male gender	122 (28.0)	288 (36.5)	315 (43.3)	0.12	<.001	0.09	0.12	0.07	2.83 (1.76 - 3.89)	<.001
Fulltime or part time job	203 (46.7)	370 (47.0)	274 (37.7)	0.09	<.001	--	-0.13	-0.09	-2.45 (-3.49 - -1.40)	<.001
High education level	285 (65.5)	479 (60.8)	348 (47.9)	0.15	<.001	--	-0.18	-0.13	-4.03 (-5.06 - -2.99)	<.001
Living with partner	97 (22.3)	458 (58.1)	468 (64.4)	0.33	<.001	0.34	0.45	0.06	6.60 (5.60 - 7.59)	<.001
Comorbid depression	211 (48.5)	407 (51.6)	442 (60.8)	0.10	<.001	--	0.22	0.09	2.52 (1.48 - 3.56)	<.001
Substance abuse /dep.	28 (6.4)	39 (4.9)	25 (3.4)	--	0.06	--	--	--	-2.88 (-5.33 - -0.43)	0.02
Alcohol abuse/dep.	23 (5.3)	43 (5.5)	54 (7.4)	--	0.20	--	--	--	2.40 (0.24 - 4.56)	0.03
Multiple anxiety disorders	80 (18.4)	122 (15.5)	102 (14.0)	--	0.14	--	--	--	1.12 (-0.31 - 2.56)	0.12
Panic disorder	178 (40.9)	352 (44.7)	286 (39.3)	--	0.10	--	--	--	-0.30 (-0.10 - 0.04)	0.39
Agoraphobia	75 (17.2)	148 (18.8)	210 (28.9)	--	<.001	--	0.12	0.12	0.21 (0.13 - 0.29)	<.001
Social phobia	173 (39.8)	242 (30.7)	171 (23.5)	--	<.001	-0.09	-0.23	-0.08	-0.22 (-0.29 - -0.15)	<.001
Generalised anxiety disorder	92 (21.1)	177 (22.5)	171 (23.5)	--	0.64	--	--	--	0.04 (-0.04 - 0.12)	0.35

Comparisons between the three age groups were made using Chi-squared test with post-hoc comparisons using Bonferroni correction for multiple testing. The MINI International Neuropsychiatric Interview-Plus (MINI-Plus) was used to collect DSM-IV-TR diagnostic information (type of anxiety disorder, number of simultaneously occurring anxiety disorders, presence of a comorbid mood disorder, comorbid alcohol- or substance abuse or -dependence); DSM-IV-TR denotes Diagnostic Statistical Manual-fourth edition, text revision; E denotes the early adult group (18-25; n=435); M denotes the mid-adult group (26-40; n=788); L denotes the late adult group (41-65; n=727).

Table 3.2 Anxiety symptoms as measured with the Brief Anxiety Scale (BAS) per age group in 1950 outpatients diagnosed with DSM-IV-TR anxiety disorders (panic disorder with or without agoraphobia, agoraphobia without panic, social phobia and/or generalised anxiety disorder).

Mean (Standard Deviation)	Early adult (E) 18-25 (n=435)	Mid adult (M) 26-40 (n=788)	Late adult (L) 41-65 (n=727)	Categorical comparison overall Eta squared	p	Cohen's d post-hoc E-M	E-L	M-L	Linear comparison B (95%CI)	p
Aches and pains	1.93 (1.37)	2.09 (1.45)	2.29 (1.52)	0.01	<.001	--	-0.25	--	0.85 (0.50 - 1.20)	<.001
Inner tension	3.03 (1.00)	3.15 (1.01)	3.29 (1.00)	0.01	<.001	--	-0.26	--	1.24 (0.72 - 1.75)	<.001
Hypochondria	0.51 (0.97)	0.63 (1.12)	0.62 (1.08)	--	0.14	--	--	--	0.13 (-0.36 - 0.61)	0.60
Worries	1.90 (1.60)	2.02 (1.63)	1.82 (1.64)	--	0.07	--	--	--	-0.15 (-0.47 - 0.17)	0.36
Phobia	2.25 (1.82)	2.12 (1.84)	2.16 (1.87)	--	0.52	--	--	--	-0.15 (-0.43 - 0.13)	0.30
Hostility	1.63 (1.39)	1.73 (1.38)	1.49 (1.40)	--	.003	--	--	--	-0.71 (-1.08 - -0.34)	<.001
Reduced sleep	1.81 (1.59)	2.22 (1.68)	2.43 (1.74)	0.02	<.001	-0.25	-0.37	--	0.94 (0.63 - 1.24)	<.001
Rep. aut. dist.	2.49 (1.10)	2.56 (1.18)	2.67 (1.16)	--	0.02	--	--	--	0.50 (0.05 - 0.95)	0.03
App. aut. dist.	1.15 (1.09)	1.01 (1.07)	1.04 (1.08)	--	0.09	--	--	--	-0.39 (-0.97 - 0.10)	0.12
App. muscle tension	1.69 (1.11)	1.68 (1.15)	1.70 (1.18)	--	0.90	--	--	--	0.04 (-0.42 - 0.49)	0.88

Comparisons between the three age groups were made using Chi-squared test with post-hoc comparisons using Bonferroni correction for multiple testing. Anxiety symptoms were measured with the Brief Anxiety Scale (Tyrer et al., 1984). DSM-IV-TR denotes Diagnostic Statistical Manual-fourth edition, text revision; E denotes the early adult group (18-25; n=435); M denotes the mid-adult group (26-40; n=788); L denotes the late adult group (41-65; n=727); Rep. aut. dist. denotes the subscale reported autonomic disturbances; App. aut. dist. denotes the subscale apparent autonomic disturbances; App muscle tension denotes the subscale apparent muscle tension.

3

Table 3.3 General psychiatric symptoms as measured with the Montgomery Åsberg Depression Rating Scale (MADRS) and the Brief Symptom Inventory (BSI) per age group in 1950 outpatients diagnosed with DSM-IV-TR anxiety disorders (panic disorder with or without agoraphobia, agoraphobia without panic, social phobia and/or generalised anxiety disorder).

Mean (Standard Deviation)	Early adult (E) 18-25 (n=435)	Mid adult (M) 26-40 (n=788)	Late adult (L) 41-65 (n=727)	Categorical comparison						Linear comparison	
				overall Eta squared	p	Cohen's d post-hoc E-M	E-L	M-L		B (95%CI)	p
MADRS	18.69 (8.30)	20.38 (8.31)	21.82 (8.54)	0.01	<.001	-0.20	-0.37	-0.17		0.187 (0.127 -0.248)	<.001
BSI Depression	1.86 (0.98)	1.84 (0.97)	1.84 (0.98)	--	0.92	--	--	--		-0.11 (-0.65 - 0.42)	0.69
BSI Somatisation	1.30 (0.80)	1.37 (0.87)	1.35 (0.89)	--	0.44	--	--	--		0.15 (-0.45 - 0.75)	0.63
BSI Obs. Comp.	1.77 (0.92)	1.91 (0.94)	1.89 (0.95)	--	0.03	--	--	--		0.31 (-0.24 -0.86)	0.27
BSI Int. sens.	2.06 (1.08)	1.94 (1.07)	1.73 (1.06)	0.01	<.001	--	0.38	0.20		-1.35 (-1.83 - 0.87)	<.001
BSI Anxiety	2.01 (0.86)	2.07 (0.87)	2.05 (0.87)	--	0.53	--	--	--		0.14 (-0.46 - 0.74)	0.65
BSI Hostility	1.18 (0.93)	1.12 (0.92)	0.95 (0.85)	0.01	<.001	--	0.26	0.19		-1.62 (-2.19 - -1.04)	<.001
BSI Phobic anxiety	1.76 (0.99)	1.72 (0.96)	1.65 (0.99)	--	0.11	--	--	--		-0.67 (-1.20 - -0.13)	0.01
BSI Paranoid id.	1.34 (0.97)	1.37 (1.00)	1.29 (0.98)	--	0.24	--	--	--		-0.44 (-0.97 - 0.09)	0.10
BSI Psychoticism	1.47 (0.81)	1.50 (0.84)	1.38 (0.83)	--	0.02	--	--	--		-0.85 (-1.47 - -0.22)	.008

Comparisons between the three age groups were made using ANOVA with post-hoc comparisons using Bonferroni correction for multiple testing. BSI denotes Brief Symptom Inventory (Derogatis & Melisaratos, 1983); DSM-IV-TR denotes Diagnostic Statistical Manual-fourth edition, text revision; E denotes the early adult group (18-25; n=435); M denotes the mid-adult group (26-40; n=788); L denotes the late adult group (41-65; n=727); BSI Obs. Comp denotes the subscale obsessive compulsiveness; BSI int. sens. Denotes the subscale interpersonal sensitivity; BSI Paranoid id. Denotes the subscale paranoid ideation.

Table 3.4 Generic health status as measured with the Short Form-36 (SF-36) per age group in 1950 outpatients diagnosed with DSM-IV-TR anxiety disorders (panic disorder with or without agoraphobia, agoraphobia without panic, social phobia and/or generalised anxiety disorder).

Mean (Standard Deviation)	Early adult (E) 18-25 (n=435)	Mid adult (M) 26-40 (n=788)	Late adult (L) 41-65 (n=727)	Categorical comparison						Linear comparison	
				overall		Cohen's d post-hoc					
				Eta squared	p	E-M	E-L	M-L		B (95%CI)	p
Physical functioning	20.05 (20.42)	23.93 (22.05)	30.77 (24.40)	0.03	<.001	-0.18	-0.48	-0.29		0.09 (0.07 - 0.11)	<.001
Social functioning	57.01 (27.02)	60.64 (24.37)	61.90 (24.37)	--	.005	--	--	--		0.03 (0.01 - 0.05)	0.003
Role limitations physical	56.78 (39.36)	64.78 (38.48)	71.70 (36.83)	0.02	<.001	-0.21	-0.39	-0.18		0.04 (0.03 - 0.05)	<.001
Role limitations emotional	70.88 (34.54)	80.16 (30.43)	78.40 (32.07)	0.01	<.001	-0.29	-0.23	--		0.02 (0.01 - 0.04)	0.007
Mental health	62.45 (15.17)	62.69 (15.07)	63.88 (16.19)	--	0.21	--	--	--		0.04 (0.00 - 0.07)	0.04
Vitality	64.54 (15.45)	67.26 (15.93)	68.65 (16.43)	0.01	<.001	-0.17	-0.27	--		0.07 (0.03 - 0.10)	<.001
Bodily pain	32.77 (24.38)	36.71 (27.15)	39.95 (28.22)	0.01	<.001	-0.27	--	--		0.04 (0.02 - 0.06)	<.001
General health perception	49.86 (20.24)	50.91 (19.51)	52.24 (20.56)	--	0.13	--	--	--		0.02 (-0.01 - 0.05)	0.11

Comparisons between the three age groups were made using ANOVA with post-hoc comparisons using Bonferroni correction for multiple testing. Generic health status was measured using the Short Form-36 (Aaronson et al., 1998; SF-36); SF-36 scores were inverted. DSM-IV-TR denotes Diagnostic Statistical Manual-fourth edition, text revision; E denotes the early adult group (18-25; n=435); M denotes the mid-adult group (26-40; n=788); L denotes the late adult group (41-65; n=727).

3

Reference List

Aaronson, N. K., Muller, M., Cohen, P. D. A., Essink-Bot, M. L., Fekkes, M., Sanderman, R. et al. (1998). Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. *Journal of Clinical Epidemiology, 51,* 1055-1068.

American Psychiatric Association (2000). *Diagnostic and Statistical Manual of Mental Disorders, Fouth Edition, Text Revision (DSM-IV-TR)*. Washington DC: American Psychiatric Association.

Angst, J. & Vollrath, M. (1991). The natural history of anxiety disorders. *Acta Psychiatr Scand., 84,* 446-452.

Åsberg, M., Montgomery, S. A., Perris, C., Schalling, D., & Sedvall, G. (1978). Comprehensive Psychopathological Rating-Scale. *Acta Psychiatrica Scandinavica,* 5-27.

Barlow, D. H., DiNardo, P. A., Vermilyea, B. B., Vermilyea, J., & Blanchard, E. B. (1986). Co-morbidity and depression among the anxiety disorders. Issues in diagnosis and classification. *J.Nerv.Ment.Dis., 174,* 63-72.

Brenes, G. A., Penninx, B. W., Judd, P. H., Rockwell, E., Sewell, D. D., & Wetherell, J. L. (2008). Anxiety, depression and disability across the lifespan. *Aging Ment.Health, 12,* 158-163.

Cairney, J., Corna, L. M., Veldhuizen, S., Herrmann, N., & Streiner, D. L. (2008). Comorbid depression and anxiety in later life: patterns of association, subjective well-being, and impairment. *Am.J.Geriatr.Psychiatry, 16,* 201-208.

De Beurs, E., den Hollander-Gijsman, M. E., van Rood, Y. R., van der Wee, N. J. A., Giltay, E. J., van Noorden, M. S. et al. (2011). Routine Outcome Monitoring in the Netherlands: Practical Experiences with a Web-Based Strategy for the Assessment of Treatment Outcome in Clinical Practice. *Clinical Psychology & Psychotherapy, 18,* 1-12.

De Beurs, E. & Zitman, F. G. (2006). De Brief Symptom Inventory (BSI) De betrouwbaarheid van een handzaam alternatief voor de SCL-90. *Maandblad Geestelijke Volksgezondheid, 61,* 120-141.

Derogatis, L. R. & Melisaratos, N. (1983). The Brief Symptom Inventory - An Introductory Report. *Psychological Medicine, 13,* 595-605.

Goekoop, J. G., Hoeksema, T., Knoppertvanderklein, E. A. M., Klinkhamer, R. A., Vangaalen, H. A. E., Vanlonden, L. et al. (1992). Multidimensional Ordering of Psychopathology - A Factor-Analytic Study Using the Comprehensive Psychopathological Rating-Scale. *Acta Psychiatrica Scandinavica, 86,* 306-312.

Gretarsdottir, E., Woodruff-Borden, J., Meeks, S., & Depp, C. A. (2004). Social anxiety in older adults: phenomenology, prevalence, and measurement. *Behav.Res.Ther., 42,* 459-475.

Husain, M. M., Rush, A. J., Sackeim, H. A., Wisniewski, S. R., McClintock, S. M., Craven, N. et al. (2005). Age related characteristics of depression: a preliminary STAR*D report. *Am.J.Geriatr.Psychiatry, 13,* 852-860.

Knauper, B. & Wittchen, H. U. (1994). Diagnosing major depression in the elderly: evidence for response bias in standardized diagnostic interviews? *J.Psychiatr Res., 28,* 147-164.

Lecrubier, Y., Sheehan, D. V., Weiller, E., Amorim, P., Bonora, I., Sheehan, K. H. et al. (1997). The Mini International Neuropsychiatric Interview (MINI). A short diagnostic structured interview: Reliability and validity according to the CIDI. *European Psychiatry, 12,* 224-231.

Lenze, E. J. & Wetherell, J. L. (2011). A lifespan view of anxiety disorders. *Dialogues.Clin.Neurosci., 13,* 381-399.

Lutz, W. & KC, S. (2011). Global human capital: integrating education and population. *Science, 333,* 587-592.

Regier, D. A., Narrow, W. E., & Rae, D. S. (1990). The epidemiology of anxiety disorders: the Epidemiologic Catchment Area (ECA) experience. *J.Psychiatr Res., 24 Suppl 2,* 3-14.

Robins, L. N., Helzer, J. E., Weissman, M. M., Orvaschel, H., Gruenberg, E., Burke, J. D., Jr. et al. (1984). Lifetime prevalence of specific psychiatric disorders in three sites. *Arch.Gen.Psychiatry, 41,* 949-958.

Roy-Byrne, P., Craske, M. G., Sullivan, G., Rose, R. D., Edlund, M. J., Lang, A. J. et al. (2010). Delivery of Evidence-Based Treatment for Multiple Anxiety Disorders in Primary Care A Randomised Controlled Trial. *Jama-Journal of the American Medical Association, 303,* 1921-1928.

Sareen, J., Houlahan, T., Cox, B. J., & Asmundson, G. J. (2005). Anxiety disorders associated with suicidal ideation and suicide attempts in the National Comorbidity Survey. *J.Nerv.Ment.Dis., 193,* 450-454.

Schat, A., van Noorden, M. S., Noom, M. J., Giltay, E. J., van der Wee, N. J., Vermeiren, R. R. et al. (2013). Predictors of outcome in outpatients with anxiety disorders: the Leiden routine outcome monitoring study. *J.Psychiatr Res., 47,* 1876-1885.

Schieman, S., Van, G. K., & Taylor, J. (2001). Status, role, and resource explanations for age patterns in psychological distress. *J.Health Soc.Behav., 42,* 80-96.

Schneider, G., Driesch, G., Kruse, A., Wachter, M., Nehen, H. G., & Heuft, G. (2004). What influences self-perception of health in the elderly? The role of objective health condition, subjective well-being and sense of coherence. *Arch.Gerontol.Geriatr., 39,* 227-237.

Scott, K. M., Von, K. M., Alonso, J., Angermeyer, M., Bromet, E. J., Bruffaerts, R. et al. (2008). Age patterns in the prevalence of DSM-IV depressive/anxiety disorders with and without physical co-morbidity. *Psychological Medicine, 38,* 1659-1669.

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E. et al. (1998). The Mini-International Neuropsychiatric Interview (MINI): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry, 59,* 22-33.

Somers, J. M., Goldner, E. M., Waraich, P., & Hsu, L. (2006). Prevalence and incidence studies of anxiety disorders: A systematic review of the literature. *Canadian Journal of Psychiatry-Revue Canadienne de Psychiatrie, 51,* 100-113.

Tyrer, P., Owen, R. T., & Cicchetti, D. V. (1984). The Brief Scale for Anxiety - A Subdivision of the Comprehensive Psychopathological Rating-Scale. *Journal of Neurology Neurosurgery and Psychiatry, 47,* 970-975.

Uhlhaas, P. J., Roux, F., Singer, W., Haenschel, C., Sireteanu, R., & Rodriguez, E. (2009). The development of neural synchrony reflects late maturation and restructuring of functional networks in humans. *Proc.Natl.Acad.Sci.U.S A, 106,* 9866-9871.

van Noorden, M. S., Minkenberg, S. E., Giltay, E. J., den Hollander-Gijsman, M. E., van Rood, Y. R., van der Wee, N. J. et al. (2011). Pre-adult versus adult onset major depressive disorder in a naturalistic patient sample: the Leiden Routine Outcome Monitoring Study. *Psychological Medicine, 41,* 1407-1417.

Van Vliet, I. M. & De Beurs, E. (2007). Het MINI Internationaal Neuropsychiatrisch Interview (MINI) een kort gestructureerd diagnostisch psychiatrisch inerview voor DSM-IV- en ICD-10-stoornissen. *tijdschrift voor psychiatrie, 49,* 393-397.

Ware, J. E. & Sherbourne, C. D. (1992). The Mos 36-Item Short-Form Health Survey (Sf-36) .1. Conceptual-Framework and Item Selection. *Medical Care, 30,* 473-483.

3

Wilkowska-Chmielewska, J., Szelenberger, W., & Wojnar, M. (2013). Age-dependent symptomatology of depression in hospitalized patients and its implications for DSM-5. *J.Affect.Disord., 150,* 142-145.

Wolitzky-Taylor, K. B., Castriotta, N., Lenze, E. J., Stanley, M. A., & Craske, M. G. (2010). Anxiety disorders in older adults: a comprehensive review. *Depress.Anxiety, 27,* 190-211.

Wong, D. W., Hall, K. H., Justice, C. A., & Wong-Hernandez, L. W. (2015). Chapter 1: Human Development through the lifespan. In *Counseling Individuals Through the Lifespan* (Sage Publications Inc.

Zitman, F. G. (2012). [ROM in mood, anxiety and somatoform disorders: a promising technique with pleasing results]. *Tijdschr.Psychiatr., 54,* 173-177.

Chapter 4

Predictors of outcome in outpatients with anxiety disorders: The Leiden Routine Outcome Monitoring Study

Abstract

Little is known about the predictors of outcome in anxiety disorders in naturalistic outpatient settings. We analysed 2-year follow-up data collected through Routine Outcome Monitoring (ROM) in a naturalistic sample of 917 outpatients in psychiatric specialty care in order to identify factors predicting outcome. We included patients with panic disorder with or without agoraphobia, agoraphobia without panic, social phobia, or generalised anxiety disorder. Main findings from Cox regression analyses demonstrated that several socio-demographic variables (having a non-Dutch ethnicity [HR = 0.71)], not having a daily occupation [HR = 0.76]) and clinical factors (having a diagnosis of agoraphobia [HR = 0.67], high affective lability [HR = 0.80] and behaviour problems [HR = 0.84]) decreased chances of response (defined as 50% reduction of anxiety severity) over the period of two years. Living with family had a protective predictive value [HR = 1.41]. These results may imply that factors that could be thought to limit societal participation are associated with elevated risk of poor outcome. A comprehensive ROM screening process at intake may aid clinicians in the identification of patients at risk of chronicity.

4.1. Introduction

Anxiety disorders are highly prevalent (Wittchen et al., 2011) and are associated with marked functional impairment, high disease burden, substantial costs (Gustavsson et al., 2010), and a chronic course (Angst & Vollrath, 1991; Baldwin et al., 2010; Penninx et al., 2011). The manifesto for a European anxiety disorders network (Baldwin et al., 2010) states that, although psychological and pharmacological treatment have been proven effective in (randomised) clinical trials (RCT), for a substantial number of patients in clinical practice they do not translate into good outcome. Therefore, studies on predictors of response in naturalistic settings need to be conducted (Baldwin et al., 2010; Rothwell, 2005).

Previous studies have focused on various socio-demographic predictors of outcome of anxiety disorders. Different studies failed to demonstrate an association with gender (Tyrer et al., 2004; Yonkers et al., 2003; Serretti et al., 2009). Older age was associated with longer time to remission in treated as well as untreated panic disorder with or without agoraphobia (PD/A), agoraphobia without panic (AP), social phobia (SP), generalised anxiety disorder (GAD) and/or depression (MDD) (Penninx et al., 2011). Conversely, older age was associated with lower severity at one-year follow-up and a steeper decline in anxiety over time in subjects with PD/A and GAD but not in SP (Ramsawh et al., 2009). Others found no predictive value of age (Chavira et al., 2009; Van Ameringen et al., 2004; Beutel et al., 2011; Beard et al., 2010; Serretti et al., 2009). Additional socio-demographic factors that have been linked to poor outcome in anxiety disorders are: lower education-level (Ramsawh et al., 2009), and being unemployed and having low socioeconomic status in PD/A (Roy-Byrne et al., 2003). Finally, although no association with ethnicity has been established, results do render further research necessary (Serretti et al., 2009).

Besides socio-demographic characteristics, several clinical factors have been studied in relation to outcome in anxiety disorders. First of all, in a sample diagnosed with GAD, SP and/or PD/A, patients with SP were least likely to have recovered at 12-year follow-up (Bruce et al., 2005). PD patients without agoraphobia were most likely to recover (Bruce et al., 2005; Roy-Byrne et al., 2003). In SP comorbid PD/A predicted poor outcome (Beard et al., 2010). In a sample of inpatients diagnosed with PD/A, AP, SP, GAD, posttraumatic stress disorder (PTSD), obsessive compulsive disorder (OCD) and/or specific phobia (SPP), poor outcome was predicted by comorbid eating disorders and having multiple anxiety disorders (Beutel et al., 2011). The presence of comorbid MDD or alcohol abuse or dependence was associated with worse 12-year outcome in PD/A, SP and GAD (Bruce et al., 2005), although other studies showed no association with MDD (Roy-Byrne et al., 2003; Serretti et al., 2009; Beutel et al., 2011). Comorbid personality disorders or maladaptive personality traits have repeatedly been associated with poor outcome (Beutel et al., 2011; Ansell et al., 2011; Telch et al., 2011).

4

Finally, early age of onset of the anxiety disorder predicted remission in treated as well as untreated PD/A, AP, SP, GAD and/or MDD (Penninx et al., 2011) and in SP in a Sertraline RCT (Van Ameringen et al., 2004). Although in PD/A, SP and GAD, early onset did not predict recovery while it did predict relapse in PD/A (Ramsawh et al., 2011).

However, generalizability of research findings to patients seen in everyday clinical practice is often limited (Hoertel et al., 2012). This lack of generalizability could result from the use of strict in and exclusion criteria (Tyrer et al., 2004; Chavira et al., 2009; Roy-Byrne et al., 2003; Roy-Byrne et al., 2006; Van Ameringen et al., 2004), the focus on a single treatment modality (Telch et al., 2011; Van Ameringen et al., 2004; Serretti et al., 2009) and the focus on a narrowly defined patient group (Beutel et al., 2011; Chavira et al., 2009; Roy-Byrne et al., 2003; Roy-Byrne et al., 2006; Telch et al., 2011; Beard et al., 2010; Van Ameringen et al., 2004). Also, in observational cohort studies, high selectiveness may result from patients' motivation to participate in long-term follow-up studies stretching over a decade (Yonkers et al., 2003; Bruce et al., 2005; Ramsawh et al., 2009; Ramsawh et al., 2011; Beard et al., 2010).

Therefore, the present study aimed at establishing predictors of outcome in a large naturalistic cohort of outpatients suffering from anxiety disorders with a follow-up of up to 2 years. We used a broad range of patient characteristics that have been gathered as part of standard clinical procedure as potential predictors, avoiding the previously discussed limitations to generalizability. Although in the Diagnostic and Statistical Manual of Mental Disorders fourth edition-text revision (DSM-IV-TR), the category of anxiety disorders comprises PD/A, AP, SP, GAD, PTSD, SPP, OCD and acute stress disorder; marked differences exist with regard to aetiology, expression and clinical course between PD/A, AP, SP and GAD on the one hand, and PTSD, SPP, OCD and acute stress disorder on the other (Friedman et al., 2011; Stein et al., 2010; Lebeau et al., 2010). Therefore, following a common approach (Penninx et al., 2011; Bruce et al., 2005; Ramsawh et al., 2009; Ramsawh et al., 2011), this study focused primarily on predictors of outcome in patients diagnosed with PD/A, AP, SP and/or GAD.

4.2. Method

4.2.1. Routine outcome monitoring

As part of routine practice at the facilities involved in this study, all patients were administered an extensive battery of self-report and observer-rated measures at intake and at follow-up, every 3-4 months of treatment. This procedure is known as Routine Outcome Monitoring (ROM) and it continues for as long as the patient is being treated. Therefore the total number of assessments per patient varies as it depends on the duration of treatment. A more extensive description can be found in De Beurs et al. (2011). Both generic and disorder-specific

questionnaires were administered by formally trained psychiatric nurses and through computerized self-report, supervised by trained psychiatric nurses. This computerized administration prevents missing data within questionnaires as item-completion is necessary for progression to the next item (De Beurs et al., 2011). Inter-rater reliability in a small sample of research nurses on several questionnaires has been tested and was within acceptable range (Cohen's κ= 0.55-0.73; De Beurs et al., 2011). The primary goal of this data-collection is to inform both clinicians and patients. An estimated average of 80% of all patients is assessed at intake (van Noorden et al., 2012; Zitman, 2012). Data were anonymised and their use in scientific research was approved by the Ethical Review Board at the Leiden University Medical Centre (LUMC).

4.2.2. Patients and procedure

Subjects were outpatients referred to Rivierduinen, a regional mental healthcare provider, or the psychiatry department of the LUMC between March 2004 and November 2009. To allow two years of follow-up for all patients, follow-up data were collected until the end of November 2011. Inclusion criteria held that patients must be aged between 18 and 65, have adequate command of the Dutch language and meet DSM-IV-TR diagnostic criteria for one or more of the following disorders: PD/A, AP, SP or GAD. The patient population from which we drew our sample contained patients diagnosed with mood- and somatoform- as well as anxiety disorders; therefore, a risk of over-diagnosing has been suggested when using a semi-structured interview in a clinical sample (Zimmerman & Chelminski, 2003). Also, our dataset did not include clinical diagnoses (i.e. diagnoses made by treating psychiatrist). We therefore filtered out patients who did meet the criteria for anxiety diagnosis but were unlikely to have been treated for anxiety, by setting a criterion of moderate to severe baseline anxiety scores. Moderate to severe baseline severity was defined as 10.38 on the Brief Anxiety Scale (BAS; Tyrer et al., 1984), equalling the average BAS score in a group of general practice patients diagnosed with anxiety disorders (Tyrer et al., 1984), and 6 on the Brief Symptom Inventory-12 item version (BSI-12), with scores <6 signifying no to mild anxiety (Roy-Byrne et al., 2010). All patients received standard outpatient care, consisting of psychotherapy, pharmacotherapy or combination therapy, based on a stepped care model and in concordance with Dutch evidence-based treatment guidelines (van Fenema et al., 2012). Absence of follow-up assessments and missing data (resulting from the incidental failure to administer complete questionnaires), served as exclusion criteria.

4.3. Measures

4.3.1. Predictors of 2-year outcome

Besides patients' age and gender, a wide range of demographic variables was ascertained. Marital status was categorized as 'married or cohabiting' versus 'being unmarried and living without a partner.' Dutch ethnicity was assumed when both the patient and the patient's parents were born in the Netherlands (excluding former Dutch colonies). Education was divided into three levels, 'low education' (no education, primary school until approximately 10th grade), 'medium education' (ranging from 11th grade through high school and community college) and 'high education' (college undergraduate/graduate and higher). Patients were asked about their daily routine, patients who were employed full-time or part-time, were taking care of children, or were receiving education, were classified as 'having a daily occupation'. Patients who were unemployed, retired or on sick leave (without having any care giving responsibilities or receiving education), were classified as 'having no daily occupation'. Living situation was categorized as 'living independently with a partner and/or children', 'living independently alone', and 'living with family'.

DSM-IV-TR diagnostic information was assessed by trained psychiatric nurses using the Dutch version of the MINI International Neuropsychiatric Interview-Plus (MINI-Plus; Sheehan et al., 1998; Van Vliet & De Beurs, 2007). The MINI-Plus has good psychometric properties, with good sensitivity and specificity for all diagnoses except AP, GAD and bulimia, and adequate validity compared to the Composite International Diagnostic Interview, with inter-rater reliability between 0.88 and 1.00 and test-retest reliability between 0.76 and 0.93 (Lecrubier et al., 1997). The MINI-Plus was used to ascertain the presence of anxiety disorders and comorbid depressive or dysthymic disorders, somatoform disorders (hypochondriasis, pain disorder, body dysmorphic disorder, somatization disorder or undifferentiated somatoform disorder), alcohol abuse or dependence and drug abuse or dependence. The number of comorbid anxiety disorders, including comorbid PTSD and OCD (not primary focus in this study) was dichotomized into "single anxiety disorder" versus "multiple anxiety disorders". Age of onset of anxiety disorder was defined as the age at which the disorder (not comprising PTSD or OCD) first manifested, based on the question: "What age were you when these symptoms first emerged?" Age of onset was classified into pre-adult onset (<18 years) and adult onset (≥18 years; van Noorden et al., 2011).

As part of the standard ROM procedure, several additional scales were administered at baseline. Maladaptive personality traits were assessed using the Dimensional Assessment of Personality Pathology short form (DAPP-SF; van Kampen et al., 2008), a short version of the DAPP-BQ (Livesley et al., 1998). The DAPP-SF consists of 136 items on a 5-point Likert scale. 18

Subscales are computed by taking the average of the subscale items (range 1-5); higher scores are associated with pathology, whereas lower scores indicate normality. It has good internal consistency, with Cronbach's alphas ranging from 0.78 to 0.89 across subscales (van Kampen et al., 2008). The 25-item abbreviated Comprehensive Psychopathological Rating Scale (CPRS), besides measuring anxiety on the BAS, also measures psychomotor inhibition (Inh) with 5 items and depressive symptoms (Montgomery-Åsberg Depression Rating Scale [MADRS]) with 10 items. Items for both scales are measured on a 7-point Likert scale (0-6) and add up to a total score (range Inh 0-30; MADRS 0-60), with higher scores indicating more severe symptoms. The MADRS has good internal consistency with Cronbach's alpha equalling 0.86 (Montgomery and Åsberg, 1979). Generic health status was examined using the Dutch version of the Short Form-36 (SF-36; Ware & Sherbourne, 1992; Aaronson et al., 1998) a 36-item self-report survey, screening eight domains of general health: physical functioning, social functioning, role limitations due to physical health problems, role limitations due to emotional problems, general mental health perception, vitality, bodily pain, and general health perception. Measurement scales vary per subscale, ranging from yes/no to answers on a 3-, 5- or 6-point Likert scale. All raw scores are linearly converted to 0-100 subscales, with higher scores representing higher levels of functioning or wellbeing. The subscales of the SF-36 have moderate to good psychometric properties, with Cronbach's alphas between 0.66 and 0.93 (Aaronson et al., 1998).

4.3.2. Outcome measures

Primary outcome in this study was severity of anxiety symptomatology, which was assessed at baseline and follow-up using a self-report as well as an observational measure: the Dutch versions of the BSI-12 (De Beurs & Zitman, 2006; Roy-Byrne et al., 2010) and the BAS (Tyrer et al., 1984). The BSI-12 is a self-report measure comprising items of the anxiety and somatization subscales of the Brief Symptom Inventory 18-item version (Zabora et al., 2001), which is in turn derived from the Brief Symptom Inventory (Derogatis & Melisaratos, 1983), and has good internal consistency with Cronbach's alphas between 0.79 and 0.84 (Franke et al., 2011) and 0.86 in our cohort. The total score equals the sum score of 12 items on a 5-point Likert scale (0-4; range 0e48). The BAS is a 10-item observer-rated scale derived from the CPRS (Åsberg et al., 1978; Goekoop et al., 1992). The total score equals the sum-score of all 10 items on a 7-point Likert scale (0-6; range 0-60). It has adequate internal consistency with Cronbach's alpha of 0.43 in our cohort. Both scales assess the main components of all anxiety disorders, covering psychic and somatic components, and on both scales a higher score corresponds to more severe anxiety. Response was defined as at least 50% improvement on both the BSI-12 and the BAS (van Noorden et al., 2012; Roy-Byrne et al., 2010).

4.3.3. Statistical analyses

Baseline categorical characteristics are presented as number (percentage); continuous variables are presented as mean (standard deviation; SD) with interquartile range (IQR). Comparisons of demographics between included and excluded patients were made using χ^2 and independent samples t-tests for categorical and continuous variables respectively. Follow-up was censored at 24 months. Associations between time to response and social demographic and clinical factors were examined with Cox proportional hazards analysis. As the precise point in time at which response was achieved was not known, interval censoring was applied by defining the moment of response as the midpoint between the last and penultimate assessment (Hosmer et al., 2008). The percentage of cumulative response in the total sample was calculated using Kaplan-Meier analysis. Univariable Hazard Ratios (HR) and 95% confidence intervals (CI) were calculated for response. To facilitate comparability of effect sizes between continuous predictors, scores were standardized by calculating Z-scores for use in analyses. In addition, as higher scores on the SF-36 correspond with better functioning, whereas in all other instruments used in this study a higher score corresponds with greater severity, original SF-36 scores were inverted (i.e. subtracted from 100).

Following the first two steps of the purposeful selection method (Hosmer et al., 2008), all candidate predictor variables that achieved significance levels of 0.10 in univariable analysis were entered in multivariable analysis. Failure to achieve significance at p 0.10 in the resulting multivariable model resulted in removal except for age, gender and the four dichotomized main diagnostic categories in this study (i.e., PD/A, AP, SP and GAD), which were forced into the model (i.e. step 1). Backward stepwise removal of covariates was checked using the p-values of the Wald test and the partial likelihood ratio test, with values >0.05 demonstrating that removal was justified (i.e. step 2). Post-hoc interaction analyses using dummy variables were performed if considered relevant. Two measures of model performance were calculated: the measure of explained randomness $R^{2p,e}$ (O'Quigley et al., 2005); and $R^{2p,v}$ (Royston, 2006); which more closely resembles the measure of explained variation in linear regression (Hosmer et al., 2008). Kaplan-Meier survival curves were constructed for all variables in the final model. Sensitivity analyses were performed using a less strict response criterion of 40% improvement as well as a more strict definition of 60% improvement on BAS and BSI-12. All tests were two-tailed with $p < 0.05$ denoting statistical significance. IBM SPSS for Windows 20.0 was used for data analysis (IBM Corp., Armonk, NY, USA).

Figure 4.1 Flowchart of inclusion and exclusion
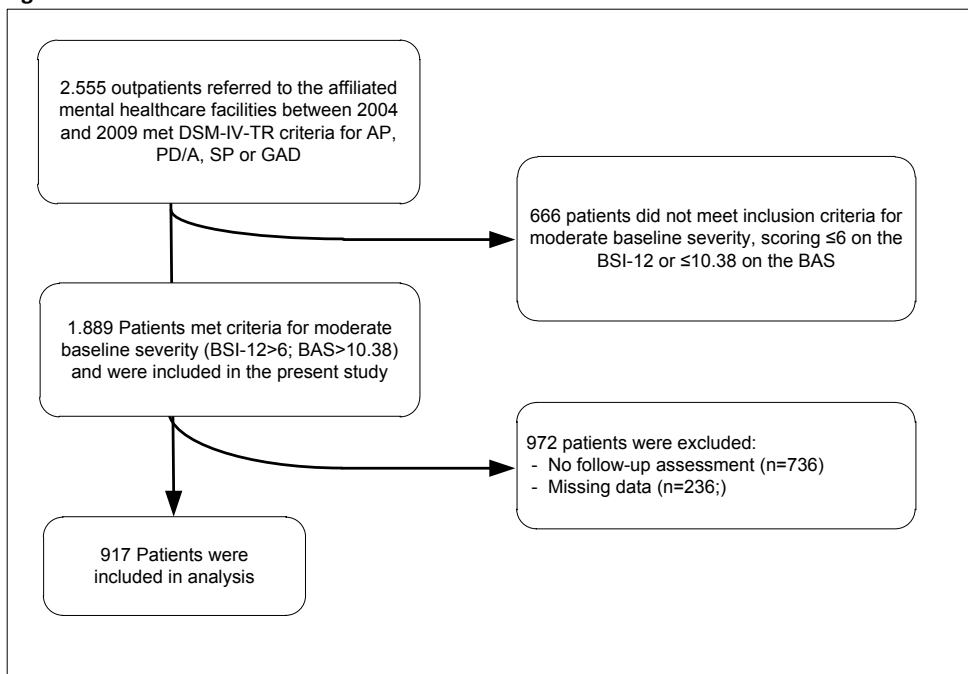
The MINI International Neuropsychiatric Interview-Plus was used to collect diagnostic information. AP denotes agoraphobia without panic; BAS, Brief Anxiety Scale; BSI-12, Brief Symptom Inventory twelve item version; DSM-IV-TR, Diagnostic and Statistical Manual of mental disorders fourth edition- text revision; GAD, generalised anxiety disorder; PD/A, panic disorder with or without agoraphobia; ROM, routine outcome monitoring; SP, social phobia.

4.4. Results

4.4.1. Sample characteristics

Between 2004 and 2009, a total of 1.889 patients met the diagnostic criteria for PD/A, AP, SP and/or GAD, with at least moderate baseline severity as measured on the BSI-12 and the BAS according to the previously specified criteria. Figure 4.1 presents a flowchart of inclusion, 736 cases did not have follow-up, 153 cases had to be excluded as entire questionnaires (DEMOG, DAPP-SF and SF-36) had not been administered at baseline. From a further 7 patients, no age of onset of anxiety disorder could be obtained. For some patients, baseline measurements had taken place over several assessment sessions with different time intervals, in 76 cases these intervals exceeded 3 weeks, which was deemed unacceptable. This resulted in the exclusion of 972 patients, leaving a sample of 917 patients. Baseline sample characteristics are presented in table 4.1. The occurrence of anxiety disorders is presented in figure 4.2, showing PD/A was

most prevalent at 43%, followed by SP (29%), GAD (23%) and AP (22%). In total, 31% of patients presented with comorbid anxiety disorders (including OCD and PTSD). Comorbid mood disorder occurred in 52% of patients, 14% of patients presented with a comorbid somatoform disorder, 4% suffered from comorbid alcohol abuse or dependence and 4% presented with comorbid drug abuse or dependence.

The 917 patients who were included for analyses did not differ from the 972 excluded patients with regard to age or gender. Inclusion was associated with Dutch ethnicity (83% vs. 75% in the excluded group; χ^2 (1, 1679) = 13.180, p < 0.001, phi = 0.090), with higher prevalence of high education-level (19% vs. 14% in the excluded group; χ^2 (2, 1679) = 11.581, p = 0.003, phi =0.08) and with a diagnosis of comorbid depressive disorder (52% vs. 66% in the excluded group; χ^2 (1, 1889) = 4.162, p = 0.04, phi = 0.05). Included patients had significantly lower BSI-12 scores than excluded patients (M = 19.9, SD = 9.0 vs. M = 21.5, SD = 9.6; t (1886.95) = 3.88, p < 0.001), eta squared = 0.008, Cohen's d = 0.26. Similar differences, with slightly higher scores in the excluded group, existed on several DAPP-SF scales, the MADRS, Inh and SF-36 (data not shown).

4.4.2. Univariable predictors of response

Over the 2-year follow-up period, the cumulative proportion responding was 63.6%. The median follow-up was 308 days (IQR = 114-620). At 2 years, 856 patients (93%) had reached an endpoint, 61 patients (7%) still continued treatment. Univariable categorical predictors of response are shown in Table 4.2. Response over 2-year follow-up at p 0.10 was predicted by having non- Dutch ethnicity as opposed to Dutch ethnicity, living independently with a partner and/or children as opposed to residing with family, low as opposed to high education-level, having no daily occupation, suffering from multiple simultaneously occurring anxiety disorders, comorbid mood disorder, comorbid alcohol abuse or dependence, a diagnosis of AP or the absence of a diagnosis of PD/A. Univariable continuous predictors of response are presented in Table 4.3, showing associations with poor response forage, a range of DAPP-SF personality traits and the SF-36 scales measuring general health and bodily pain.

4.4.3. Multivariable predictors of response

Survival was best predicted by a set of thirteen covariates, $R^{2p,e}$ = 0.18 (O'Quigley et al., 2005); $R^{2p,v}$ = 0.12 (Royston, 2006). Table 4.4 shows HR's with CI and p-values for each of the covariates. All covariates except age, gender, PD/A, SP and GAD reliably predicted time to response at p 0.10. Patients suffering from AP had a 33% decreased chance of response. Patients with non-Dutch ethnicity had 29% less chance of responding within 2 years. Not

having a daily occupation decreased chances of response with 24%. A low education-level decreased chances of response with 24% although findings were non-significant. Living with family increased chances of response with 41%. Alcohol abuse or dependence decreased chances of response by 46% although findings were non-significant. A single SD increase on DAPP-SF subscales affective lability or conduct problems resulted in a respective 20% and 16% reduction of chances of response within two years. Figure 3 shows the Kaplan-Meier survival curves of naturalistic treatment response over the 2-year follow-up period.

Finally, the concurrence of multiple anxiety disorders versus single anxiety disorder, although univariably significant, did not independently predict outcome. Depressive or dysthymic comorbidity, somatoform comorbidity, marital status, drug abuse or dependence, pre-adult onset and severity of depressive symptoms as measured with the MADRS, all failed to achieve both univariable and multivariable significance. Sensitivity analyses, as described in the method section, confirmed findings for all covariates except for the associations with alcohol and ethnicity, which were less robust (data not shown).

4.5. Discussion

This study aimed at identifying predictors of 2-year outcome in a broad range of anxiety disorders in a naturalistic outpatient psychiatric specialty care setting. Eight independent socio-demographic and clinical predictors of response in PD/A, AP, SP and GAD emerged. With respect to socio-demographic factors, non-Dutch ethnicity, no daily occupation and low education-level (although non-significant) decreased chances of response, while living with family was protective. Regarding clinical factors, a diagnosis of AP, comorbid alcohol abuse or dependence (although non-significant), high scores on DAPP-SF affective lability and behaviour problems all decreased chances of response. These results largely confirm and contribute to earlier findings. First, findings of poor response in non-Dutch patients have not been previously reported. Although this might be explained by cultural differences or social barriers, or by members from ethnic minority groups receiving less adequate care (Lagomasino et al., 2011; Weisberg et al., 2007), it must be stressed that no information on the cultural background of the non-Dutch patients in our sample was available, therefore, these interpretations remain speculative and it is difficult to make further inferences. Findings of no daily occupation and lower education-levels predicting nonresponse, confirm earlier reports (Ramsawh et al., 2009; Roy-Byrne et al., 2003). This might bear on the broader concept of lower social economic status posing a risk factor (Roy-Byrne et al., 2003; Roy-Byrne et al., 2006), although both factors could also be a consequence of greater severity or chronicity of anxiety disorder and it should be noted that low education level did not reach significance in our model.

Figure 4.2 Prevalence of DSM-IV-TR anxiety disorders in the sample (n=917)
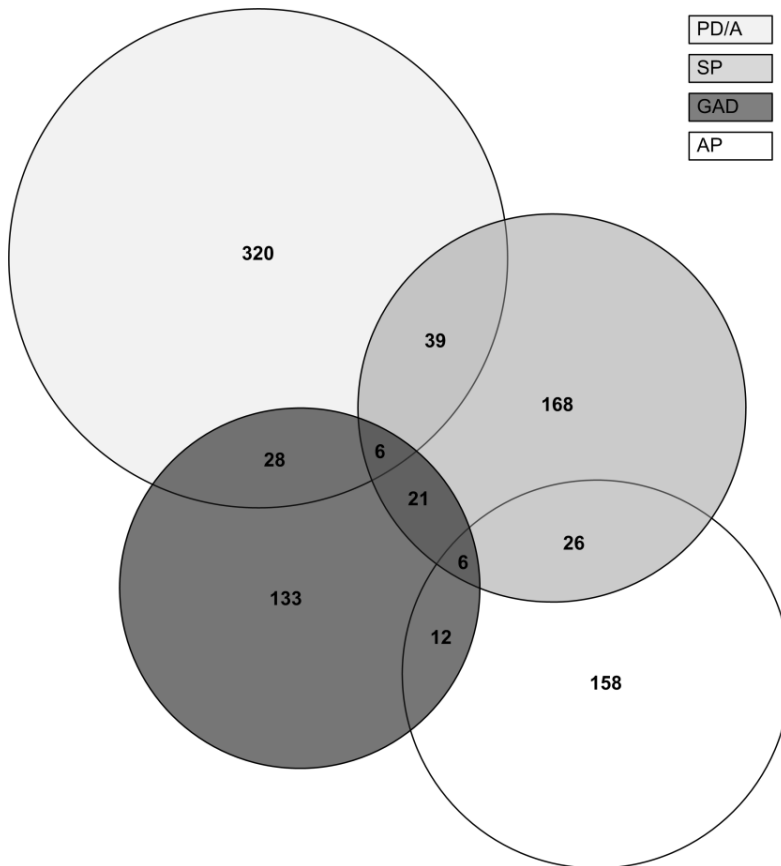
Numbers represent numbers of patients in each diagnostic category. The MINI International Neuropsychiatric Interview-Plus was used to collect diagnostic information. AP denotes agoraphobia without panic; DSM-IV-TR, Diagnostic and Statistical Manual of mental disorders fourth edition- text revision; GAD, generalised anxiety disorder; PD/A, panic disorder with or without agoraphobia; SP, social phobia.

Table 4.1 Baseline characteristics in 917 outpatients diagnosed with panic disorder with or without agoraphobia, agoraphobia, social phobia or generalised anxiety disorder.

Categorical variables	n	%
Male gender	329	35.9%
Non-Dutch ethnicity	158	17.2%
Married or living together	484	52.8%
Living situation		
- living independently with partner and /or children	576	62.8%
- living independently and alone	195	21.3%
- residing with family	146	15.9%
Education-level		
- high	174	19.0%
- medium	377	41.1%
- low	366	39.9%
Daily occupation	553	60.3%
Comorbid DSM-IV-TR depressive or dysthymic disorder	475	51.8%
Comorbid DSM-IV-TR somatoform disorder	124	13.5%
Comorbid alcohol abuse or dependence	42	4.6%
Comorbid drug abuse or dependence	34	3.7%
Pre-adult onset of anxiety disorder	345	37.6%
DSM-IV-TR panic disorder with or without agoraphobia	393	42.9%
DSM-IV-TR agoraphobia	202	22.0%
DSM-IV-TR social phobia	266	29.0%
DSM-IV-TR generalised anxiety disorder	206	22.5%
single anxiety disorder	626	68.3%
Continuous variables	**Mean (±SD)**	**IQR**
Age	36.9 (11.8)	27.0 - 46.0
BSI-12 score	19.9 (9.0)	13.0 -26.0
BAS score	19.0 (5.6)	15.0 - 22.0
MADRS score	20.0 (8.5)	14.0 - 26.0
Inh score	3.6 (3.0)	2.0 - 5.0
SF-36		
- physical functioning	75.4 (22.7)	60.0 - 95.0
- social functioning	40.3 (25.2)	25.0 - 62.5
- physical problems	35.3 (39.1)	0 - 75.0
- emotional problems	23.6 (32.9)	0 - 33.3
- mental health	37.8 (15.7)	28.0 - 48.0
- vitality	33.4 (16.1)	20.0 - 45.0
- bodily pain	65.1 (26.9)	44.9 - 89.8
- general health	50.6 (19.9)	35.0 - 65.0

Categorical variables are presented as n (percentage), continuous variables are presented as mean (± standard deviation [SD]), interquartile range (IQR). The MINI International Neuropsychiatric Interview-Plus was used to collect diagnostic information. BAS denotes Brief Anxiety Scale; BSI-12, Brief Symptom Inventory twelve item version; DSM-IV-TR, Diagnostic and Statistical Manual of mental disorders fourth edition- text revision; Inh, Inhibition scale derived from the Comprehensive Psychopathological Rating Scale; MADRS, Montgomery Åsberg Depression Rating Scale; SF-36,Short Form-36.

4

Table 4.2 Univariable Hazard Ratios of response for baseline categorical variables in 917 patients diagnosed with panic disorder with or without agoraphobia, agoraphobia, social phobia or generalised anxiety disorder.

Categorical variables	HR (95% CI)	p-value
Female gender	1 (ref.)	
Male gender	0.95 (0.77-1.17)	0.62
Dutch ethnicity	1 (ref.)	
Non-Dutch ethnicity	0.70 (0.52-0.95)	0.02
Married or living together	1 (ref.)	
Not married or cohabiting	1.01 (0.82-1.24)	0.91
Living situation independently with partner and /or children	1 (ref.)	
Living situation independently and alone	0.94 (0.72-1.23)	0.65
Living situation with family	1.39 (1.06-1.83)	0.02
Education level high	1 (ref.)	
Education level medium	1.03 (0.79-1.36)	0.82
Education level low	0.74 (0.56-0.98)	0.04
Daily occupation	1 (ref.)	
No daily occupation	0.74 (0.59-0.91)	0.005
Single anxiety disorder	1 (ref.)	
Multiple anxiety disorders	0.79 (0.63-1.00)	0.05
No comorbid depressive or dysthymic disorder	1 (ref.)	
Comorbid depressive or dysthymic disorder	0.84 (0.69-1.04)	0.10
No comorbid somatoform disorder	1 (ref.)	
Comorbid somatoform disorder	0.99(0.72-1.34)	0.92
No alcohol abuse or dependence	1 (ref.)	
Alcohol abuse or dependence	0.46 (0.24-0.89)	0.02
No drug abuse or dependence	1 (ref.)	
Drug abuse or dependence	1.00 (0.60- 1.68)	0.99
Adult onset	1 (ref.)	
Pre-adult onset	1.02 (0.82-1.26)	0.88
No DSM-IV-TR panic disorder with or without agoraphobia	1 (ref.)	
DSM-IV-TR panic disorder with or without agoraphobia	1.26 (1.03-1.55)	0.03
no DSM-IV-TR agoraphobia	1 (ref.)	
DSM-IV-TR agoraphobia	0.64 (0.48-0.85)	0.002
no DSM-IV-TR social phobia	1 (ref.)	
DSM-IV-TR social phobia	0.91 (0.73-1.15)	0.43
no DSM-IV-TR generalised anxiety disorder	1 (ref.)	
DSM-IV-TR generalised anxiety disorder	1.03 (0.81-1.32)	0.80

Hazard Ratios (HR) are presented with 95% confidence interval (CI) and p-value; ref. signifies the reference category. Response was defined as ≥50% reduction on the BSI-12 and the BAS. The MINI International Neuropsychiatric Interview-Plus was used to collect diagnostic information DSM-IV-TR, Diagnostic and Statistical Manual of mental disorders fourth edition-text revision.

Table 4.3 Univariable Hazard Ratios of response for baseline continuous variables in 917 patients diagnosed with panic disorder with or without agoraphobia, agoraphobia, social phobia or generalised anxiety disorder.

Continuous variables	HR (95% CI)	p-value
Age	0.90 (0.81-1.00)	0.05
MADRS score	0.97 (0.87-1.09)	0.66
Inh score	1.05 (0.95-1.18)	0.33
DAPP-SF		
- submissiveness	0.90 (0.81-1.00)	0.04
- cognitive distortion	0.83 (0.75-0.92)	0.001
- identity problems	0.86 (0.77-0.95)	0.005
- affective lability	0.78 (0.70-0.87)	<0.001
- stimulus seeking	0.92 (0.82-1.03)	0.14
- compulsivity	0.92 (0.83-1.02)	0.12
- restricted expression	0.94 (0.85-1.04)	0.35
- callousness	0.93 (0.83-1.04)	0.19
- oppositionality	0.83 (0.75-0.92)	<0.001
- intimacy problems	0.91 (0.82-1.01)	0.07
- rejection	1.04 (0.94-1.15)	0.41
- anxiousness	0.84 (0.76-0.94)	0.002
- conduct problems	0.81 (0.71-0.92)	0.001
- suspiciousness	0.83 (0.74-0.93)	0.001
- social avoidance	0.87 (0.79-0.97)	0.01
- narcissism	0.96 (0.86-1.07)	0.46
- insecure attachment	0.89 (0.81-0.99)	0.04
- self-harm	0.84 (0.75-0.95)	0.004
SF-36		
- physical functioning	0.93 (0.84-1.04)	0.22
- social functioning	0.95 (0.85-1.06)	0.37
- physical problems	0.95 (0.86-1.06)	0.38
- emotional problems	0.95 (0.85-1.07)	0.40
- mental health	0.98 (0.87-1.10)	0.68
- vitality	0.97 (0.86-1.09)	0.58
- bodily pain	0.89 (0.80-0.99)	0.04
- general health	0.80 (0.71-0.89)	<0.001

Hazard Ratios (HR) are presented with 95% confidence interval (CI)l and p-value, ref. signifies the reference category. Response was defined as ≥50% reduction on the BSI-12 and the BAS; BAS denotes Brief Anxiety Scale; BSI-12, Brief Symptom Inventory twelve item version; DAPP-SF, Dimensional Assessment of Personality Pathology-Short Form; DSM-IV-TR, Diagnostic and Statistical Manual of mental disorders fourth edition- text revision; Inh, Inhibition scale derived from the Comprehensive Psychopathological Rating Scale; MADRS, Montgomery Åsberg Depression Rating Scale; SF-36, Short Form-36. To facilitate comparability of hazard ratios, z-values were used and SF-36 scores were inverted.

4

Table 4.4 Multivariable Hazard Ratios of response in 917 patients diagnosed with panic disorder, agoraphobia, social phobia or generalised anxiety disorder.

		HR (95% CI)	p value
Block 1	Age	1.00 (0.88- 1.13)	0.95
	Gender		
	- Female	1 (ref.)	
	- Male	1.12 (0.88-1.43)	0.36
	DSM-IV-TR panic disorder with or without agoraphobia		
	- no PD	1 (ref.)	
	- PD	1.11 (0.79-1.55)	0.56
	DSM-IV-TR agoraphobia		
	- no AP	1 (ref.)	
	- AP	0.67 (0.45-0.99)	0.04
	DSM-IV-TR social phobia		
	- no SP	1 (ref.)	
	- SP	0.92 (0.67-1.26)	0.59
	DSM-IV-TR generalised anxiety disorder		
	- no GAD	1 (ref.)	
	- GAD	1.07 (0.77-1.48)	0.71
Block 2	Ethnicity		
	- Dutch	1 (ref.)	
	- Non-Dutch	0.71 (0.52-0.96)	0.02
	Occupation		
	- daily occupation	1 (ref.)	
	- no daily occupation	0.76 (0.61-0.95)	0.02
	Education-level		
	- High	1 (ref.)	
	- Medium	1.00 (0.75-1.34)	0.98
	- Low	0.76 (0.56-1.02)	0.07
	Living situation		
	- Independently with partner and/or children	1 (ref.)	
	- Independently alone	0.95 (0.72-1.24)	0.69
	- With family	1.41 (1.01-1.97)	0.045
	Alcohol abuse or dependence		
	- No alcohol abuse or dependence	1 (ref.)	
	- Alcohol abuse or dependence	0.54 (0.27-1.06)	0.07
	DAPP-SF affective lability	0.80 (0.71-0.89)	<0.001
	DAPP-SF conduct problems	0.84 (0.73-0.98)	0.02

Hazard Ratios (HR) are presented with 95% confidence interval (CI) and p-value, ref. signifies the reference category. Response was defined as ≥50% reduction on the BSI-12 and the BAS. The MINI International Neuropsychiatric Interview-Plus was used to collect diagnostic information. AP denotes agoraphobia without panic; BAS, Brief Anxiety Scale; BSI-12, Brief Symptom Inventory twelve item version; DAPP-SF, Dimensional Assessment of Personality Pathology-Short Form; DSM-IV-TR, Diagnostic and Statistical Manual of mental disorders fourth edition- text revision; GAD, generalised anxiety disorder; PD/A, panic disorder with or without agoraphobia; SP, social phobia. To facilitate comparability of hazard ratios among continuous variables, z-values were used. The variables in block 1 (Age, gender, panic disorder with or without agoraphobia, agoraphobia, social phobia and generalised anxiety disorder) were forced in the model, the variables in Block 2 were selected through a backward stepwise procedure described in the methods section.

The finding that living with family was a protective factor was counter-intuitive as in the Netherlands it is abnormal for adults to live with family and this could be perceived as a sign of poor functioning. In addition, family members often accommodate anxiety, which is known to contribute to maintaining anxiety (Chambless, 2012). However, as the group of patients living with family in our study largely consisted of younger patients (e.g. under 26), a group in which living with family might be considered a more 'normal' and therefore possibly healthy attribute, it could be hypothesized that this association is typical for younger patients. Finally the present findings concur with studies reporting no predictive value of age (Chavira et al., 2009; Van Ameringen et al., 2004; Beutel et al., 2011; Beard et al., 2010; Serretti et al., 2009).

With regard to clinical factors, a diagnosis of AP was associated with poor response, partially corroborating previous findings (Beard et al., 2010). Agoraphobia was associated with a higher degree of morbidity and more treatment resistant symptoms of phobic avoidance in patients with PD/A (Keller et al., 1994), possibly, present findings reflect a broader refractoriness of agoraphobia. Comorbid alcohol abuse or dependence was associated with poor response. Although this finding was based on a relatively small group of patients and was not significant, it does support previous reports (Bruce et al., 2005). Alcohol abuse or dependence is frequently reported in anxiety disorders (Kushner et al., 2000), with suggestions of the two disorders feeding into each other, possibly through self-medication (Menary et al., 2011). Finally, affective lability, a factor found to be related to neuroticism and emotional dysregulation (Van Kampen et al., 2008), and behaviour problems posed risk factors, confirming earlier reports of personality disorders or maladaptive personality traits predicting poor outcome (Ansell et al., 2011; Telch et al., 2011; Beutel et al., 2011).

Other candidate clinical predictors like SP, comorbid MDD, somatoform disorder, the concurrence of multiple anxiety disorders, or drug abuse or dependence were not independently associated with response. These findings contradict earlier reports (Bruce et al., 2005; Beutel et al., 2011), although the absence of an association with MDD has been previously reported (Beutel et al., 2011; Roy-Byrne et al., 2003; Serretti et al., 2009). Part of the dissimilar findings may be due to methodological differences. Pre-adult onset did not predict response, substantiating previous findings (Ramsawh et al., 2011), but contradicting others (Penninx et al., 2011; Van Ameringen et al., 2004). Possibly this finding is specific to MDD and SP. Also, the retrospective method of determining age of onset might have resulted in a retrospective bias, although this is true for the majority of studies assessing age of onset (Simon & Vonkorff, 1995; Kessler et al., 2007). Another possible explanation might lie in the existence of different age of onset distributions for different anxiety disorders (Ramsawh et al., 2011).

4

The present study has high external validity due to the large sample size and the naturalistic approach, with limited use of in- and exclusion criteria. The use of a structured clinical diagnostic instrument, self-report measures as well as observer-rated measures, computerized data collection, and data collection by trained research nurses who were not involved in treatment, further strengthen our study. Nevertheless, results have to be interpreted in light of a number of limitations. First of all, the design may be subject to selection bias (Rothwell, 2005). We have no information on patients not included in ROM and they might differ from included patients. However, inclusion in ROM is high at about 80% and a previous study of our depressed sample demonstrated no differences in baseline characteristics between patients who were and were not included (van der Lem et al., 2011). Second, as in many observational studies, attrition is high and we do not know the reasons for loss to follow-up (van Noorden et al., 2012). Furthermore, treatment data were unavailable, therefore we could not incorporate this in analyses. Previous studies in our ROM cohort did demonstrate that treatment for anxiety disorders is generally delivered according to guidelines and exists of pharmacotherapy (23%), psychotherapy (59%) or combination therapy (16%) (van Fenema et al., 2012).

Additionally, no data on psychiatric history, somatic comorbidity, cultural background or family history were available. Also, prevalence of agoraphobia in our sample was high compared to reports based on the general population (Somers et al., 2006), although in a recent Dutch general population study, comparable prevalence has been reported (Penninx et al., 2011). The MINI lacks sensitivity and specificity with regard to AP in clinical samples (Lecrubier et al., 1997). Possibly the high prevalence of AP is a by-product of other diagnoses. Therefore, results with regard to AP may reflect a negative predictive value of agoraphobic symptoms occurring with other disorders, rather than of a diagnosis of AP per se. Furthermore, as age of onset was assessed retrospectively, measurement error is possible (Simon & Vonkorff, 1995; Knauper et al., 1999). Memory for psychiatric history has been demonstrated to be unreliable (Moffitt et al., 2010; Giuffra & Risch, 1994) and the possibility of underreporting of psychiatric history should be taken into account. Also, response was measured over a limited period of up to 2 years without taking possible relapse into account, subjects with less than 2-year follow-up who did not reach the response criterion were classified as non-responders. This classification is arbitrary and could have influenced results. Finally, due to the observational design, results reflect associations; therefore, causality cannot be inferred. However, our results provide a valuable addition to and validation of previous findings (Rothwell, 2005; van der Lem et al., 2011).

In conclusion, we have identified important predictors of outcome in anxiety disorders from a broad set of general social demographic as well as clinical patient characteristics. Our results show that patients who are non-Dutch, have no daily occupation,

have a low education-level, do not live with family, suffer from alcohol abuse or dependence, are diagnosed with AP and display high levels of affect lability and behaviour problems, are at elevated risk of poor response. Possibly these findings indicate that the same factors that may limit patients' participation in society, e.g. no occupation, low education, agoraphobia, or maladjusted personality characteristics, are associated with impaired response. As this study is explorative in nature, additional studies examining a broad spectrum of possible predictors are called for. Even so, valuable new insights have been added, advocating broad screening of patients at intake on various domains to help clinicians identify patients who are at risk of poor outcome as they deserve special attention in treatment.

Figure 4.3 Kaplan Meier curves for response in 917 patients with DSM-IV-TR anxiety disorders
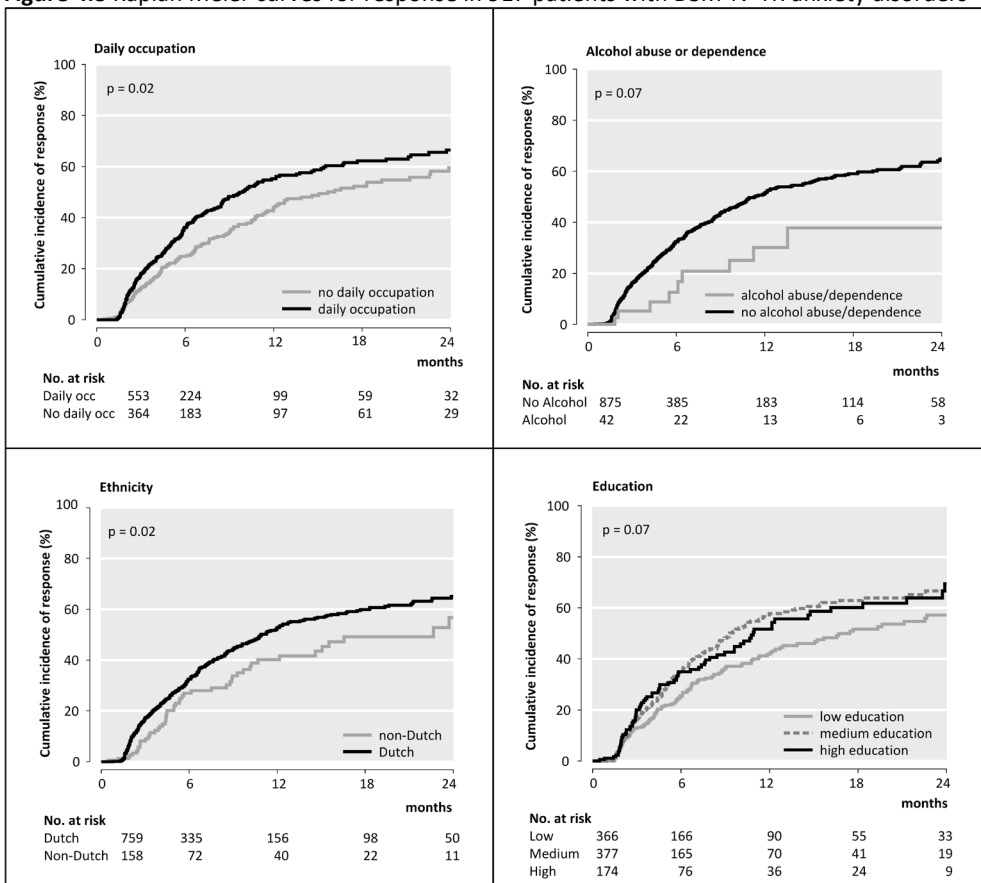
Figure 4.3 *(continued)*
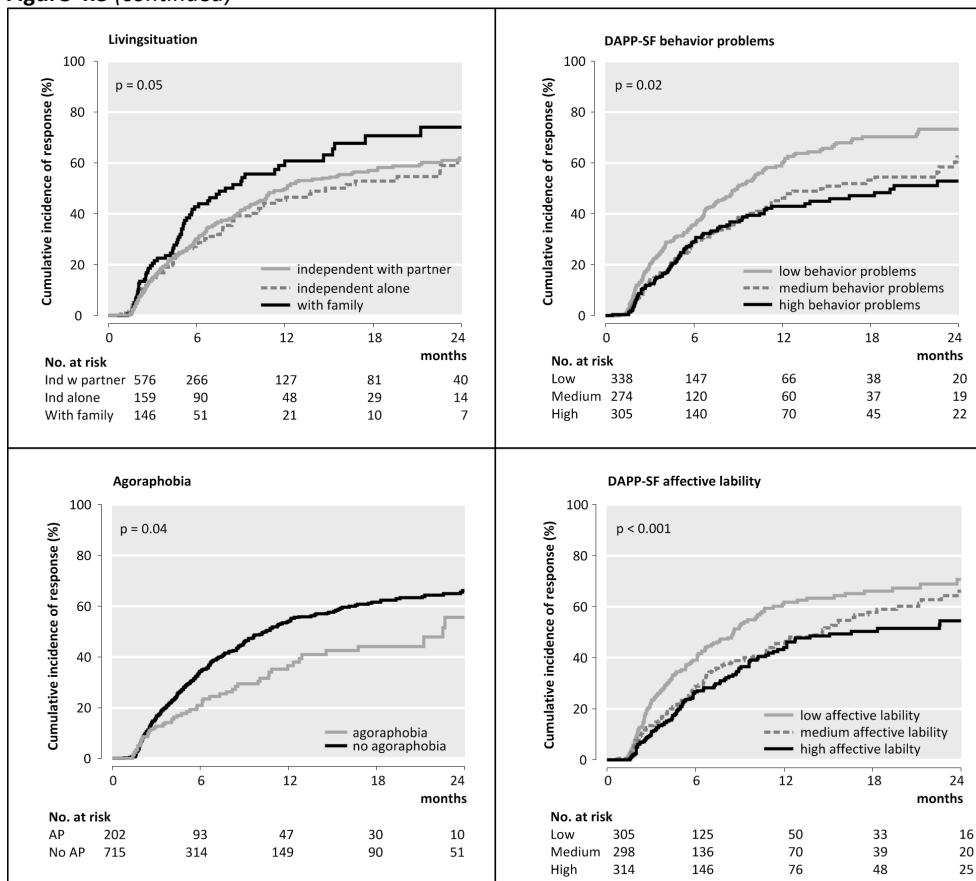
Patients were diagnosed with panic disorder with or without agoraphobia, agoraphobia, social phobia or generalised anxiety dis-order. Kaplan Meier curves are shown for the cumulative incidence of response, de-fined as ≥ 50% reduction on the BSI-12 and the BAS in a naturalistic sample. DAPP-SF denotes Dimensional Assessment of Personality Pathology Short Form. To faci-litate compa-rability, tertiles were construc-ted for DAPP-SF affective lability and DAPP-SF behaviour pro-blems. The MINI International Neuropsychiatric Interview- plus was used to collect diagnostic information.

Reference List

Aaronson NK, Muller M, Cohen PDA, Essink-Bot ML, Fekkes M, Sanderman R, et al. Translation, validation, and norming of the Dutch language version of the SF-36 health survey in community and chronic disease populations. J Clin Epidemiol 1998;51:1055-68.

Angst J, Vollrath M. The natural-history of anxiety disorders. Acta Psychiatr Scand 1991;84:446-52.

Ansell EB, Pinto A, Edelen MO, Markowitz JC, Sanislow CA, Yen S, et al. The association of personality disorders with the prospective 7-year course of anxiety disorders. Psychol Med 2011;41:1019-28.

Åsberg M, Montgomery SA, Perris C, Schalling D, Sedvall G. Comprehensive psychopathological rating-scale. Acta Psychiatr Scand 1978:5-27.

Baldwin DS, Allgulander C, Altamura AC, Angst J, Bandelow B, den Boer J, et al. Manifesto for a European anxiety disorders research network. Eur Neuropsychopharmacol 2010;20:426-32.

Beard C, Moitra E, Weisberg RB, Keller MB. Characteristics and predictors of social phobia course in a longitudinal study of primary-care patients. Depress Anxiety 2010;27:839-45.

Beutel ME, Bleichner F, von Heymann F, Tritt K, Hardt J. Inpatient psychosomatic treatment of anxiety disorders: comorbidities, predictors, and outcomes. Int J Clin Health Psychol 2011;11:443-57.

Bruce SE, Yonkers KA, Otto MW, Eisen JL, Weisberg RB, Pagano M, et al. Influence of psychiatric comorbidity on recovery and recurrence in generalised anxiety disorder, social phobia, and panic disorder: a 12-year prospective study. Am J Psychiatry 2005;162:1179-87.

Chambless DL. Adjunctive couple and family intervention for patients with anxiety disorders. J Clin Psychol 2012;68:548-60.

Chavira DA, Stein MB, Golinelli D, Sherbourne CD, Craske MG, Sullivan G, et al. Predictors of clinical improvement in a randomised effectiveness trial for primary care patients with panic disorder. J Nerv Ment Dis 2009;197:715-21.

De Beurs E, den Hollander-Gijsman ME, van Rood YR, van der Wee NJA, Giltay EJ, van Noorden MS, et al. Routine outcome monitoring in the Netherlands: practical experiences with a web-based strategy for the assessment of treatment outcome in clinical practice. Clin Psychol Psychother 2011;18:1-12.

De Beurs E, Zitman FG. De brief symptom inventory (BSI) De betrouwbaarheid van een handzaam alternatief voor de SCL-90. Maandbl Geest Volksgezondh 2006;61:120-41.

Derogatis LR, Melisaratos N. The brief symptom inventory e an introductory report. Psychol Med 1983;13:595-605.

Franke GH, Ankerhold A, Haase M, Jager S, Togel C, Ulrich C, et al. The usefulness of the brief symptom inventory 18 (BSI-18) in psychotherapeutic patients. Psychother Psychosom Med Psychol 2011;61:82-6.

Friedman MJ, Resick PA, Bryant RA, Strain J, Horowitz M, Spiegel D. Classification of trauma and stressor-related disorders in DSM-5. Depress Anxiety 2011;28:737-49.

Giuffra LA, Risch N. Diminished recall and the cohort effect of major depression - a simulation study. Psychol Med 1994;24:375-83.

4

Goekoop JG, Hoeksema T, Knoppert van der Klein EAM, Klinkhamer RA, Van Gaalen HAE, Van Londen L, et al. Multidimensional ordering of psychopathology a factor-analytic study using the comprehensive psychopathological rating-scale. Acta Psychiatr Scand 1992;86:306-12.

Gustavsson A, Svensson M, Jacobi F, Allgulander C, Alonso J, Beghi E, et al. Cost of disorders of the brain in Europe. Eur Neuropsychopharmacol 2010;2011(21): 718-79.

Hoertel N, Le Strat Y, Blanco C, Lavaud P, Dubertret C. Generalizability of clinical trial results for generalised anxiety disorder to community samples. Depress Anxiety 2012;29:614-20.

Hosmer DJ, Lemeshow S, May S. Applied survival analysis: regression modeling of time to event data (Wiley Series in probability and statistics). Wiley-Interscience; 2008.

Keller MB, Yonkers KA, Warshaw MG, Pratt LA, Gollan JK, Massion AO, et al. Remission and relapse in subjects with panic disorder and panic with agoraphobia - a prospective short-interval naturalistic follow-up. J Nerv Ment Dis 1994;182:290-6.

Kessler RC, Angermeyer M, Anthony JC, de Graaf R, Demyttenaere K, Gasquet I, et al. Lifetime prevalence and age-of-onset distributions of mental disorders in the World Health Organization's world mental health survey initiative. World Psychiatry 2007;6:168-76.

Knauper B, Cannel CF, Schwarz N, Bruce ML, Kessler RC. Improving accuracy of major depression age-of-onset reports in the US national comorbidity survey. Int J Methods Psychiatr Res 1999;8:39-48.

Kushner MG, Abrams K, Borchardt C. The relationship between anxiety disorders and alcohol use disorders: a review of major perspectives and findings. Clin Psychol Rev 2000;20:149-71.

Lagomasino IT, Stockdale SE, Miranda J. Racial-ethnic composition of provider practices and disparities in treatment of depression and anxiety. Psychiatr Serv 2011;62:1019-25.

Lebeau RT, Glenn D, Liao B, Wittchen HU, Beesdo-Baum K, Ollendick T, et al. Specific phobia: a review of DSM-IV specific phobia and preliminary recommendations for DSM-V. Depress Anxiety 2010;27:148-67.

Lecrubier Y, Sheehan DV, Weiller E, Amorim P, Bonora I, Sheehan KH, et al. The Mini International Neuropsychiatric Interview (MINI). A short diagnostic structured interview: reliability and validity according to the CIDI. Eur Psychiatry 1997;12: 224-31.

Livesley WJ, Jang KL, Vernon PA. Phenotypic and genetic structure of traits delineating personality disorder. Arch Gen Psychiatry 1998;55:941-8.

Menary KR, Kushner MG, Maurer E, Thuras P. The prevalence and clinical implications of self-medication among individuals with anxiety disorders. J Anxiety Disord 2011;25:335-9.

Moffitt TE, Caspi A, Taylor A, Kokaua J, Milne BJ, Polanczyk G, et al. How common are common mental disorders? Evidence that lifetime prevalence rates are doubled by prospective versus retrospective ascertainment. Psychol Med 2010;40:899-909.

Montgomery SA, Åsberg M. New depression scale designed to be sensitive to change. Br J Psychiatry 1979;134:382-9.

O'Quigley J, Xu R, Stare J. Explained randomness in proportional hazards models. Stat Med 2005;24:479-89.

Penninx BWJH, Nolen WA, Lamers F, Zitman FG, Smit JH, Spinhoven P, et al. Two year course of depressive and anxiety disorders: results from the Netherlands study of depression and anxiety (NESDA). J Affect Disord 2011;133:76-85.

Ramsawh HJ, Raffa SD, Edelen MO, Rende R, Keller MB. Anxiety in middle adulthood: effects of age and time on the 14-year course of panic disorder, social phobia and generalised anxiety disorder. Psychol Med 2009;39:615-24.

Ramsawh HJ, Weisberg RB, Dyck I, Stout R, Keller MB. Age of onset, clinical characteristics, and 15-year course of anxiety disorders in a prospective, longitudinal, observational study. J Affect Disord 2011;132:260-4.

Rothwell PM. Treating individuals 1-external validity of randomised controlled trials: "To whom do the results of this trial apply?". Lancet 2005;365:82-93.

Roy-Byrne P, Craske MG, Sullivan G, Rose RD, Edlund MJ, Lang AJ, et al. Delivery of evidence-based treatment for multiple anxiety disorders in primary care a randomised controlled trial. JAMA 2010;303:1921-8.

Roy-Byrne P, Sherbourne C, Miranda J, Stein M, Craske M, Golinelli D, et al. Poverty and response to treatment among panic disorder patients in primary care. Am J Psychiatry 2006;163:1419-25.

Roy-Byrne PP, Russo J, Cowley DS, Katon WJ. Unemployment and emergency room visits predict poor treatment outcome in primary care panic disorder. J Clin Psychiatry 2003;64:383-9.

Royston P. Explained variation for survival models. Stata J 2006;6:83-96.

SerrettiA, ChiesaA, Calati R, Perna G, Bellodi L, De Ronchi D.Commongenetic, clinical; demographic and psychosocial predictors of response to pharmacotherapy in mood and anxiety disorders. Int Clin Psychopharmacol 2009;24:1-18.

Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J,Weiller E, et al. The Mini-International Neuropsychiatric Interview (MINI): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59:22-33.

Simon GE, Vonkorff M. Recall of psychiatric history in cross-sectional surveys - implications for epidemiologic research. Epidemiol Rev 1995;17:221-7.

Somers JM, Goldner EM, Waraich P, Hsu L. Prevalence and incidence studies of anxiety disorders: a systematic review of the literature. Can J Psychiatry 2006;51:100-13.

Stein DJ, Fineberg NA, Bienvenu OJ, Denys D, Lochner C,Nestadt G, et al. Should OCD be classified as an anxiety disorder in DSM-V? Depress Anxiety 2010;27:495-506.

Telch MJ, Kamphuis JH, Schmidt NB. The effects of comorbid personality disorders on cognitive behavioral treatment for panic disorder. J Psychiatr Res 2011;45: 469-74.

Tyrer P, Owen RT, Cicchetti DV. The brief scale for anxiety e a subdivision of the comprehensive psychopathological rating-scale. J Neurol Neurosurg Psychiatry 1984;47:970-5.

Tyrer P, Seivewright H, Johnson T. The Nottingham study of neurotic disorder: predictors of 12-year outcome of dysthymic, panic and generalised anxiety disorder. Psychol Med 2004;34:1385-94.

Van Ameringen M, Oakman J, Mancini C, Pipe B, Chung H. Predictors of response in generalised social phobia: effect of age of onset. J Clin Psychopharmacol 2004;24:42-8.

Van der Lem R, Van der Wee NJA, Van Veen T, Zitman FG. The generalizability of antidepressant efficacy trials to routine psychiatric out-patient practice. Psychol Med 2011;41:1353-63.

Van Fenema E, van der Wee NJA, Bauer M, Witte CJ, Zitman FG. Assessing adherence to guidelines for common mental disorders in routine clinical practice. Int J Qual Health Care 2012;24:72-9.

Van Kampen D, De Beurs E, Andrea H. A short form of the dimensional assessment of personality pathology-basic questionnaire (DAPP-BQ): the DAPP-SF. Psychiatry Res 2008;160:115-28.

Van Noorden MS, Minkenberg SE, Giltay EJ, Den Hollander-Gijsman ME, Van Rood YR, van der Wee NJ, et al. Pre-adult versus adult onset major depressive disorder in a naturalistic patient sample: the Leiden routine outcome monitoring study. Psychol Med 2011;41:1407-17.

Van Noorden MS, Van Fenema EM, Van der Wee NJA, Van Rood YR, Carlier IVE, Zitman FG, et al. Predicting outcomes of mood, anxiety and somatoform disorders: the Leiden routine outcome monitoring study. J Affect Disord 2012;142: 122-31.

Van Vliet IM, De Beurs E. Het MINI Internationaal Neuropsychiatrisch Interview (MINI) een kort gestructureerd diagnostisch psychiatrisch interview voor DSMIV- en ICD-10-stoornissen. Tijdschr Psychiatr 2007;49:393-7.

Ware JE, Sherbourne CD. The Mos 36-item short-form health survey (SF-36). 1. Conceptual-framework and item selection. Med Care 1992;30:473-83.

Weisberg RB, Dyck I, Culpepper L, Keller MB. Psychiatric treatment in primary care patients with anxiety disorders: a comparison of care received from primarycare providers and psychiatrists. Am J Psychiatry 2007;164:276-82.

Wittchen HU, Jacobi F, Rehm J, Gustavsson A, Svensson M, Jonsson B, et al. The size and burden of mental disorders and other disorders of the brain in Europe 2010. Eur Neuropsychopharmacol 2011;21:655-79.

Yonkers KA, Bruce SE, Dyck IR, Keller MB. Chronicity, relapse, and illness course of panic disorder, social phobia, and generalised anxiety disorder: findings in men and women from 8 years of follow-up. Depress Anxiety 2003;17:173-9.

Zabora J, BrintzenhofeSzoc K, Jacobsen P, Curbow B, Piantadosi S, Hooker C, et al. A new psychosocial screening instrument for use with cancer patients. Psychosomatics 2001;42:241-6.

Zimmerman M, Chelminski I. Clinician recognition of anxiety disorders in depressed outpatients. J Psychiatr Res 2003;37:325-33.

Zitman FG. ROM bij stemmings- angst- en somatoforme stoornissen; bemoedigende resultaten. Tijdschr Psychiatr 2012;54:173-7.

Chapter 5

An evaluation of prognostic factors associated with remission of suicidal ideation in anxious and depressed outpatients: the Leiden Routine Outcome Monitoring study

Abstract

Suicidal ideation frequently occurs in anxiety and mood disorders. Although in some patients suicidal ideation subsides, in others it persists. Identifying patients at risk of sustained suicidal ideation could aid therapeutic decisions and prevent suicide. Routinely collected data of 777 anxious and/or depressed outpatients with baseline suicidal ideation (measured with Montgomery-Åsberg Depression Rating Scale item 10) and up to 2-years follow-up, were analysed with survival analysis. Low education levels predicted a 14% lower chance of remission of suicidal ideation; a single standard deviation (SD) increase in baseline depression and self-harm scores corresponded to 16% and 23% lower chances of remission. Finally, one SD decrease in general health perception scores corresponded to an 8% reduced chance of remission. Our results underpin the needs of patients with suicidal ideation with low education levels, severe depression, severe self-harm and poor general health perception, who are at increased risk of sustained suicidal ideation.

5.1 Introduction

Among outpatients with mood- and anxiety disorders, thoughts of suicide frequently occur. Prevalences range from 8% in agoraphobia to 84% in major depressive disorder (Eikelenboom et al., 2012). Suicidal ideation (SI) reflects severe suffering, and is a strong predictor of suicide attempts (Ahrens et al., 2000; ten Have et al., 2009) and as such, is targeted in treatment guidelines (Jacobs & Brewer, 2006; van Hemert et al., 2012). Although SI often diminishes during the course of treatment, in a substantial number of subjects it persists over time (Borges et al., 2008), increasing the risk of death by suicide (Hubers et al., submitted for publication). Although numerous studies have focussed on predictors of attempted or completed suicide (Ryan & Large, 2013), relatively little attention has been paid to predicting the course of SI. The identification of patients at risk of sustained SI is urgent, as this could aid clinicians when making therapeutic decisions and, ultimately, prevent suicide.

Previous studies have identified a number of prognostic factors associated with remission of SI: older age, lower education, lower income, cardiovascular disease, trauma, dysthymic disorder, depressive symptoms, anxiety, baseline severity of SI, self-harm, psychotic experiences (hearing sounds or voices that others did not hear), neuroticism, defeat, and externalising behaviour were all associated with lower chances of remission of SI (Enns et al., 2003; Prinstein et al., 2008; Cukrowicz et al., 2009; ten Have et al., 2009; Taylor et al., 2011; Kelleher et al., 2014a). However, previous study populations were diverse (e.g., general population (ten Have et al., 2009; Kelleher et al., 2014a), students (Taylor et al., 2011), adolescent inpatients (Enns et al., 2003; Prinstein et al., 2008), and depressed in- and outpatients (Cukrowicz et al., 2009)), study periods varied from 12 weeks to two years, and the relative prognostic significance of the factors previously identified in different studies remains to be determined, as they were never studied simultaneously. A study focussing on a broad set of previously identified prognostic factors in a naturalistic patient group that often presents with SI will clarify the relative prognostic value of each candidate variable. This will inform clinicians as to what easily obtainable patient characteristics are associated with remission of SI in clinical practice, and help future research aimed at developing a prediction model for remission of SI.

The present study was aimed at evaluating prognostic factors associated with remission of SI over a two-year follow-up period. We analysed data from adult outpatients with SI in a naturalistic treatment setting who were diagnosed with depression and/or anxiety disorder(s). We included a broad set of previously identified prognostic factors: age, education, dysthymic disorder, depression severity, anxiety severity, baseline severity of SI, self-harm, psychotic experiences, neuroticism, and externalising symptoms. In addition to these previously identified prognostic factors, based on clinical experience, we expected that

impulsiveness and subjective general health might also be associated with the course of SI. Both have both been cross-sectionally associated with SI (Goodwin & Olfson, 2002; Brezo et al., 2006). Results of this study will present a synthesis of previous findings. This study is the first to simultaneously evaluate multiple previously identified correlates of the course of SI in a clinical setting. Findings will help clinicians to identify patients at risk of sustained SI, to facilitate treatment decisions, and eventually to prevent suicides.

5.2 Material and methods

5.2.1 Patients and procedure

All subjects were outpatients at Rivierduinen, a mental healthcare provider in the Leiden area in The Netherlands, or at the department of psychiatry of the Leiden University Medical Centre (LUMC). All patients were aged 18 through 65, had adequate command of the Dutch language, and met diagnostic statistical manual of mental disorders- fourth edition-text revision (DSM-IV-TR; American Psychiatric Association, 2000) criteria for one or more of the following disorders: minor or major depressive disorder, dysthymia, panic disorder with or without agoraphobia, agoraphobia without panic, social phobia, generalised anxiety disorder, obsessive compulsive disorder, specific phobia, or post-traumatic stress disorder. In addition, all patients had SI, defined as a score of 2 or higher (Perroud et al., 2009a; Perroud et al., 2009b; van Noorden et al., 2010) on the Montgomery-Åsberg Depression Rating Scale (MADRS; Montgomery & Åsberg, 1979) item 10 on suicidal thoughts (see section 2.2 Measures). All patients were administered self-report and observer-rated measures at intake, and were typically offered repeat questionnaires every 3-4 months of treatment by trained research nurses. This procedure was aimed primarily at informing patients and clinicians and is known as Routine Outcome Monitoring (ROM; De Beurs et al., 2011). Patients who did not have any follow-up assessments or who had missing data (primarily resulting from the failure to administer complete questionnaires) were excluded form analyses. In concordance with Dutch guidelines, all patients received standard outpatient care, which is based on a stepped care model and consists of psychotherapy, pharmacotherapy, or combination therapy (van Fenema et al., 2012). Data were anonymised and their use in scientific research was approved by the Ethical Review Board at the LUMC.

5.2.2 Measures

Primary outcome in this study was SI, which was assessed by a psychiatric research nurse at baseline and follow-up with item 10 of the MADRS (Perroud et al., 2009a; Perroud et al.,

2009b; van Noorden et al., 2010) (figure 1). This item evaluates the presence of suicidal thoughts over the previous week on a seven-point Likert scale by assessing: "Suicidal Thoughts-Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts and the preparations for suicide. Suicide attempts should not in themselves influence the rating"(Åsberg et al., 1978). A score of 0 indicates the patient enjoys life and takes it as it comes; a score of 2 is defined as "weary of life. Fleeting suicidal thoughts," a score of 4 signifies the patient feels he/she is probably better off dead and has suicidal thoughts but no specific plans or intention; and a score of 6 indicates the presence of explicit suicide plans and active preparations. We used a cut-off, with scores of 2 or higher indicating presence of SI and scores below 2 indicating absence or remission of SI (Perroud et al., 2009a; Perroud et al., 2009b; van Noorden et al., 2010). This cut-off has been demonstrated to discriminate well between subjects with and without SI according to a three-questionnaire composite score based on an item response theory graded response model (Perroud et al., 2009b). Age, gender, and education level (low: primary through lower secondary education/ high: higher secondary education through university) were determined at baseline. Baseline DSM-IV-TR diagnostic information was collected using the Dutch version of the MINI International Neuropsychiatric Interview-Plus (MINI-Plus; Sheehan et al., 1998; Van Vliet & De Beurs, 2007). The MINI-Plus has good psychometric properties, with inter-rater reliability between 0.88 and 1.00 and test-retest reliability between 0.76 and 0.93; and adequate validity compared to the Composite International Diagnostic Interview-1 (Lecrubier et al., 1997).

Baseline depression severity was assessed using the MADRS, a 10-item observer-rated scale derived from the abbreviated Comprehensive Psychopathological Rating Scale (CPRS; Åsberg et al., 1978; Goekoop et al., 1992). Items are scored on a 7-point Likert scale (0-6) and the total score is the sum-score of all items. The MADRS has good internal consistency with Cronbach's alpha = 0.86 (Montgomery & Åsberg, 1979). As MADRS item 10 on SI was the primary outcome measure in this study, we calculated an adjusted MADRS score (MADRS-adj), leaving out the suicidal ideation item (item number 10) and summing the remaining 9 items (range 0-54) (Cukrowicz et al., 2009). Anxiety severity at baseline was assessed with the Brief Anxiety Scale (BAS). The BAS is a 10-item observer-rated scale derived from the CPRS. Items cover the main components of all anxiety disorders, including psychological and somatic components, and are scored on a 7-point Likert-scale (0-6), adding up to a total score (range 0-60). Self-harm, psychotic experiences, neuroticism, externalizing behaviour, and impulsiveness were assessed using the Dimensional Assessment of Personality Pathology short form (DAPP-SF; van Kampen et al., 2008), the abbreviated version of the DAPP-BQ (Livesley et al., 1998). Self-harm was measured using the self-harm subscale, psychotic experiences were measured using the cognitive distortion subscale, neuroticism was measured using the affective lability subscale, externalising behaviour was measured using the conduct problems subscale, and

impulsiveness was measured using the stimulus seeking subscale. The DAPP-SF consists of 136 items on a 5-point Likert scale (1-5). Subscales are computed by taking the average of the subscale items (range 1-5). Higher scores are associated with pathology, whereas lower scores indicate normality. The DAPP-SF has good internal consistency with Cronbach's alphas ranging from 0.78-0.89 across subscales (van Kampen et al., 2008). Finally, subjective general health was measured using the general health perception subscale of the Dutch Short Form-36 (SF-36; Ware & Sherbourne, 1992; Aaronson et al., 1998). The SF-36 is a 36-item self-report survey, screening eight domains of general health, suitable for use in diverse populations, including psychiatric patients (McHorney et al., 1994). Measurement scales vary, ranging from yes/no to answers on a 3-, 5- or 6-point scale. Raw scores are linearly converted to 0-100 subscales with higher score representing higher levels of functioning or wellbeing. The SF-36 has good psychometric properties, with Cronbach's alphas between 0.66 and 0.93 (Aaronson et al., 1998).

Figure 5.1 MADRS item 10 on suicidal ideation

---

10.   *Suicidal Thoughts*

Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and the preparations for suicide. Suicidal attempts should not in themselves influence the rating.

     0   Enjoys life or takes it as it comes.

     1

     2   Weary of life. Only fleeting suicidal thoughts.

     3

     4   Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intentions.

     5

     6   Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

5.2.3 Statistical analyses

Baseline categorical patient characteristics are presented as number (percentage), continuous variables are presented as mean (M) (± standard deviation (SD)) with interquartile range (IQR). Comparisons of demographics between included and excluded patients were made using χ2 and independent samples t-tests for categorical and continuous variables respectively. Associations between time to remission (MADRS item 10 < 2) and patient characteristics were examined with a Cox proportional hazards model. Cox proportional hazards model is uniquely suited for analysing data of subjects with variable durations of follow-up. As the precise point

in time at which remission was achieved was not known, endpoint was defined as the midpoint between the assessment at which remission was detected and the previous assessment. Maximum follow-up was 24 months. Patients who did not experience an event by that time were censored. The median duration of follow-up was assessed with the reverse Kaplan-Meier method (Schemper & Smith, 1996). The percentage of cumulative remission in the total sample was estimated with the Kaplan-Meier estimator. Hazard Ratios (HR) and their corresponding 95% confidence intervals (CI) were estimated for risks factors associated with time to remission using a Cox model. To facilitate comparability between continuous prognostic factors, z-scores were calculated and used in analyses. To facilitate comparability of HRs, SF-36 general health scores were inverted (i.e. subtracted from 100) so higher scores corresponded to poor subjective general health.

All candidate prognostic variables that achieved significance levels of < 0.10 in univariable analysis were entered in multivariable analysis using a Cox model. Failure to achieve significance (p ≥ 0.05) in the resulting multivariable model resulted in removal, except for the variables age and gender. Backward stepwise removal of covariates was checked using the p-values of the Wald test and the partial likelihood ratio test, with values ≥ 0.10 demonstrating that removal was justified. To visualise remission over time, 1 minus Kaplan-Meier curves were constructed for all variables in the final model, with separate curves for different levels of categorical variables and tertiles for continuous variables. To explore if the model had predictive value, Harrell's c-statistic was calculated. The c-statistic estimates the probability of concordance between predicted and observed responses (Gonen & Heller, 2005). All tests were two-tailed.

As patients who have recovered from SI could experience relapse (Williams et al., 2006), sensitivity analyses were performed whereby the resulting model was entered on sustained remission. Sustained remission was defined as achieving a score of < 2 on MADRS item 10 without relapsing during the remainder of the follow-up period. In addition, as previous studies varied with regard to follow-up period, we entered the model on remission at six-month- as well as one-year follow-up. Finally, special attention was paid to the potential censoring mechanism in this study. Censoring occurs when a patient has not yet experienced the event of interest by the end of the study. This can occur as a result of loss to follow-up, because a patient experiences a different event that prevents the occurrence of the event of interest (competing risk), or due to administrative censoring (reaching the end of the follow-up period at two years after baseline). A basic assumption in survival analysis is that censoring is non-informative, i.e. the censoring mechanism is independent of the event of interest. In this study, however, one might hypothesize that censoring was not independent of the event being studied (remission of SI): as ROM was periodical and voluntary, it is conceivable that a patient has had a ROM-assessment reflecting persistence of SI, whereupon the patient improved,

completed treatment, and did not return for further assessment. This would mean that achieving remission might have increased patients' chances of being censored. Classical survival techniques cannot be used when the independence assumption between time to event and time to censoring is violated. To further explore this aspect the Inverse Probability Censoring Weighted (IPCW) estimator (Robins & Rotnitzky, 1992; Robins, 1993; Robins & Finkelstein, 2000) was applied to correct for possible informative censoring. More details concerning IPCW and the application to the present data set are described in Willems et al. (Willems et al., submitted for publication). We used R version 3.0.2 (R foundation for Statistical Computing) and SPSS 20.0 (IBM Corp., Armonk, NY, USA) to perform the analysis.

5.3 Results

5.3.1 Sample Characteristics

Between April 2004 and September 2010, a total of 1364 outpatients, diagnosed with DSM-IV-TR mood and/or anxiety disorder(s), expressed suicidal thoughts at intake when presented with MADRS item 10 (score 2 or higher, see figure 1). Of these patients, 575 (42.2%) did not have follow-up ROM assessments. For an additional 12 (0.9%) patients baseline data were missing; consequently, 777 (56.9%) patients were included for analyses. Figure 2 represents a flowchart of inclusion and exclusion. Baseline sample characteristics of the 777 patients in our sample are shown in table 5.1. DSM-IV-TR minor or major depressive disorder occurred in 671 (86.4%) patients, 31 (4.0%) patients suffered from dysthymia. Anxiety disorders occurred in 400 patients, 281 of them had a single anxiety disorder, and 119 patients had multiple anxiety disorders. Anxiety disorders were distributed as follows: 93 (12.0%) patients met diagnostic criteria for panic disorder with or without agoraphobia, 77 (10.0%) patients were diagnosed with agoraphobia without panic, 104 (13.4%) patients had social phobia, 67 (8.6%) patients had generalised anxiety disorder, 62 (8.0%) patients had obsessive compulsive disorder, 11 (1.4%) patients had specific phobia, and post-traumatic stress disorder occurred in 130 (16.7%) patients. Alcohol abuse or dependence occurred in 58 (7.5%) patients, whereas substance abuse or dependence was present in 40 (5.1%) patients. In total, 377 (48.5%) patients met DSM-IV-TR diagnostic criteria for depressive disorder without anxiety disorder, 75 (9.7%) patients met DSM-IV-TR diagnostic criteria for anxiety disorder without depressive disorder, and 325 (41.8%) patients met DSM-IV-TR diagnostic criteria for combined depressive and anxiety disorder.

No significant differences existed between the 777 patients who were included and the 587 excluded patients with regard to gender, education level, diagnosis of dysthymic disorder, depression severity, anxiety severity, baseline SI severity, DAPP-SF cognitive

distortion, and general health perception. Inclusion was associated with age, with patients in the included group being older than those in the excluded group (M = 39.1; SD = 11.8 versus M = 37.1; SD = 12.6; t(1218.41) = -3.004, p = .003), Cohen's d = -0.172. DAPP-SF stimulus seeking scores were lower in the included group (M = 2.25; SD = 0.82 versus M = 2.38; SD = 0.88; t(1358) = 2.728; p = .006), Cohen's d = 0.148. And DAPP-SF behavioural problems scores were lower in the included group (M = 1.52; SD = 0.63 versus M = 1.67; SD = 0.74; t(1134.53) = 3.753; p < .001), Cohen's d = 0.223.

5.3.2 Univariable prognostic factors associated with remission

The median duration of follow-up was 520 days (95% CI = 369 - 671). The cumulative proportion of patients achieving remission of SI during the two-year follow-up period was 76.4% (n = 594), while at two-year follow-up, 40 patients still had SI and continued treatment. The following characteristics were associated with a lower chance of remission at p < 0.10

Table 5.1 Baseline characteristics in 777 depressed and/or anxious outpatients with suicidal ideation.

Categorical variables	n	%
Gender		
- male	299	38.5%
- female	478	61.5%
Education-level		
- high	426	54.8%
- low	351	45.2%
Major depressive disorder	671	86.4%
Dysthymic disorder	31	4.0%
Anxiety disorder	400	51.5%
Continuous variables	**Mean (±SD)**	**IQR**
Age	39.1 (11.8)	30.0 - 48.0
Suicidal ideation score (MADRS item 10)	2.6 (0.9)	2.0 - 3.0
Depression severity (adjusted MADRS score)	24.9 (6.7)	20.0 - 29.0
Anxiety severity (BAS score)	17.8 (6.3)	13.0 - 22.0
Self-harm (DAPP-SF)	2.7 (1.0)	1.8 - 3.5
Psychotic experiences (DAPP-SF)	2.7 (1.0)	1.8 - 3.5
Neuroticism (DAPP-SF)	3.5 (0.8)	3.0 - 4.1
Externalizing behaviour (DAPP-SF)	1.5 (0.6)	1.0 - 1.8
Impulsiveness (DAPP-SF)	2.3 (0.8)	1.6 - 2.8
General health perception (SF-36)	44.8 (19.9)	30.0 - 55.0

Categorical variables are presented as n (percentage), continuous variables are presented as mean (± standard deviation (SD)), interquartile range (IQR). The MINI International Neuropsychiatric Interview-Plus was used to collect diagnostic information. The Montgomery Åsberg Depression Rating Scale item 10 was used to asses suicidal ideation. BAS denotes Brief Anxiety Scale; adjusted MADRS, Montgomery Åsberg Depression Rating Scale minus the suicidal ideation item; DAPP-SF, Dimensional Assessment of Personality Pathology- Short Form; SF-36, Short Form-36.

5

(Table 5.2): female gender, lower education, higher SI score at baseline, higher baseline depression score, higher baseline anxiety severity score, higher self-harm score, more severe psychotic experiences, higher baseline neuroticism score, more severe externalising behaviour, and more negative subjective general health. Age, dysthymic disorder, and impulsiveness were not associated with remission at $p < 0.10$.

5.3.3 Multivariable prognostic factors associated with remission

Table 5.3 shows HRs with 95% CI's and p-values for each variable included in the model. Patients with a low education level had a 14% smaller chance of achieving remission of SI ($p = 0.09$) than patients with a high education level; an increase of one SD in depression score resulted in a 16% decreased chance of remission of SI ($p < 0.001$); a single SD increase in the self-harm score resulted in a 23% smaller chance of remission ($p < 0.001$); a single SD increase on the inverted subjective general health (indicating poorer subjective general health) resulted in an 8% lower chance of remission ($p = 0.04$). Figure 3 shows the 1 minus Kaplan-Meier curves for cumulative remission over the two-year follow-up period for each of these prognostic variables. Although statistically significant in univariable analyses, baseline anxiety scores, baseline SI scores, and scores for psychotic experiences, neuroticism, and externalising behaviour did not show significant association with time to remission in the multivariable model. The c -statistic was equal to 0.57.

5.3.4 Sensitivity analyses

When the model was entered on sustained remission (n = 533); HRs remained comparable to those in the original model (results not shown). Entering the model on remission at six-month as well as one-year follow-up also yielded similar HRs (results not shown). Application of the IPCW method on the data set under study showed no evidence for the presence of dependent censoring. Technical details concerning IPCW method and results for the present dataset are further discussed in Willems et al. (Willems et al., 2016).

Table 5.2 Univariable Hazard Ratios of baseline variables for remission of suicidal ideation in 777 depressed and/or anxious outpatients with suicidal ideation at baseline.

Categorical variables	HR (95% CI)	p-value
Gender		
- male	1 (ref.)	
- female	0.86 (0.73-1.02)	0.07
Education-level		
- high	1 (ref.)	
- low	0.84 (0.77-0.99)	0.04
Dysthymic disorder		
- no dysthymic disorder	1 (ref.)	
- dysthymic disorder	1.03 (0.68-1.56)	0.89
Continuous variables	**HR (95% CI)**	**p-value**
Age	0.99 (0.91-1.07)	0.75
Suicidal ideation score (MADRS item 10)	0.83 (0.76-0.90)	<.001
Depression severity (adjusted MADRS score)	0.81 (0.75-0.88)	<.001
Anxiety severity (BAS score)	0.90 (0.83-0.98)	0.01
Self-harm (DAPP-SF)	0.75 (0.69-0.81)	<.001
Psychotic experiences (DAPP-SF)	0.89 (0.83-0.97)	.005
Neuroticism (DAPP-SF)	0.93 (0.86-1.00)	0.05
Externalizing behaviour (DAPP-SF)	0.92 (0.84-0.99)	0.04
Impulsiveness (DAPP-SF)	1.01 (0.93-1.09)	0.90
General health perception/ general health perception (SF-36)	0.85 (0.78-0.91)	<.001

Hazard Ratios (HR) are presented with 95% confidence interval (CI) and p-value; ref. signifies the reference category. Remission was defined as a score at follow-up of 1 or less on item 10 of the Montgomery Åsberg Depression Rating Scale. The MINI International Neuropsychiatric Interview-Plus was used to collect diagnostic information. BAS denotes Brief Anxiety Scale; adjusted MADRS, Montgomery Åsberg Depression Rating Scale minus the suicidal ideation item (item 10); DAPP-SF, Dimensional Assessment of Personality Pathology-Short Form; SF-36, Short Form-36. To facilitate comparability of HRs among continuous variables, z-scores were used and SF-36 general health scores were inverted so that higher scores on all measures correspond to greater severity/pathology. HRs <1 indicate lower chances of remission of suicidal ideation whereas HRs >1 indicate better chances of remission of suicidal ideation.

5

Figure 5.2 Flowchart of inclusion and exclusion in this study

A total of 1364 outpatients diagnosed with DSM-IV-TR mood and/or anxiety disorder(s) expressed suicidal thoughts when presented with MADRS item 10 between April 2004 and September 2010.

587 (43.1%) patients were excluded:

- 575 (42.2%) subjects had no follow-up data

- 12 (0.9%) patients had missing data

777 (56.9%) patients were included for analyses
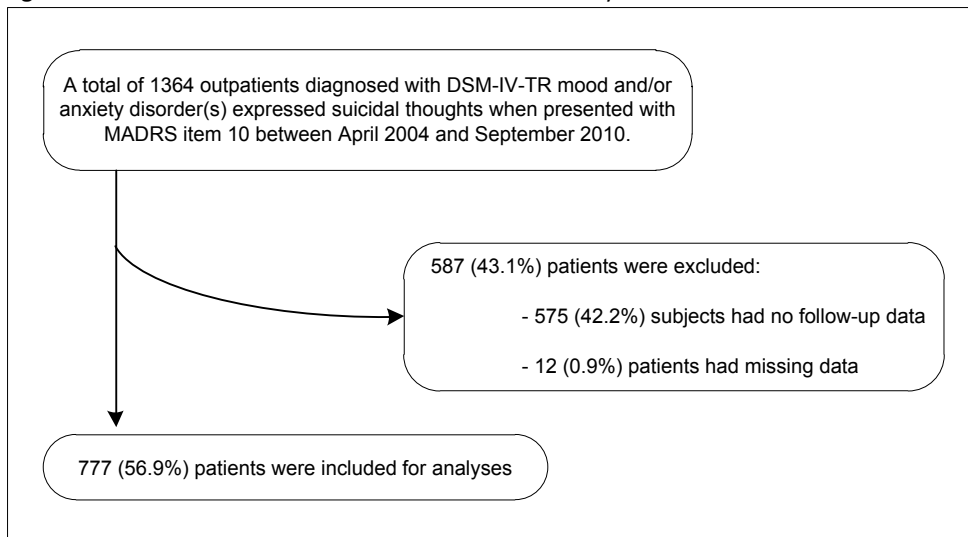
The MINI International Neuropsychiatric Interview was used to collect diagnostic information; DSM-IV-TR denotes diagnostic statistical manual of mental disorders- fourth edition-text revision; MADRS, Montgomery Åsberg depression Rating Scale.

Table 5.3 Multivariable Hazard Ratios of baseline variables for remission of suicidal ideation in 777 depressed and/or anxious outpatients with suicidal ideation at baseline.

	HR (95% CI)	p-value
Age	1.02 (0.94 – 1.11)	0.61
Female gender	0.89 (0.75 – 1.06)	0.18
Low education level	0.86 (0.73 – 1.02)	0.09
Depression severity (adjusted MADRS score)	0.84 (0.77 – 0.91)	<.001
Self-harm (DAPP-SF)	0.77 (0.71 – 0.84)	<.001
Subjective general health (general health SF-36)	0.92 (0.85 – 1.00)	0.04

Hazard Ratios (HR) are presented with 95% confidence interval (CI) and p-value; ref. signifies the reference category. Remission was defined as a score at follow-up of 1 or less on item 10 of the Montgomery Åsberg Depression Rating Scale. The MINI International Neuro-psychiatric Interview-Plus was used to collect diagnostic information. Adjusted MADRS denotes Montgomery Åsberg Depression Rating Scale minus the suicidal ideation item (item 10); DAPP-SF, Dimensional Assessment of Personality Pathology- Short Form; SF-36, Short Form-36. To facilitate comparability of HRs among continuous variables, z-scores were used and SF-36 general health scores were inverted so that higher scores on all measures correspond to greater severity/pathology. HRs <1 indicate lower chances of remission of suicidal ideation whereas HRs >1 indicate better chances of remission of suicidal ideation.

5.4 Discussion

This study was aimed at the evaluation of previously identified prognostic factors in the course of SI in a naturalistic sample of outpatients with DSM-IV-TR depression and/or anxiety disorder(s). A longer time to remission of SI over a 2-year follow-up period was associated with a lower level of education, higher depression severity, more severe self-harm, and a poorer subjective general health. Overall, our findings confirm previous reports. An association between sustained or aggravated SI and low education level has previously been found in the general population (ten Have et al., 2009). A low education level is a known risk factor for suicide attempts; possibly through association with lower social economic status (Schmidtke et al., 1996), the same may apply to sustained SI. High baseline depression severity has been identified as a prognostic factor in the course of SI in adolescent (Prinstein et al., 2008) and older (Cukrowicz et al., 2009) patients in previous studies. Present findings indicate that these previous results can be generalised to an adult depressed/anxious outpatient population.

The same goes for the association between self-harm and poorer chances of remission of SI, which was previously reported in adolescent inpatients (Prinstein et al., 2008). Finally, our findings indicate that poor subjective general health was associated with smaller chances of remission. Poor subjective general health has previously been associated with increased risk of SI (Goodwin & Olfson, 2002) but has not been studied in the context of the course of SI. It has been suggested that (feelings of) poor general health could lead to the idea that life is not worth living, or that SI may lead to a negative perception of health (Goodwin & Olfson, 2002), or alternatively, that self-perceived poor health and SI may share an underlying personality construct (Goodwin & Olfson, 2002). However, as our findings reflect associations, causality cannot be attributed.

Previous findings of associations between time to remission and anxiety (ten Have et al., 2009), baseline SI severity (Prinstein et al., 2008), psychotic experiences, and neuroticism (Enns et al., 2003) were confirmed in univariable analyses, but not in the multivariable model, indicating that they did not add explained variance to the variables present in the final model. Higher baseline anxiety severity and higher severity of baseline SI could complicate treatment in general, and thereby predispose patients for poor outcome. Psychotic experiences have been linked to the presence of multiple comorbid Axis I diagnoses (Kelleher et al., 2014b), poorer general and occupational functioning (Kelleher et al., 2014b), neurocognitive deficits (Kelleher et al., 2013a; Barnett et al., 2006), childhood trauma (Kelleher et al., 2013b), and poor coping skills (Lataster et al., 2006; Lin et al., 2011), all of which could be hypothesised to lead to a persistence of SI (Kelleher et al., 2014a). Neuroticism has been suggested to reflect a general tendency to experience negative affect and, as such, contribute to continuation of SI

(Enns et al., 2003). Our findings do however not mean that these factors do not play a role in individual cases.

Some previously identified prognostic factors were not associated with the course of SI in our sample. Earlier findings of a predictive value for age (Cukrowicz et al., 2009) were not confirmed. Possibly, the association between age and remission of SI was non-linear and existed exclusively for older (60 years or older) patients in the previous study, but not in our adult (18-65 years) population. A diagnosis of dysthymic disorder was not associated with remission of SI in our sample although this association did emerge in a previous general population study (ten Have et al., 2009). Possibly, this association was specific for general population subjects and did not emerge in our clinical sample, as psychopathology was uniformly present in our sample. Also, it must be noted that dysthymic disorder only occurred in 4% of our sample. Interestingly, we did not confirm reports of an association between high externalising personality traits and better chances of remission of SI (Prinstein et al., 2008), but instead, found that in our sample high externalisation decreased chances of remission. Possibly the association found by Prinstein et al. (Prinstein et al., 2008) is unique to adolescents.

Another possible explanation of the discrepancy between findings may lie in the operationalization of externalisation: Prinstein et al. relied on parent reports of externalising behaviour (Prinstein et al., 2008); we used data from the conduct problems subscale of the DAPP-SF, which measures elements of aggression and rule-breaking embedded in personality. Our finding of poorer chances of remission of SI in those with more externalising behaviour however, is in line with reports of externalising personality traits being associated with increased risk of suicidality (Verona et al., 2004). Also, the hypothesized predictive value of impulsiveness was not found. Finally, although we successfully identified a set of prognostic factors in remission of SI on population level, the c-statistic indicates that our final model has only modest predictive value on individual patient level. Possibly, the exclusive focus on patient characteristics in our study and the previous studies does not provide sufficient information towards prediction, as SI may be associated with contextual factors as well. Further research aimed at prediction of sustained SI may benefit from including contextual factors like life events and social support.

Our study has several strengths: our sample is large and naturalistic, allowing for comorbidity and including not only depressed but also anxious patients. We used a structured clinical diagnostic instrument, computerised data-collection, and data-collection by trained research nurses, all as part of standard care. In addition, we have studied a broad set of potentially relevant patient characteristics, extending upon previous findings, to determine the relative prognostic value of easily obtainable patient characteristics towards remission of SI. However, several limitations exist: First of all, although our data-collection covered a broad range of variables, we were unable to include all previously identified prognostic factors

associated with SI: in our sample no information on childhood trauma (ten Have et al., 2009), cardiovascular disease (ten Have et al., 2009), or level of defeat (Taylor et al., 2011) was available. Second, attrition in our sample was high and the reasons for loss to follow-up (including possible attempted or completed suicide) were unknown. However, attrition is common in observational studies and comparisons between subjects with and without follow-up demonstrated that no important differences existed. Furthermore, application of the IPCW method (Willems et al., submitted for publication) showed no evidence of presence of informative censoring. This indicates that loss to follow-up was not associated with the identified predictors of the course of SI, and as such, findings do not point at completed suicide as a reason for loss to follow-up. Also, we used a single item to assess SI, which may be less suited than a dedicated suicidality questionnaire. It has been demonstrated that different instruments for assessing SI provide diverging estimates of SI prevalence (Vuorilehto et al., 2014). However, a previous study demonstrated that the cut-off < 2 on MADRS item 10 discriminated well between subjects with and without SI, as assessed with a three questionnaire composite score (Perroud et al., 2009b). Furthermore, we have no information on psychiatric history, including previous suicidal behaviour. This information might be relevant and future studies might improve on current findings by including this information. Finally, no information on treatment was available, as such, unfortunately, this could not be included in analyses. However, previous studies in our cohort have demonstrated that treatment was delivered according to guidelines, existing of pharmacotherapy (23%), psychotherapy (59%), or combination therapy (16%) (van Fenema et al., 2012). In spite of these limitations, this study has been the first to simultaneously evaluate previously identified prognostic factors for SI. In addition, we studied these factors in a clinical setting in which SI is highly prevalent. As such, we identified a set of prognostic factors associated independently with remission of SI generalizable to outpatients with depression and/or anxiety disorder(s). Caregivers should be alert to patients presenting with SI who have low education levels, more severe depression, poor subjective general health perception, and who have a history of self-harm.

5

Figure 5.3 1-minus Kaplan-Meier curves, presenting cumulative incidence of remission of suicidal ideation in 777 outpatients diagnosed ith DSM-IV-TR depressive and anxiety disorders.
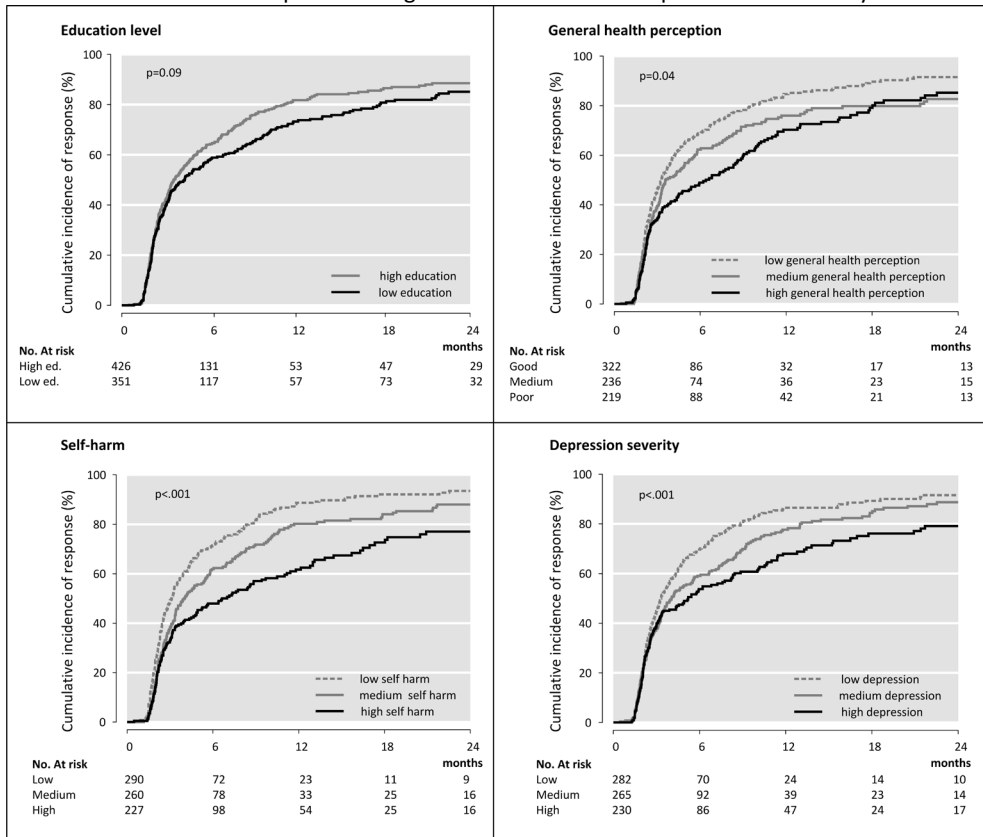
1-minus Kaplan-Meier curves are shown for the cumulative incidence of remission of suicidal ideation, defined as a score of 2 or less on item 10 of the Montgomery Åsberg Depression Rating Scale (MADRS) on suicidal ideation. To facilitate presentation, tertiles were constructed for (inverted) general health perception (measured with Short Form-36 subscale general health perception), self-harm (measured with Dimensional Assessment of Personality pathology-Short Form), and depression severity (measured with the MADRS, excluding item 10).

Reference List

Aaronson NK, Muller M, Cohen PDA, Essink-Bot ML, Fekkes M, Sanderman R, Sprangers MAG, Velde AT, Verrips E (1998). Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. *Journal of Clinical Epidemiology,* 51, 1055-1068.

Ahrens B, Linden M, Zaske H, Berzewski H (2000). Suicidal behavior - Symptom or disorder? *Comprehensive Psychiatry*, 41, 116-121.

American Psychiatric Association (2000). *Diagnostic and Statistical Manual of Mental Disorders, Fouth Edition, Text Revision (DSM-IV-TR)*. American Psychiatric Association: Washington DC:.

Åsberg M, Montgomery SA, Perris C, Schalling D, Sedvall G (1978). Comprehensive Psychopathological Rating-Scale. *Acta Psychiatrica Scandinavica,* 271, 5-27.

Barnett JH, Salmond CH, Jones PB, Sahakian BJ (2006). Cognitive reserve in neuropsychiatry. *Psychological Medicine*, 36, 1053-1064.

Borges G, Angst J, Nock MK, Ruscio AM, Kessler RC (2008). Risk factors for the incidence and persistence of suicide-related outcomes: A 10-year follow-up study using the National Comorbidity Surveys. *Journal of Affective Disorders,* 105, 25-33.

Brezo J, Paris J, Turecki G (2006). Personality traits as correlates of suicidal ideation, suicide attempts, and suicide completions: a systematic review. *Acta Psychiatrica Scandinavica*, 113,180-206.

Cukrowicz KC, Duberstein PR, Vannoy SD, Lynch TR, McQuoid DR, Steffens DC (2009). Course of suicide ideation and predictors of change in depressed older adults. *Journal of Affective Disorders,* 113, 30-36.

De Beurs E, den Hollander-Gijsman ME, van Rood YR, van der Wee NJA, Giltay EJ, van Noorden MS, van der Lem R, van Fenema E, Zitman FG (2011). Routine Outcome Monitoring in the Netherlands: Practical Experiences with a Web-Based Strategy for the Assessment of Treatment Outcome in Clinical Practice. *Clinical Psychology & Psychotherapy*, 18, 1-12.

Eikelenboom M, Smit JH, Beekman ATF, Penninx BWJH (2012). Do depression and anxiety converge or diverge in their association with suicidality? *Journal of Psychiatric Research*, 46, 608-615.

Enns MW, Cox BJ, Inayatulla M (2003). Personality predictors of outcome for adolescents hospitalized for suicidal ideation. *Journal of the American Academy of Child and Adolescent Psychiatry,* 42, 720-727.

Goekoop JG, Hoeksema T, Knoppertvanderklein EAM, Klinkhamer RA, Vangaalen HAE, Vanlonden L, Deweme R, Zwinderman AH (1992). Multidimensional Ordering of Psychopathology - A Factor-Analytic Study Using the Comprehensive Psychopathological Rating-Scale. *Acta Psychiatrica Scandinavica,* 86, 306-312.

Gonen M, Heller G (2005). Concordance probability and discriminatory power in proportional hazards regression. *Biometrika*, 92, 965-970.

Goodwin R, Olfson M (2002). Self-perception of poor health and suicidal ideation in medical patients. *Psychological Medicine*, 32, 1293-1299.

Hubers AAM, Moaddine S, Peersmann SHM, Stijnen T, van Duijn E, van der Mast RC, Dekkers OM, Giltay EJ (2015). Suicidal ideation and subsequent completed suicide in both psychiatric and non-psychiatric populations: a meta-analysis. *Submitted for publication.*

Jacobs DG, Brewer ML (2006). Application of the APA Practice Guidelines on suicide to clinical practice. *Central Nervous System Spectrums,* 11, 447-454.

5

Kelleher I, Clarke MC, Rawdon C, Murphy J, Cannon M (2013a). Neurocognition in the extended psychosis phenotype: performance of a community sample of adolescents with psychotic symptoms on the MATRICS neurocognitive battery. *Schizophrenia Bulletin*, 39, 1018-1026.

Kelleher I, Keeley H, Corcoran P, Ramsay H, Wasserman C, Carli V, Sarchiapone M, Hoven C, Wasserman D, Cannon M (2013b). Childhood trauma and psychosis in a prospective cohort study: cause, effect, and directionality. *American Journal of Psychiatry*, 170, 734-741.

Kelleher I, Cederlof M, Lichtenstein P (2014a). Psychotic experiences as a predictor of the natural course of suicidal ideation: a Swedish cohort study. *World Psychiatry*, 13, 184-188.

Kelleher I, Devlin N, Wigman JT, Kehoe A, Murtagh A, Fitzpatrick C, Cannon M (2014b). Psychotic experiences in a mental health clinic sample: implications for suicidality, multimorbidity and functioning. *Psychological Medicine*, 44, 1615-1624.

Lataster T, van OJ, Drukker M, Henquet C, Feron F, Gunther N, Myin-Germeys I (2006). Childhood victimisation and developmental expression of non-clinical delusional ideation and hallucinatory experiences: victimisation and non-clinical psychotic experiences. *Social Psychiatry and Psychiatric Epidemiology*, 41, 423-428.

Lecrubier Y, Sheehan DV, Weiller E, Amorim P, Bonora I, Sheehan KH, Janavs J, Dunbar GC (1997). The Mini International Neuropsychiatric Interview (MINI). A short diagnostic structured interview: Reliability and validity according to the CIDI. *European Psychiatry*, 12, 224-231.

Lin A, Wigman JT, Nelson B, Vollebergh WA, van OJ, Baksheev G, Ryan J, Raaijmakers QA, Thompson A, Yung AR (2011). The relationship between coping and subclinical psychotic experiences in adolescents from the general population--a longitudinal study. *Psychological Medicine,* 41, 2535-2546.

Livesley WJ, Jang KL, Vernon PA (1998). Phenotypic and genetic structure of traits delineating personality disorder. *Archives of General Psychiatry*, 55, 941-948.

McHorney CA, Ware JE, Lu JFR, Sherbourne C (1994). The MOS 36-Item Short-Form Health Survey (SF-36): III. Tests of Data Quality, Scaling Assumptions, and Reliability across Diverse Patient Groups. *Medical Care*, 32, 40-66.

Montgomery SA, Åsberg M (1979). New Depression Scale Designed to be Sensitive to Change. *British Journal of Psychiatry*, 134, 382-389.

Perroud N, Aitchison KJ, Uher R, Smith R, Huezo-Diaz P, Marusic A, Maier W, Mors O, Placentino A, Henigsberg N, Rietschel M, Hauser J, Souery D, Kapelski P, Bonvicini C, Zobel A, Jorgensen L, Petrovic A, Kalember P, Schulze TG, Gupta B, Gray J, Lewis CM, Farmer AE, McGuffin P, Craig I (2009a). Genetic predictors of increase in suicidal ideation during antidepressant treatment in the GENDEP project. *Neuropsychopharmacology*, 34, 2517-2528.

Perroud N, Uher R, Marusic A, Rietschel M, Mors O, Henigsberg N, Hauser J, Maier W, Souery D, Placentino A, Szczepankiewicz A, Jorgensen L, Strohmaier J, Zobel A, Giovannini C, Elkin A, Gunasinghe C, Gray J, Campbell D, Gupta B, Farmer AE, McGuffin P, Aitchison KJ (2009b). Suicidal ideation during treatment of depression with escitalopram and nortriptyline in Genome-Based Therapeutic Drugs for Depression (GENDEP): a clinical trial. *BMC Medicine* 7, 60.

Prinstein MJ, Nock MK, Simon V, Aikins JW, Cheah CSL, Spirito A (2008). Longitudinal trajectories and predictors of adolescent suicidal ideation and attempts following inpatient hospitalization. *Journal of Consulting and Clinical Psychology*, 76, 92-103.

Robins JM (1993). Information recovery and bias adjustment in proportional hazards regression analysis of randomised trials using surrogate markers. *Proceedings of the Biopharmaceutical Section, American Statistical Association*. p. 24-33.

Robins JM, Finkelstein DM (2000). Correcting for noncompliance and dependent censoring in an AIDS clinical trial with inverse probability of censoring weighted (IPCW) log-rank tests. *Biometrics*, 56, 779-788.

Robins JM, Rotnitzky A (1992). recovery of information and adjustment for dependent censoring using surrogate markers. In *AIDS Epidemiology* (ed. Jewell NP, Dietz K, Farewell VT), pp. 297-331. Birkhäuser: Boston.

Ryan CJ, Large MM (2013). Suicide risk assessment: where are we now? *Medical Journal of Australia*, 198, 462-463.

Schemper M, Smith TL (1996). A note on quantifying follow-up in studies of failure time. *Controlled Clinical Trials,* 17, 343-346.

Schmidtke A, BilleBrahe U, Deleo D, Kerkhof A, Bjerke T, Crepet P, Haring C, Hawton K, Lonnqvist J, Michel K, Pommereau X, Querejeta I, Phillipe I, SalanderRenberg E, Temesvary B, Wasserman D, Fricke S, Weinacker B, SampaioFaria JG (1996). Attempted suicide in Europe: Rates, trends and sociodemographic characteristics of suicide attempters during the period 1989-1992. Results of the WHO/EURO Multicentre Study on Parasuicide. *Acta Psychiatrica Scandinavica,* 93, 327-338.

Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC (1998). The Mini-International Neuropsychiatric Interview (MINI): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry*, 59, 22-33.

Taylor PJ, Gooding PA, Wood AM, Johnson J, Tarrier N (2011). Prospective Predictors of Suicidality: Defeat and Entrapment Lead to Changes in Suicidal Ideation over Time. *Suicide and Life-Threatening Behavior*, 41, 297-306.

Ten Have M, de Graaf R, van Dorsselaer S, Verdurmen J, van't Land H, Vollebergh W, Beekman A (2009). Incidence and Course of Suicidal Ideation and Suicide Attempts in the General Population. *Canadian Journal of Psychiatry-Revue Canadienne de Psychiatrie,* 54, 824-833.

Van Fenema E, van der Wee NJA, Bauer M, Witte CJ, Zitman FG (2012). Assessing adherence to guidelines for common mental disorders in routine clinical practice. *International Journal for Quality in Health Care*, 24, 72-79.

Van Hemert AM, Kerkhof AJFM, de Keijser J, Verwey B, van Boven C, Hummelen JW, de Groot MH, Lucassen P, Meerdikveldboom J, Steendam M, Stringer B, Verlinde AA, van de Grind G (2012). *MDR diagnostiek en behandeling van suicidaal gedrag versie 1.0.* Utrecht: de Tijdstroom.

Van Kampen D, De Beurs E, Andrea H (2008). A short form of the Dimensional Assessment of Personality Pathology-Basic Questionnaire (DAPP-BQ): The DAPP-SF. *Psychiatry Research,* 160, 115-128.

Van Noorden MS, Giltay EJ, den Hollander-Gijsman ME, van der Wee NJA, van Veen T, Zitman FG (2010a). Gender differences in clinical characteristics in a naturalistic sample of depressive outpatients: The Leiden Routine Outcome Monitoring Study. *Journal of Affective Disorders*, 125, 116-123.

Van Vliet IM, De Beurs E (2007). Het MINI Internationaal Neuropsychiatrisch Interview (MINI) een kort gestructureerd diagnostisch psychiatrisch interview voor DSM-IV- en ICD-10-stoornissen. *Tijdschrift voor psychiatrie,* 49, 393-397.

Verona E, Sachs-Ericsson N, Joiner TE, Jr (2004). Suicide attempts associated with externalizing psychopathology in an epidemiological sample. American Journal of Psychiatry, 161, 444-451.

5

Vuorilehto M, Valtonen HM, Melartin T, Sokero P, Suominen K, Isometsa ET (2014). Method of assessment determines prevalence of suicidal ideation among patients with depression. European Psychiatry, 29, 338-344.

Ware JE, Sherbourne CD (1992). The Mos 36-Item Short-Form Health Survey (Sf-36) .1. Conceptual-Framework and Item Selection. *Medical Care*, 30, 473-483.

Willems SJW, Schat A, van Noorden MS, Fiocco M (2015). Correcting for Informative Censoring by applying the Inverse Probability Censoring Weighted Estimator. *Submitted for publication*.

Williams JMG, Crane C, Barnhofer T, Van der Does AJW, Segal ZV (2006). Recurrence of suicidal ideation across depressive episodes. *Journal of Affective Disorders*, 91, 189-194.

Chapter 6

Concordance between self-reported and observer-rated anxiety severity in outpatients with anxiety disorders

Abstract

Anxiety severity measures can be self-report or observer-rated. Although mostly these measures concur, they can diverge markedly. We examined concordance between two anxiety scales: the observer-rated Brief Anxiety Scale (BAS) and the self-report Brief Symptom Inventory-12 item version (BSI-12), and described associations between patient characteristics and discordance. The study used an observational design, using prospective data from 2004 outpatients with DSM-IV-TR panic disorder with/without agoraphobia, agoraphobia without panic, social phobia and/or generalised anxiety disorder. Overall agreement was described using Pearson product-moment correlation coefficient. Associations between patient characteristics and discordance (defined as |ZBAS-ZBSI-12|≥1) were evaluated with univariable and multivariable multinomial logistic regression. Overall correlation between BAS and BSI-12 was positive and strong (r=0.61). Discordance occurred in 23.6% of patients ([ZBAS≥ZBSI-12+1]=12.4%; [ZBAS≤ZBSI-12-1]=11.2%). Patients with higher observed- than self-reported anxiety severity did not differ from concordant patients. Patients with lower observed- than self-reported anxiety severity more often had panic disorder, less often had social phobia, and had higher scores on cluster B and C personality characteristics than concordant patients. Lower observed- than self-reported anxiety severity was best predicted by panic disorder, social phobia, and affective lability. Results demonstrate that the use of a single source of information gives a one-sided view of pathology. A multi-method approach is highly preferable, as this allows for assessment across different domains and through multiple sources of information, and as such, provides clinicians with vital information.

6.1 Introduction

When quantifying the severity of psychiatric disorders, clinicians rely on psychiatric rating scales. These scales can be either observer-rated or self-report. Observer-rated instruments are often regarded as the primary source of information (Hamilton, 1976; Moller, 2000). Self-report measures on the other hand, are more efficient in terms of time and costs and are therefore increasing in popularity in clinical practice, where the need to quantify symptom severity competes with the need to economise. Interestingly, several studies have demonstrated that observer-rated severity does not necessarily correspond to patient-reported severity. Previous research on depression rating scales demonstrated that correlations between observer- and self-rated severity ranged from 0. (Dorz et al., 2004), 0.28 (Dunlop et al., 2011), 0.40 (Enns et al., 2000), 0.45 (Rane et al., 2010), and 0.46 (Dunlop et al., 2011), to 0.59 and 0.60 (Carter et al., 2010). Although repeated measures, even by the same rater, will always show some discrepancy due to random error, the discrepancy between observer- and self-reported severity seems to consist of more than random error, as it has been linked to several patient characteristics, such as age (Carter et al., 2010; Dorz et al., 2004; Enns et al., 2000), gender (Carter et al., 2010; Jolly et al., 1994), education level (Enns et al., 2000), marital status (Dorz et al., 2004), and psychiatric history (Dorz et al., 2004). In addition, the level of concordance between observer-rated and self-report instruments appears to be related to personality. Lower scores on observer-rated relative to self-report instruments were associated with more personality disorder in depression (Dorz et al., 2004; Rane et al., 2010), as well as high neuroticism, low extraversion, low agreeableness (Enns et al., 2000), high novelty seeking, and high reward dependence (Carter et al., 2010).

The majority of these previous studies has focussed on depression (Carter et al., 2010; Dorz et al., 2004; Dunlop et al., 2011; Enns et al., 2000; Rane et al., 2010), with only one study describing concordance in generalised anxiety disorder (Hopko et al., 2000), one study focussing on patients with symptoms of anxiety and depression in primary care (Lubaczewski et al., 2014), and one study of concordance in adolescent inpatients with a variety of diagnoses (Jolly et al., 1994). In addition, although associations between discordance and the presence of personality disorders as well as NEO five personality factors have been studied, no in depth exploration of personality and concordance exists. We therefore conducted a study of concordance between observer-rated and self-report instruments measuring anxiety severity in a large naturalistic sample of outpatients with commonly occurring anxiety disorders (panic disorder with or without agoraphobia, agoraphobia without panic, social phobia, and generalised anxiety disorder) with special focus on associations with personality traits. We set out to describe concordance between an observer-rated measure of anxiety severity, the Brief Anxiety Scale (BAS; Tyrer et al., 1984), and a self-report measure of anxiety severity (the Brief

Symptom Inventory-12 item version [BSI-12] (De Beurs & Zitman, 2006; Roy-Byrne et al., 2010), on group-level. Next, we examined associations between concordance and a set of patient characteristics that were previously associated with concordance in depression, as well as an extensive set of personality traits. Finally, we analysed which patient characteristics best predicted discordance. Results may help to weigh the benefits and costs of self-report and observer-rated measures in quantifying anxiety severity.

6.2 Methods

6.2.1 Participants

All subjects were outpatients at the department of psychiatry of the Leiden University Medical Centre or an affiliated regional mental healthcare provider. Within both centres, as part of routine clinical practice, all patients were administered an extensive battery of diagnostic and psychometric measures by trained research nurses and through supervised computerised self-report at baseline and approximately every three months of follow-up (although for the purpose of the present study we used only the baseline data). This procedure is known as routine outcome monitoring (ROM), and is described in more detail by De Beurs et al. (2011). Patients were aged 18 through 65 and had adequate command of the Dutch language. All patients had been referred by their general practitioner for treatment of mood, anxiety or somatoform disorders and met DSM-IV-TR diagnostic criteria for at least one or more of the following disorders: panic disorder with or without agoraphobia, agoraphobia without panic, social phobia, and generalised anxiety disorder (allowing for comorbid mood or somatoform disorders). Patients who had missing data, resulting either from the incidental failure to administer complete questionnaires or the incidental occurrence of a large time gap (more than 21 days) between the administration of questionnaires, were excluded from the analyses.

6.2.2 Measures

6.2.2.1 Anxiety severity

Observer-rated anxiety severity was assessed using the BAS (Tyrer et al., 1984). The BAS is a 10-item observer-rated scale derived from the abbreviated Comprehensive Psychopathological Rating Scale (CPRS; Åsberg et al., 1978; Goekoop et al., 1991). The total score equals the sum-score of all 10 items on a 7-point Likert scale (0-6) (range 0-60). It has adequate internal consistency with Cronbach's alpha of 0.65 in our cohort. Both scales assess the main components of all anxiety disorders, covering psychic and somatic components. Patient

reported severity of anxiety symptomatology was measured at intake with the Dutch version of the BSI-12 (De Beurs & Zitman, 2006; Roy-Byrne et al., 2010). The BSI-12 is a self-report measure comprising items of the anxiety and somatization subscales of the 18-item version of the BSI, which has in turn been derived from the BSI (Zabora et al., 2001). The total score equals the sum-score of 12 items on a 5-point Likert scale (0-4) (range 0-48). It has good internal consistency with Cronbach's alphas between 0.79 and 0.84 (Franke et al., 2011). Internal consistency (i.e., Cronbach's alpha) in our cohort was 0.90. On both scales a higher score corresponds to more severe anxiety. Figure 1 lists the items comprising both the BAS and the BSI-12.

Figure 6.1 Item content of the observer-rated Brief Anxiety Scale (BAS) and the self-report Brief Symptom Inventory-12 item version (BSI-12)

Items BAS (observer rated	Items BSI-12 (self report)
Autonomic disturbances- reported	Nervousness
Aches and pains	Faintness
Inner tension	Pains in chest
Hypochondriasis	Suddenly scared
Worrying over trifles	Feeling fearful
Phobias	Nausea
Hostile feelings	Trouble getting breath
Reduced sleep	Numbness
Autonomic disturbances-observed	Feeling weak
Muscular tension	Feeling tense
	Spells of panic
	Feeling restless

6.2.2.2 Patient characteristics

At intake, age, gender, and education level (low: primary through lower secondary education/ high: higher secondary education through university) were assessed. The Dutch version of the MINI International Neuropsychiatric Interview-Plus (MINI-Plus; Sheehan et al., 1998; van Vliet et al., 2000) was used to collect DSM-IV-TR diagnostic information (type of anxiety disorder, number of simultaneously occurring anxiety disorders, presence of a comorbid mood disorder, presence of a comorbid somatoform disorder, comorbid alcohol- or substance abuse or -dependence). The MINI-Plus has good psychometric properties, with inter-rater reliability between 0.88 and 1.00 and test-retest reliability between 0.76 and 0.93 and adequate validity compared to the Composite International Diagnostic Interview-1 (Lecrubier et al., 1997).

6

Personality characteristics were assessed using the Dimensional Assessment of Personality Pathology short form (DAPP-SF; van Kampen et al., 2008), the abbreviated version of the DAPP-BQ (Livesley et al., 1998). The DAPP-SF consists of 136 items on a 5-point Likert scale (1-5), which can be converted into subscales by taking the average of the subscale items. 18 subscales exist (i.e., submissiveness, cognitive distortion, identity problems, affective lability, stimulus seeking, compulsiveness, restricted expression, callousness, oppositionality, intimacy problems, rejection, anxiousness, conduct problems, suspiciousness, social avoidance, narcissism, insecure attachment, and self-harm). Higher scores are associated with pathology, whereas lower scores indicate normality. The DAPP-SF has good internal consistency with Cronbach's alphas ranging from 0.78-0.89 across subscales (van Kampen et al., 2008).

6.2.3 Analyses

Sample categorical characteristics are presented as number (percentage), continuous variables are presented as mean (M) (± standard deviation [SD]). To describe overall concordance, the Pearson product-moment correlation coefficient between the BAS and the BSI-12 was computed. To quantify discordance on individual patient level, Z-scores were computed. The minimal difference for the two discordant groups was set at 1 SD, i.e. a difference of more than 1 Z-score was categorised as discordant (Dorz et al., 2004). This resulted in three levels of concordance: observer-rated (BAS) = self-report (BSI-12), observer-rated (BAS) < self-report (BSI-12), and observer rated (BAS) > self-report (BSI-12). We compared the two discordant groups (observer-rated [BAS] < self-report [BSI-12], and observer rated [BAS] > self-report [BSI-12]) with the concordant group (observer-rated [BAS] = self-report [BSI-12], reference group) with regard to age, gender, education level, anxiety diagnosis, number of simultaneously occurring anxiety disorders, presence of comorbid mood-, somatoform- and alcohol- or substance abuse or -dependence disorders, and the subscales of the DAPP-SF using univariable multinomial logistic regression. Finally, in order to identify predictors of discordance, all variables that were significantly associated in univariable analyses were entered in a multivariable model. All analyses were two-tailed, significance was set at p < 0.05, and correction for multiple testing using Bonferroni was performed.

Although all patients in our sample were diagnosed with one or more anxiety disorders according to DSM-IV-TR criteria using a validated diagnostic instrument (MINI Plus (van Vliet et al., 2000)), we have no information regarding primary diagnosis or focus of treatment as patients in our cohort were referred by their general practitioner for treatment of mood-, anxiety-, or somatoform disorder. Therefore, some patients in our sample, while meeting diagnostic criteria for an anxiety disorder, might not have been seeking treatment primarily for an anxiety disorder (but instead for a mood- or somatoform disorder). Therefore,

as a sensitivity analysis, we repeated analyses with only those subjects who met criteria for at least moderate severity on either the BAS or the BSI-12 so as to guarantee substantial anxiety severity. Moderate severity was defined as BAS ≥ 10.38 (Tyrer et al., 1984; Schat et al., 2013) and/or BSI-12 ≥ 6 (Roy-Byrne et al., 2010;Schat et al., 2013). We used SPSS version 20.0 (IBM Corp., Armonk, NY, USA).

6.3 Results

6.3.1 Sample characteristics

Between March 2004 and October 2009, a total of 2555 patients met DSM-IV-TR diagnostic criteria for panic disorder with or without agoraphobia, agoraphobia without panic, social phobia, and generalised anxiety disorder. 551 patients had to be excluded, as they had not completed all questionnaires or a large time gap (more than 21 days) existed between completion of distinct questionnaires. Therefore, 2004 patients were included for analyses. Figure 2 shows a flowchart of inclusion and exclusion. Although differences between included and excluded patients with regard to age, number of patients diagnosed with generalised anxiety disorder, comorbid depression and somatoform disorder, BAS score, BSI-12 score, DAPP-SF scores (subscales cognitive distortion, identity problems, affective lability, rejection, and self-harm) were significant at $p < 0.05$ (results not shown), these differences were very small, with eta squares ranging from .001 to .01 and Cramer's Phi's between .004 and .058. A total of 1275 (63.6%) patients were female and the mean age of the total sample was 36.1 years (SD = 11.7). Panic disorder with or without agoraphobia occurred in 778 (38.8%) patients, agoraphobia without panic occurred in 436 (21.8%) patients; 648 (32.3%) patients were diagnosed with social phobia, and 425 (21.2%) had generalised anxiety disorder. A total of 571 (28.5%) patients met diagnostic criteria for multiple simultaneously occurring anxiety disorders. Comorbid mood disorder occurred in 902 (45%) patients, while 234 (11.7%) patients met diagnostic criteria for comorbid somatoform disorder.

6

Figure 6.2 Flowchart of inclusion
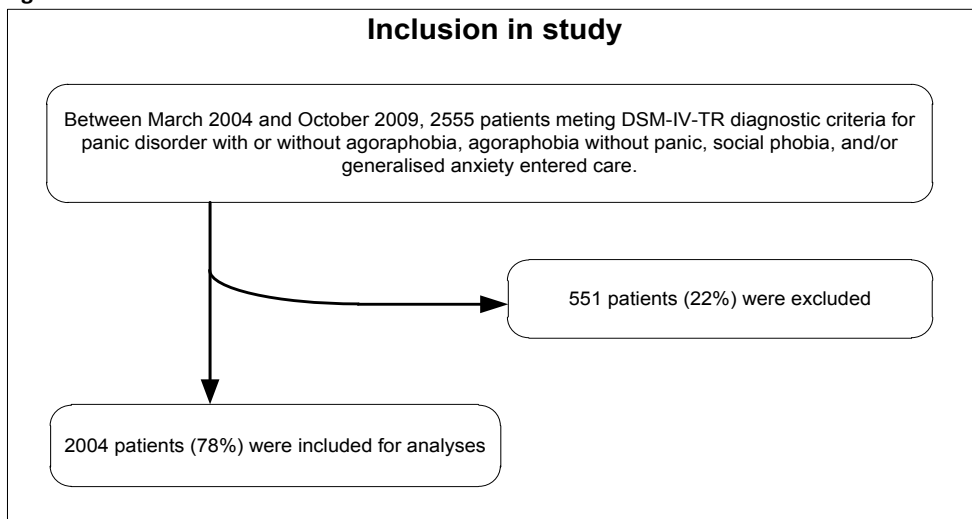
DSM-IV-TR denotes Diagnostic Statistical Manual-fourth edition, text revision

6.3.2 Concordance

The relationship between observer-rated (BAS) and self-report (BSI-12) anxiety severity in the total sample was positive and strong; r = 0.61, n = 2004, p < .001. Based on their standardized difference score, patients were categorised in three groups: observer-rated (BAS) = self-report (BSI-12), where Z-BAS was equal to Z-BSI-12 ±1 (n = 1531; 76.4%); observer-rated (BAS) < self-report (BSI-12), where Z-BAS was equal to Z-BSI minus at least 1 (n = 225; 11.2%); and observer-rated (BAS) > self-report (BSI-12), where Z-BAS was equal to Z-BSI-12 plus at least 1 (n = 248; 12.4%). Table 6.1 shows sample characteristics for these three groups of outpatients. Table 6.2 shows associations of patient characteristics with level of concordance (BAS > BSI-12 and BAS < BSI-12 compared to BAS ≈ BSI-12). Patients with higher observer-rated anxiety severity relative to self-report anxiety severity (BAS > BSI-12) did not differ from the concordant group (BAS ≈ BSI-12) with regard to any of the patient characteristics.

Compared to patients whose anxiety severity scores were concordant (BAS ≈ BSI-12), patients whose observed anxiety severity was lower than what they reported (BAS < BSI-12) more often had a diagnosis of panic disorder with or without agoraphobia (OR = 1.23; 95% CI = 1.68-2.96; p < .001), and were less often diagnosed with social phobia (OR = 0.53; 95% CI = 0.38-0.74; p < .001). In addition, patients with lower observed compared to self-rated anxiety severity had higher scores on DAPP-SF subscales cognitive distortion (OR = 1.52; 95% CI = 1.32-1.74; p < .001), identity problems (OR = 1.47; 95% CI = 1.26-1.70; p < .001), affective lability (OR = 1.67; 95% CI = 1.40-1.99; p < .001), oppositionality (OR = 1.32; 95% CI = 1.12-1.55; p = 0.001),

anxiousness (OR = 1.35; 95% CI = 1.15-1.59; p < .001), suspicion (OR = 1.29; 95% CI = 1.13-1.47; p < .001), and insecure attachment (OR = 1.31; 95% CI = 1.15-1.49; p < .001) (table 6.2). Figure 3 shows OR's and CI's for significant associations. When, after checking for collinearity, these variables were entered in multivariable logistic regression, panic disorder with or without agoraphobia (OR = 1.89; 95% CI = 1.39-2.58; p < .001), social phobia (OR = 0.61; 95% CI = 0.42-0.89; p = 0.01), and affective lability (OR = 1.41; 95% CI = 1.07-1.85; p = 0.02) best predicted lower observed compared to self-reported anxiety severity (table 6.3). When analyses were repeated with only those patients who met criteria for at least moderate severity (BAS ≥ 10.38 (Tyrer et al., 1984; Schat et al., 2013) and/or BSI-12 ≥ 6 (Roy-Byrne et al., 2010; Schat et al., 2013), (n = 1852) results did not change (results not shown).

6.4 Discussion

We set out to describe concordance between an observer rated (BAS) and self-report (BSI-12) measure of anxiety severity in a naturalistic sample of outpatients diagnosed with panic disorder with or without agoraphobia, agoraphobia without panic, social phobia, and/or generalised anxiety disorder. In addition to describing the level of concordance in our sample, we studied associations between patient characteristics and discordance, and examined which patient characteristics best predicted discordance.

The overall correlation between observer rated and self-report measures of anxiety severity in our sample was positive and strong. However, for a substantial group of patients, considerable discordance existed, with observer-rated anxiety severity exceeding self-reported anxiety severity in 12.4% of patients, and lower observer-rated than self-reported anxiety in 11.2% of patients. These percentages were comparable to results from a previous study applying the same methodology, with depressed patients and depression measures, in which these groups consisted of 17.7% and 15.5% of patients respectively (Dorz et al., 2004). Although a by definition unknown proportion of the discordance must be attributed to random measurement error, the discordance could be partially associated with patient characteristics.

The group of patients with higher observed anxiety relative to self-reported anxiety did not differ from the concordant group with regard to patient characteristics. The group of patients that had lower observed anxiety than what was reported, however, was more often diagnosed with panic disorder with or without agoraphobia compared to the concordant group, but less often had social phobia. Also, this group scored higher on personality aspects cognitive distortion, identity problems, affective lability, oppositionality, anxiousness, suspicion, and insecure attachment than the concordant group. Lower observed than self-reported anxiety severity was best predicted by panic disorder with or without agoraphobia, social phobia, and affective lability.

6

Table 6.1 Baseline characteristics of 2004 outpatients diagnosed with DSM-IV-TR anxiety disorders per level of concordance between observer-rated (BAS) and self-report (BSI-12) anxiety questionnaire.

|	observer ≈ self n=1531	observer>self n=248	observer<self n= 225
Age	36.21 (11.66)	37.06 (11.65)	34.44 (11.71)
Gender			
-male	563 (36.8%)	85 (34.3%)	81 (36.0%)
-female	968 (63.2%)	163 (65.7%)	144 (64.0%)
Education level			
-high	918 (60.0%)	138 (55.6%)	124 (55.1%)
-low	613 (40.0%)	110 (44.4%)	101 (44.9%)
Panic disorder with/without agoraphobia	576 (37.6%)	73 (29.4%)	129 (57.3%)
Agoraphobia without panic	330 (21.6%)	55 (22.2%)	51 (22.7%)
Social phobia	501 (32.7%)	101 (40.7%)	46 (20.4%)
Generalised anxiety disorder	333 (21.8%)	60 (24.2%)	32 (14.2%)
Multiple anxiety disorders	409 (26.7%)	85 (34.3%)	77 (34.2%)
Comorbid mood	669 (43.7%)	130 (52.4%)	103 (45.8%)
Comorbid somatoform	165 (10.8%)	41 (16.5%)	28 (12.4%)
Comorbid alcohol	91 (5.9%)	13 (5.2%)	10 (4.4%)
Comorbid substance	72 (4.7%)	9 (3.6%)	10 (4.4%)
DAPP-SF subscales			
Submissiveness	3.05 (0.96)	3.05 (0.92)	3.10 (1.00)
Cognitive dist.	2.36 (0.98)	2.24 (0.92)	2.79 (1.04)
Identity problems	3.08 (1.03)	3.07 (0.94)	3.45 (0.99)
Affective lability	3.25 (0.89)	3.23 (0.76)	3.61 (0.85)
Stimulus seeking	2.07 (0.78)	2.01 (0.72)	2.16 (0.87)
Compulsiveness	2.93 (0.92)	2.91 (0.95)	3.09 (1.00)
Restricted expres.	3.26 (0.85)	3.32 (0.84)	3.31 (0.87)
Callousness	1.77 (0.59)	1.73 (0.56)	1.90 (0.64)
Oppositionality	2.79 (0.89)	2.76 (0.84)	3.00 (0.90)
Intimacy problems	2.34 (0.81)	2.45 (0.86)	2.45 (0.86)
Rejection	2.30 (0.82)	2.13 (0.82)	2.34 (0.87)
Anxiousness	3.45 (0.93)	3.52 (0.84)	3.69 (0.91)
Conduct problems	1.43 (0.58)	1.38 (0.53)	1.48 (0.66)
Suspicion	2.23 (1.02)	2.29 (0.98)	2.51 (1.08)
Social avoidance	3.16 (1.08)	3.24 (1.05)	3.29 (1.08)
Narcissism	2.41 (0.82)	2.30 (0.80)	2.54 (0.83)
Insecure att.	3.03 (1.12)	2.88 (1.04)	3.36 (1.16)
Self-harm	1.62 (0.89)	1.59 (0.79)	1.75 (0.94)

Data are mean (standard deviation) or number (percentage), when appropriate. The MINI International Neuropsychiatric Interview-Plus (MINI-Plus) was used to collect DSM-IV-TR diagnostic information (type of anxiety disorder, number of simultaneously occurring anxiety disorders, presence of a comorbid mood disorder, presence of a comorbid somatoform disorder, comorbid alcohol- or substance abuse or -dependence); DSM-IV-TR denotes Diagnostic Statistical Manual-fourth edition, text revision; BAS denotes Brief Anxiety Scale; BSI-12 denotes Brief Symptom Inventory-12 item version; DAPP-SF denotes Dimensional Assessment of Personality Pathology-short form; Cognitive dist. refers to the Cognitive distortion subscale of the DAPP-SF Restricted expres. refers to the Restricted expression subscale of the DAPP-SF; Insecure att. refers to the Insecure attachment subscale of the DAPP-SF .

Table 6.2 Associations between patient characteristics and level of concordance between observer-rated (observer; BAS) and self-report (self; BSI-12) anxiety questionnaires in 2004 outpatients with DSM-IV-TR anxiety disorders.

Reference group: observer ≈ self (n=1531)	observer > self (n=248)		observer < self (n=224)	
	OR (95% CI)	p	OR (95% CI)	p
Age	1.01 (1.00-1.02)	0.29	0.99 (0.98-1.00)	0.03
Female gender (vs male)	1.12 (0.84-1.48)	0.45	1.03 (0.77-1.38)	0.82
Low education level (vs high)	0.84 (0.64-1.10)	0.20	0.82 (0.62-1,09)	0.17
Panic disorder	0.69 (0.52-0.93)	0.01	**1.23 (1.68-2.96)**	**<.001**
Agoraphobia without panic	1.04 (0.75-1.43)	0.83	1.07 (0.76-1.49)	0.71
Social phobia	1.41 (1.07-1.86)	0.01	**0.53 (0.38-0.74)**	**<.001**
Generalised anxiety disorder	1.15 (0.84-1.57)	0.39	0.60 (0.40-0.88)	0.01
Multiple anxiety disorders	0.70 (0.53-0.93)	0.01	0.70 (0.52-0.94)	0.02
Comorbid mood disorder	1.42 (1.09-1.86)	0.01	1.09 (0.82-1.44)	0.56
Comorbid somatoform disorder	1.64 (1.13-2.38)	.009	1.18 (0.77-1.80)	0.46
Comorbid alcohol abuse/dependence	0.88 (0.48-1.59)	0.66	0.74 (0.38-1.44)	0.37
Comorbid substance abuse/dependence	0.76 (0.38-1.55)	0.45	0.94 (0.48-1.85)	0.86
DAPP-SF subscales				
Submissiveness	0.99 (0.86-1.14)	0.90	1.05 (0.91-1.22)	0.52
Cognitive distortion	0.88 (0.76-1.01)	0.07	**1.52 (1.32-1.74)**	**<.001**
Identity problems	0.99 (0.87-1.12)	0.87	**1.47 (1.26-1.70)**	**<.001**
Affective lability	0.99 (0.85-1.15)	0.85	**1.67 (1.40-1.99)**	**<.001**
Stimulus seeking	0.90 (0.75-1.07)	0.23	1.15 (0.97-1.37)	0.11
Compulsiveness	0.73 (0.84-1.13)	0.73	1.20 (1.04-1.40)	0.02
Restricted expression	1.08 (0.93-1.27)	0.32	1.08 (0.91-1.27)	0.37
Callousness	0.88 (0.69-1.11)	0.27	1.39 (1.11-1.74)	.004
Oppositionality	0.97 (0.83-1.12)	0.65	**1.32 (1.12-1.55)**	**.001**
Intimacy problems	1.17 (0.99-1.37)	0.06	1.17 (0.99-1.38)	0.06
Rejection	0.78 (0.66-0.93)	0.005	1.06 (0.90-1.26)	0.48
Anxiousness	1.08 (0.93-1.25)	0.31	**1.35 (1.15-1.59)**	**<.001**
Conduct problems	0.86 (0.67-1.10)	0.24	1.14 (0.91-1.43)	0.25
Suspicion	1.06 (0.93-1.21)	0.37	**1.29 (1.13-1.47)**	**<.001**
Social avoidance	1.07 (0.95-1.22)	0.28	1.12 (0.98-1.28)	0.09
Narcissism	0.84 (0.71-1.00)	0.04	1.21 (1.02-1.43)	0.03
Insecure attachment	0.89 (0.79-1.00)	0.05	**1.31 (1.15-1.49)**	**<.001**
Self-harm	0.96 (0.82-1.13)	0.63	1.17 (1.01-1.35)	0.04

Data present Odds Ratios relative to the reference group 'no discordance' (Z-BAS ≈ (Z-BSI ±1) n=1531) obtained in univariable multinomial logistic regression. Bonferroni correction for multiple testing was made. The MINI International Neuropsychiatric Interview-Plus (MINI-Plus) was used to collect DSM-IV-TR diagnostic information (type of anxiety disorder, number of simultaneously occurring anxiety disorders, presence of a comorbid mood disorder, presence of a comorbid somatoform disorder, comorbid alcohol- or substance abuse or -dependence); DSM-IV-TR denotes Diagnostic Statistical Manual-fourth edition, text revision; BAS denotes Brief Anxiety Scale; BSI-12 denotes Brief Symptom Inventory-12 item version; OR denotes odds ratio; 95% CI denotes 95% confidence interval; DAPP-SF denotes Dimensional Assessment of Personality Pathology-short form.

6

Figure 6.3 Significant associations of patient characteristics with discordance between observer-rated (BAS) and self-report (BSI-12) measures of anxiety severity, relative to concordant patients.
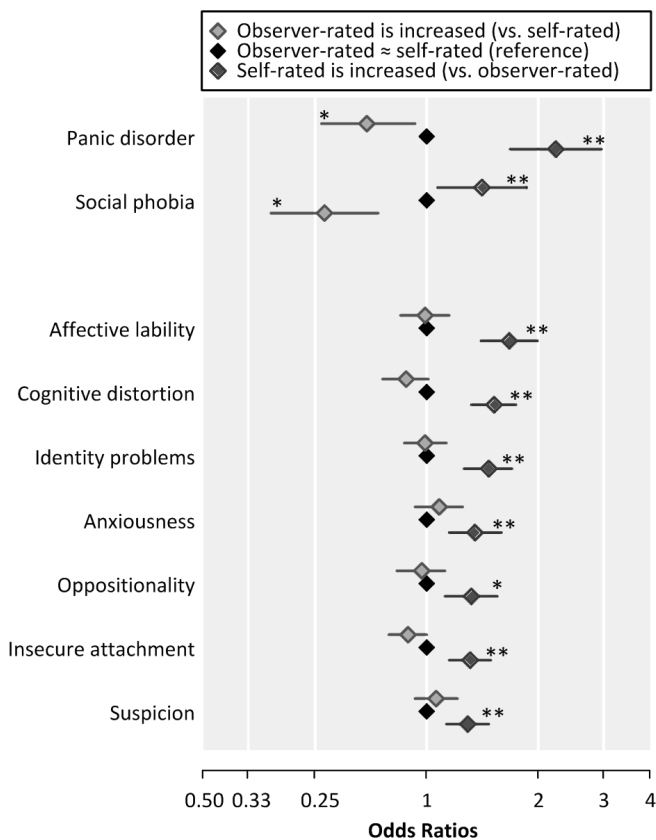
*Odds ratios with error bars representing 95% confidence intervals are shown for significant associations of patient characteristics in the observer-rated (BAS) < self-report (BSI-12) group relative to concordant patients, results for the observer-rated (BAS) > self-report (BSI-12) group are also shown, none of these were significant after Bonferroni correction; data were analysed using univariable multinomial logistic regression analysis; The MINI International Neuropsychiatric Interview-Plus (MINI-Plus) was used to collect DSM-IV-TR diagnostic information; Affective lability, cognitive distortion, identity problems, anxiousness, oppositionality, insecure attachment and suspicion are all subscales of the Dimensional Assessment of Personality Pathology-short form; ** denotes significant at p < 0.05 after Bonferroni correction for multiple testing; BAS denotes Brief Anxiety Scale; BSI-12 denotes Brief Symptom Inventory-12 item version.*

Table 6.3 Predictors of higher self-reported compared to observer rated anxiety severity in 2004 outpatients with DSM-IV-TR anxiety disorders.

reference group observer ≈ self (n=1531)	observer < self (n=224)	
	OR (95% CI)	p
Intercept -3.99		
Panic disorder with or without agoraphobia	**1.89 (1.39-2.56)**	**<.001**
Social phobia	**0.61 (0.42-0.89)**	**0.01**
DAPP-SF subscales		
Cognitive distortion	1.16 (0.96-1.52)	0.13
Identity problems	1.20 (0.96-1.52)	0.12
Affective lability	**1.41 (1.07-1.85)**	**0.02**
Oppositionality	0.99 (0.80-1.22)	0.91
Anxiousness	0.89 (0.69-1.15)	0.39
Suspicion	1.04 (0.87-1.24)	0.67
Insecure attachment	1.03 (0.88-1.20)	0.76

Data present Odds Ratios relative to the reference group 'no discordance' (Z-BAS ≈ (Z-BSI ±1) n=1531) obtained in multivariable logistic regression. The MINI International Neuropsychiatric Interview-Plus (MINI-Plus) was used to collect DSM-IV-TR diagnostic information (type of anxiety disorder, number of simultaneously occurring anxiety disorders, presence of a comorbid mood disorder, presence of a comorbid somatoform disorder, comorbid alcohol- or substance abuse or -dependence); DSM-IV-TR denotes Diagnostic Statistical Manual-fourth edition, text revision; BAS denotes Brief Anxiety Scale; BSI-12 denotes Brief Symptom Inventory-12 item version; OR denotes odds ratio; 95% CI denotes 95% confidence interval; DAPP-SF denotes Dimensional Assessment of Personality Pathology-short form.

Our finding of higher prevalence of panic disorder with or without agoraphobia, and lower presence of social phobia in the group with lower observed- relative to self-reported anxiety severity, may have several explanations. First, it may reflect a difference in response styles between patients in both diagnostic groups: panic disorder is characterised by intense panic experiences, which may lead to high self-ratings of anxiety severity, while social phobia often entails feelings of shame and self-effacing, which may in turn result in under reporting of anxiety severity. Alternatively, it may be explained in terms of item content. Possibly, the BAS contains more items on (excessive or unreasonable) fear of social situations, whereas the BSI-12 may put more emphasis on the (more physical) symptoms of panic disorder. Inspection of the items of both instruments (figure 1), as well as the presence of an opposite (although not significant after Bonferroni correction) association in the BAS > BSI-12 group support this thought.

The association between discordance and personality characteristics is in line with previous findings in depression. We found that patients whose observed anxiety severity was lower than their self-reported anxiety severity, scored higher on cognitive distortion, identity problems, affective lability, oppositionality, anxiousness, suspicion, and insecure attachment than concordant patients. As higher DAPP-SF scores indicate elevated chances of personality

6

pathology, these findings fit previous reports of higher prevalence of personality disorders in patients who reported higher depression severity relative to their observed depression severity (Dorz et al., 2004; Rane et al., 2010). Our findings are furthermore in agreement with previous more specific reports of high neuroticism, low extraversion, low agreeableness (Enns et al., 2000), novelty seeking, and reward dependence (Carter et al., 2010) in patients whose observed depression severity was lower than their self-reported depression severity. Lower observed anxiety severity compared to self-reported anxiety severity was best predicted by panic disorder with or without agoraphobia, social phobia, and affective lability. This finding indicates that especially in patients with positive scores on these characteristics, the use of both self-report and observer rated instruments is merited. Together, these findings may indicate that personality pathology, especially in clusters B and C, adds to the suffering experienced by patients in a manner that is not readily observed or recognised by research nurses or caregivers.

We did not replicate previous findings of associations between level of concordance and age (Carter et al., 2010; Dorz et al., 2004; Enns et al., 2000), gender (Carter et al., 2010; Jolly et al., 1994), education level (Enns et al., 2000) and marital status (Dorz et al., 2004). As these findings pertained largely to depression (Dorz et al., 2004; Enns et al., 2000), it is possible that they are specific to depression and depression instruments, and do not generalise to anxiety. This thought is supported by reports by Jolly et al., (Jolly et al., 1994), who found that for adolescent boys with various psychiatric diagnoses, discordance on depression instruments was higher than for girls, whereas no such difference existed for anxiety measures although no such findings have been reported for age, education level, and marital status.

As previous research on concordance has mainly focussed on depression and no comparison between the scores on questionnaires used in this study has been made before, our results are novel. Other strong points are our large sample size, the use of trained research nurses, our naturalistic sample and the thorough assessment of personality pathology. However, several potential limitations exist. First of all, we have no information on the order in which observer-rated and self-report instruments were administered, possibly, the order in which instruments were administered varied which in turn might have influenced the level of concordance (Jolly et al., 1994). Second, we had no information on primary diagnosis, which might have been associated with discordance. Third, although we excluded patients with large time gaps (more than 21 days) between the administration of the BAS and the BSI-12, smaller time gaps were allowed and incidentally occurred, which may have influenced results. However, although this might have influenced the number of cases in which discordance occurred, it is unlike to have influenced the association between patient characteristics and discordance. Fourth, we used two different instruments to measure anxiety severity, a comparison between scores on an observer rated and self-report version of the same

instrument would have been preferable. Furthermore, it must be noted that the DAPP-SF, which was used to assess personality pathology, is a self-report instrument. Possibly, the use of an observer rated measure of personality characteristics would have yielded different results. In addition, we have no information on rater-characteristics, which might be associated with discordance as well (Carter et al., 2010; van Noorden et al., 2010). On a related topic, although we did not find associations between patient characteristics and higher observer-rated-compared to self-reported anxiety severity, this does not imply the discordance in this group necessarily resulted entirely from random measurement error. Possibly, this type of discordance is related to rater-characteristics or patient characteristics that were not measured in this study. Finally, as our data are cross-sectional, our findings do not allow for causal interpretation regarding contributions of personality characteristics to discordance.

Our results demonstrate that using a single instrument in the assessment of patients' anxiety severity, could give rise to a one-sided view of pathology. These findings have practical implications for research as well as practice. As in psychiatry, patients' subjective experiences are central, it is relevant to note that for a substantial group of patients, self-reported anxiety severity does not match observed anxiety severity. In clinical studies, observer-rated instruments, while generally regarded as the primary source of information, may not suffice when measuring anxiety severity and change in anxiety severity, as (changes in) subjectively experienced anxiety severity may go un noted. In clinical practice on the other hand, the growing reliance on cheaper self-report scales may obscure anxiety severity in a substantial group of patients for whom anxiety severity would be rated higher by a trained research nurse. Also, our results demonstrate that for those patients who rate their anxiety as more severe than a trained observer would, personality pathology might be a complicating factor. Possibly, patients who have high cognitive distortion, identity problems, affective lability, oppositionality, anxiousness, suspicion, and insecure attachment, are less willing or capable to express their symptom severity to an observer. Finally, the potential presence of personality pathology is highly relevant for treatment as personality pathology may require a different approach and special attention. Therefore, in conclusion, we argue that a multi-method approach to psychiatric assessment, consisting of self-report as well as observer-rated instruments, disorder specific- as well as generic instruments, and covering aspects of symptomatology, personality and psychosocial functioning, although more expensive, is highly preferable to the use of a single self-report instrument in baseline assessment of psychopathology (Enns et al., 2000; Moller, 2000).

6

Reference List

Åsberg, M., Montgomery, S.A., Perris, C., Schalling, D., & Sedvall, G. (1978). Comprehensive Psychopathological Rating-Scale. *Acta Psychiatrica Scandinavica,* Supplement 271, 5-27.

Carter, J.D., Frampton, C.M., Mulder, R.T., Luty, S.E., & Joyce, P.R. (2010). The relationship of demographic, clinical, cognitive and personality variables to the discrepancy between self and clinician rated depression. *Journal of Affective Disorders,* 124, 202-206.

De Beurs, E., den Hollander-Gijsman, M.E., van Rood, Y.R., van der Wee, N.J.A., Giltay, E.J., van Noorden, M.S., van der Lem, R., van Fenema, E., & Zitman, F.G. (2011). Routine Outcome Monitoring in the Netherlands: Practical Experiences with a Web-Based Strategy for the Assessment of Treatment Outcome in Clinical Practice. *Clinical Psychology & Psychotherapy,* 18, 1-12.

De Beurs, E. & Zitman, F.G. (2006). De Brief Symptom Inventory (BSI) De betrouwbaarheid van een handzaam alternatief voor de SCL-90. *Maandblad Geestelijke Volksgezondheid,* 61, 120-141.

Dorz, S., Borgherini, G., Conforti, D., Scarso, C., & Magni, G. (2004). Comparison of self-rated and clinician-rated measures of depressive symptoms: a naturalistic study. *Psychology & Psychotherapy: Theory, Research and Practice,* 77, 353-361.

Dunlop, B.W., Li, T., Kornstein, S.G., Friedman, E.S., Rothschild, A.J., Pedersen, R., Ninan, P., Keller, M., & Trivedi, M.H. (2011). Concordance between clinician and patient ratings as predictors of response, remission, and recurrence in major depressive disorder. *Journal of Psychiatric Research,* 45, 96-103.

Enns, M.W., Larsen, D.K., & Cox, B.J. (2000). Discrepancies between self and observer ratings of depression. The relationship to demographic, clinical and personality variables. *Journal of Affective Disorders,* 60, 33-41.

Franke, G.H., Ankerhold, A., Haase, M., Jager, S., Togel, C., Ulrich, C., & Frommer, J. (2011). The Usefulness of the Brief Symptom Inventory 18 (BSI-18) in Psychotherapeutic Patients. *Psychotherapie Psychosomatik Medizinische Psychologie,* 61, 82-86.

Goekoop, J.G., Knoppertvanderklein, E.A.M., Hoeksema, T., Klinkhamer, R.A., Vangaalen, H.A.E., & Vandervelde, E.A. (1991). The Interrater Reliability of A Dutch Version of the Comprehensive Psychopathological Rating-Scale. *Acta Psychiatrica Scandinavica,* 83, 202-205.

Hamilton, M. (1976). Comparative value of rating scales. *British Journal of Clinical Pharmacology,* 3, 58-60.

Hopko, D.R., Bourland, S.L., Stanley, M.A., Beck, J.G., Novy, D.M., Averill, P.M., & Swann, A.C. (2000). Generalised anxiety disorder in older adults: examining the relation between clinician severity ratings and patient self-report measures. *Depression & Anxiety,* 12, 217-225.

Jolly, J.B., Wiesner, D.C., Wherry, J.N., Jolly, J.M., & Dykman, R.A. (1994). Gender and the comparison of self and observer ratings of anxiety and depression in adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry,* 33, 1284-1288.

Lecrubier, Y., Sheehan, D.V., Weiller, E., Amorim, P., Bonora, I., Sheehan, K.H., Janavs, J., & Dunbar, G.C. (1997). The Mini International Neuropsychiatric Interview (MINI). A short diagnostic structured interview: Reliability and validity according to the CIDI. *European Psychiatry,* 12, 224-231.

Livesley, W.J., Jang, K.L., & Vernon, P.A. (1998). Phenotypic and genetic structure of traits delineating personality disorder. *Archives of General Psychiatry,* 55, 941-948.

Lubaczewski, S., Shepherd, J., Fayyad, R., & Guico-Pabia, C.J. (2014). Real-world disparities between patient- and clinician-reported outcomes: results from a disease-specific program in depression and anxiety. *Professional Case Management,* 19, 63-74.

Moller, H.J. (2000). Rating depressed patients: observer- vs self-assessment. *European Psychiatry,* 15, 160-172.

Rane, L.J., Fekadu, A., Wooderson, S., Poon, L., Markopoulou, K., & Cleare, A.J. (2010). Discrepancy between subjective and objective severity in treatment-resistant depression: prediction of treatment outcome. *Journal of Psychiatric Research,* 44, 1082-1087.

Roy-Byrne, P., Craske, M.G., Sullivan, G., Rose, R.D., Edlund, M.J., Lang, A.J., Bystritsky, A., Welch, S.S., Chavira, D.A., Golinelli, D., Campbell-Sills, L., Sherbourne, C.D., & Stein, M.B. (2010). Delivery of evidence-based treatment for multiple anxiety disorders in primary care: a randomised controlled trial. *Journal of the American Medical Association,* 303, 1921-1928.

Schat, A., van Noorden, M.S., Noom, M.J., Giltay, E.J., van der Wee, N.J., Vermeiren, R.R., & Zitman, F.G. (2013). Predictors of outcome in outpatients with anxiety disorders: the Leiden routine outcome monitoring study. *Journal of Psychiatric Research,* 47, 1876-1885.

Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., & Dunbar, G.C. (1998). The Mini-International Neuropsychiatric Interview (MINI): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry,* 59, 22-33.

Tyrer, P., Owen, R.T., & Cicchetti, D.V. (1984). The Brief Scale for Anxiety - A Subdivision of the Comprehensive Psychopathological Rating-Scale. *Journal of Neurology Neurosurgery and Psychiatry,* 47, 970-975.

van Kampen, D., De Beurs, E., & Andrea, H. (2008). A short form of the Dimensional Assessment of Personality Pathology-Basic Questionnaire (DAPP-BQ): The DAPP-SF. *Psychiatry Research*, 160, 115-128.

van Noorden, M.S., Giltay, E.J., den Hollander-Gijsman, M.E., van der Wee, N.J.A., van Veen, T., & Zitman, F.G. (2010). Gender differences in clinical characteristics in a naturalistic sample of depressive outpatients: The Leiden Routine Outcome Monitoring Study. *Journal of Affective Disorders,* 125, 116-123.

van Vliet, I.M., Leroy, H., & van Megen, H.J.G.M. (2000). MINI internationaal neuropsychiatrisch interview nederlandse versie 5.0.0, 5 ed. Utrecht.

Zabora, J., BrintzenhofeSzoc, K., Jacobsen, P., Curbow, B., Piantadosi, S., Hooker, C., Owens, A., & Derogatis, L. (2001). A new psychosocial screening instrument for use with cancer patients. *Psychosomatics,* 42, 241-246.

6

Chapter 7

Discussion

7.1 Aims of this thesis

Panic disorder (PD/A), agoraphobia without panic (AP), social phobia (SP), and generalised anxiety disorder (GAD) are commonly occurring anxiety disorders that incur severe suffering and functional impairment (Wittchen et al., 2011; de Graaf et al., 2012). They often have a detrimental course (Batelaan et al., 2014) and come with substantial societal costs (Gustavsson et al., 2011). Although these anxiety disorders have been studied extensively, previous studies typically did not involve large patient groups that were comparable to those seen in clinical practice. Instead, studies focused on subjects meeting diagnostic criteria for anxiety disorders in the general population, or alternatively, on patients who met strict eligibility criteria for clinical trials, or who were willing to take part in long running studies. These subjects are likely to differ substantially from patients seen in everyday clinical practice which limits generalizability of findings to clinical practice (Black, 1996; Kessler, 2007; Rothwell, 2005; van der Lem et al., 2011; Vandenbroucke, 2008). Naturalistic epidemiological studies in representative clinical samples are needed to provide insights into patient characteristics, and evaluate their clinical significance and their relevance to prognosis (Kessler, 2007). In this thesis, characteristics of subjects meeting diagnostic criteria for PD/A, AP, SP, and/or GAD were described using data that were collected as part of routine clinical practice in mental healthcare (Leiden Routine Outcome Monitoring (ROM) Study). Together, the different chapters were aimed at describing the phenomenology of anxiety in clinical practice, focusing on characteristics with clinical relevance and course.

In the following paragraphs, the studies described in this thesis will be discussed. First, main findings will be summarised. The second chapter of this thesis, which combined data collected in the general population (Netherlands Mental Health Survey and Incidence Study-2; NEMESIS-2) with clinical data (ROM), focused on the onset of anxiety and its correlates. In chapter three, age related characteristics of outpatients with anxiety disorders were studied. The fourth chapter focused on predictors of the course of anxiety disorders in mental healthcare. Chapter five examined suicidal ideation, a complication that may occur in anxiety disorders, and evaluated the prognostic value of previously identified patient characteristics. Finally, chapter six examined measurement strategies in anxiety, by looking at concordance between self-reported and observer-rated measures of anxiety severity and its correlates. After summarising results per chapter, findings will first be discussed in light of recent literature. Next clinical implications will be considered, followed by observations and considerations on conducting research with routinely collected clinical data. Limitations will be discussed and finally, prospects for future research will be explored.

7.2 Summary of main findings

Chapter two focused on the emergence of anxiety disorders by examining the age at which subjects with anxiety disorders had experienced first onset of the disorder. While a general consensus on the negative connotation of early onset in terms of disease burden and prognosis exists (Van Ameringen et al., 2004; Campbell et al., 2003; Goodwin et al., 2001; Goldstein, et al., 1997; Iketani et al., 2004; Penninx et al., 2008; Ramsawh et al., 2011; Le Roux et al., 2005; Segui et al., 1999; Segui et al., 2000; Tibi et al., 2013), findings diverge and relevance to clinical practice remains open to question. One issue in the study of early onset of anxiety disorders is that, although typical ages of onset have been described for PD/A, AP, SP, and GAD, definitions of early onset vary. Cluster analysis has been proposed as a method to empirically define early onset cut-offs for psychiatric disorders (Anholt et al., 2014; Bauer et al., 2010; Bellivier et al., 2001; Delorme et al., 2005; Hamshere et al., 2009; Ortiz et al., 2011; Panariello et al., 2010; Tibi et al., 2013; Tibi et al., 2015; Tozzi et al., 2011; Zhu et al., 2012). Application of cluster analysis to the frequency distributions of retrospectively reported ages of onset in PD/A, AP, SP, and GAD, yielded cut-offs for early onset for each of the anxiety disorders under study: PD/A with an onset at or before age 31 qualified as early, whereas early onset AP started at or before age 21. The cut-off for early onset SP was at or before age 22, and early onset GAD started at or before age 27. In addition to empirically defining early onset, the relevance of early onset for subtyping in clinical practice was studied by applying the cut-offs to compare those with early- and late onset anxiety in the general population as well as in clinical practice. We tested the hypothesis that those with early onset anxiety disorders would have more comorbid psychiatric disorders, and were more likely to score below cut-offs for general wellbeing than those with late onset. Interestingly, few differences emerged between early- and late onset PD/A, AP, SP, and GAD. Outpatients with early onset AP did show more anxiety comorbidity than those with late onset AP, but we also found more anxiety-, as well as mood comorbidity in outpatients with late (versus early) onset SP. As such, results did not support our hypothesis of more psychiatric comorbidity and less wellbeing in early onset.

After analysing the onset of anxiety and its correlates, in chapter three we continued with a study of anxiety across the adult lifespan. We explored age related differences by comparing outpatients with commonly occurring anxiety disorders in different age groups. Although current age is usually taken into account as an important characteristic in research, to date, to our knowledge, no comprehensive account of age related characteristics of anxiety disorders exists. It is, however, highly plausible that clinically relevant differences may exist between patients aged 18 through 65. In addition to more obvious differences with regard to social demographic characteristics related to life phases, previous studies in depression demonstrated that patients in different age groups may also differ with regard to clinical

7

characteristics, like comorbidities or symptom profiles (Husain et al., 2005; Wilkowska-Chmielewska et al., 2013). In order to explore these potential differences, a total of 1950 outpatients who were diagnosed with PD/A, AP, SP, and/or GAD was divided in three age groups: young adult (18-25), mid-adult (26-40), and older adult (41-65). These three age groups were compared with regard to social demographic characteristics, psychiatric diagnostic characteristics, anxiety symptom profile, general psychiatric symptom profile, and generic health status. A combination of associations with age group emerged, among which were a higher prevalence of SP in younger patients, and more feelings of interpersonal sensitivity and hostility in younger and mid-adult patients compared to older patients. Similar to findings in two previous studies in depression (Husain et al., 2005; Wilkowska-Chmielewska et al., 2013), older patients had higher levels of physical problems and more sleep problems, and showed a relative lack of vitality. In addition, older patients more often had AP, and had an increased risk of mood comorbidity. These findings demonstrate that patients from different age groups present with differences in symptomatology that may be relevant in research as well as clinical practice.

Chapter four presents an exploration of factors relevant to the course of anxiety disorders in a naturalistic outpatient setting. Data of 917 patients diagnosed with PD/A, AP, SP, and/or GAD, with up to two years of follow-up were analysed to identify predictors of response during the course of treatment. Response was defined as a decrease of at least 50% in both self-reported and observed anxiety severity relative to baseline, at any point during the two-year follow-up period. Cox regression analyses demonstrated that several socio-demographic and clinical variables independently predicted response. Having a non-Dutch ethnicity, having no daily occupation, and having a low education level, were associated with reductions in chances of response of 29%, 24%, and 24% respectively. Patients who lived with family had a 41% better chance of response, although further analyses demonstrated that this association was specific to younger patients. Having a diagnosis of AP was associated with a 33% smaller chance of responding during follow-up, and alcohol abuse or dependence reduced chances of response with 46%. Personality traits were also associated with response: a single standard deviation increase on a continuous measure of affective lability was associated with 20% smaller chances of response; one standard deviation increase on a continuous measure of conduct problems was associated with a 16% smaller chance of response. These results do not only show what patient characteristics are associated with a detrimental course of anxiety in an outpatient setting, they also demonstrate how an extensive assessment process at intake, such as in ROM, may aid clinicians in the identification of patients who are at risk of chronicity.

In chapter five, suicidal ideation was examined. Suicidal ideation is a common complicating factor in both mood and anxiety disorders (Craske, 1999), that may or may not subside during the course of treatment (ten Have et al., 2009). The identification of

characteristics that differentiate between patients who are and are not at risk of sustained suicidal ideation may help clinicians and, ultimately, prevent actual suicide. In this chapter, we studied which patients were at risk of sustained suicidal ideation. We used the routinely collected data of 777 outpatients diagnosed with anxiety disorders and/or depression, who expressed suicidal ideation at baseline. Suicidal ideation was assessed with item 10 of the Montgomery-Åsberg Depression Rating Scale (Montgomery & Åsberg, 1979; Perroud et al., 2009a; Perroud et al., 2009b; van Noorden et al., 2010). Up to two years of naturalistic follow-up data were analysed with survival analysis, in order to evaluate a broad set of prognostic factors that were previously identified as correlates of remission of suicidal ideation conjointly. Remission of suicidal ideation was associated with education level, baseline depression scores, self-harm, and general health perception. Patients with low (versus high) education levels had a 14% lower chance of achieving remission of suicidal ideation; a single standard deviation increase in baseline depression scores and self-harm severity, corresponded to respectively 16% and 23% lower chances of remission of suicidal ideation. Finally, one standard deviation decrease in general health perception scores, corresponded to an 8% reduced chance of remission of suicidal ideation. Our results underpin addressing the needs of patients with suicidal ideation who have low education levels, severe depression, severe self-harm, and poor general health perception, as they are at increased risk of sustained suicidal ideation.

Finally, chapter six focused on the assessment of anxiety severity in clinical practice. Several measures of anxiety severity exist, and they can be categorised as observer-rated and self-report. Self-report measures are more popular in clinical practice, as they are easier and cheaper to administer. Observer-rated measures on the other hand, are regarded as a primary source of information, especially in research settings (Hamilton, 1976; Moller, 2000). Although agreement between both types of measures is usually high, in some individuals they do not concur. It is important to know in which patients these measures are likely to diverge, as in these patients reliance on either self-report or observer-rated measure may fail to detect clinically important information. In this study, patients' responses to a self-report measure of anxiety severity were compared to anxiety severity ratings made by trained psychiatric research nurses. In a sample of 2004 outpatients diagnosed with PD/A, AP, SP, and GAD, overall correlation between self-reported and observer-rated anxiety severity was positive and strong (r=0.61). Discordance occurred in 23.6% of patients, with higher scores on the observer-rated relative to the self-report measure in 12.4% of patients, and lower observer-rated relative to self-reported anxiety severity in 11.2% of patients. Patients with higher observer-rated than self-reported anxiety severity did not differ from patients for whom both measures were concordant on any of the variables included in analyses. Patients with lower observed-than self-reported anxiety severity, more often had PD/A and less often had SP than concordant patients. In addition, they scored higher on cluster B and C personality

7

characteristics than concordant patients. The general level of concordance in our sample demonstrates that on a group level, the use of either a self-reported or an observer-rated measure gives a good indication of severity. On an individual level however, our results demonstrate that when a single instrument is used, anxiety severity may be overlooked in a group of patients. Specifically, trained observers may not adequately assess anxiety severity in those patients who have higher scores on measures of cluster B and C personality traits. Therefore, when determining anxiety severity for clinical purposes, a multi-method approach, encompassing both self-report- and observer-rated measures of anxiety severity as well as assessments of personality traits, is preferable. This will allow for assessment across different domains, and through multiple sources of information. As such, a multi-method approach may provide clinicians with more relevant information than the use of a single instrument would.

7.3 General discussion

7.3.1 Relevance to literature

In chapter two we distinguished early- and late onset of the four anxiety disorders. However, when comparing those with early onset and late onset, we did not find support for our hypothesis of less wellbeing in those with early onset, nor did we replicate findings of more psychiatric comorbidity in early onset (Goodwin et al., 2001; Goldstein et al., 1997; Ramsawh et al., 2011; Segui et al., 1999; Tibi et al., 2013; Le Roux et al., 2005; Campbell et al., 2003). As previous findings with regard to types of comorbidities showed inconsistencies as well, this raises questions regarding the significance of differentiating between early and late onset of anxiety disorders in clinical practice. Possibly, our cut-off for early onset can be used to identify subtypes of anxiety disorders that share a genetic vulnerability (Goldstein et al., 1997) and higher severity. However, our findings suggest that the subtypes as defined through cluster analysis of age of onset frequency data may hold little relevance to psychiatric comorbidity or disease burden when applied in clinical practice. It must be noted though, that our analyses included only current psychiatric comorbidity and general wellbeing, and did not include previously reported associations between early onset and symptom severity (Van Ameringen et al., 2004; Segui et al., 2000; Tibi et al., 2013; Le Roux et al., 2005), childhood trauma (Tibi et al., 2013), suicidality (Iketani et al., 2004; Tibi et al., 2013), or prevalence of anxiety disorders among relatives (Goldstein et al., 1997; Tibi et al., 2015).

In contrast to the majority of previous studies on age of onset in anxiety disorders (Campbell et al., 2003; Iketani et al., 2004; Goodwin et al., 2001; Goldstein et al., 1997; Penninx et al., 2011; Ramsawh et al., 2011; Le Roux et al., 2005; Segui et al., 1999; Segui et al., 2000; Van Ameringen et al., 2004), we applied empirically defined cut-offs for early onset. This may

have contributed to the lack of replication of previous findings. In chapter four, studying prognostic factors in the course of anxiety, we did apply the same definition of early onset that had been used in two previous studies (onset before age 18; Van Ameringen et al., 2004; Penninx et al., 2011). However, discrepancies remained, as again we were unable to replicate the association between course of anxiety and early onset reported in the two previous studies, although this confirmed findings by Ramsahw et al. (2011). A recent study looking at correlates of three different course trajectories in anxiety (Batelaan et al., 2014) may elucidate these diverging findings regarding age of onset. This study demonstrated that, although onset was later in the least severe group compared to the medium severe and most severe group, disease duration (number of months during which anxiety symptoms were present over the 5 years preceding baseline) was an important predictor of class membership (Batelaan et al., 2014). This is compatible with the suggestion that findings of higher severity in early onset cases may follow from longer disease duration in this group (Tibi et al., 2013). Possibly, the erratic pattern of associations between age of onset and both comorbidity and course, follows from variations in disease duration (defined as total time during which the disorder was present) in the different samples that were not measured directly. While in most chronic diseases, disease duration (defined as total time during which the disorder was present) equals the patient's current age minus the age of onset of the disorder, this is not necessarily the case for anxiety disorders. Anxiety disorders may wax and wane over the years following their first onset (Batelaan et al., 2014; Beesdo et al., 2009). Therefore, it is possible that disease duration is not accounted for in analyses through correction for age applied in chapters two and four. As the total time during which the disorder was present was not established in our samples, unfortunately, we were unable to examine whether this variable was associated with comorbidity or wellbeing in anxiety.

While the age at the moment of onset of an anxiety disorder seemed to hold little relevance for the phenomenology or course of anxiety disorders in our sample, the current age of patients presenting with an anxiety disorder was associated with specific characteristics. We confirmed previous findings in mood disorder of more insomnia, general physical complaints, and decreased activity in older patients (Husain et al., 2005). We also found that younger patients were more often diagnosed with SP, and reported more feelings of interpersonal sensitivity and hostility. Older patients on the other hand, more frequently had AP and comorbid mood disorder, although their self-reported depression severity did not differ from that in the younger groups. As differences were small, they could be interpreted as support for the appropriateness of uniform diagnostic guidelines for the 18 through 65-year-old anxiety disordered population. However, findings also support the notion that anxiety disorders should be studied in light of life phases and changes or characteristics associated with age. This notion is further reinforced by our findings discussed in chapter four, which demonstrated that living

7

with family, a patient characteristic that could be thought to be associated with higher levels of disability, and that has been hypothesised to contribute to sustained anxiety (Chambless, 2012), was predictive of favourable course of anxiety for younger (ages 18-24) patients. This illustrates that although age was not an independent predictor of the course of anxiety, we were able to identify a subgroup according to age in which chances of response were higher for those who lived with family.

The course of anxiety in our sample was further associated with having AP. This is in accordance with results from a recent study that demonstrated poorer prognosis in subjects with more severe avoidance symptoms at baseline (Hendriks et al., 2013). Subjects with anxiety disorders with more severe avoidance symptoms have been shown to have higher levels of disability, with more cognitive and social impairment (Hendriks et al., 2014). Other predictors of a detrimental course of anxiety identified in chapter four were low education level and lack of a daily occupation. These findings may be thought to reflect a negative prognosis in outpatients whose societal participation is limited. This is in accordance with findings in a recent randomised clinical trial (RCT) that also found poorer remission among those patients who were unemployed, and in addition demonstrated a detrimental course of anxiety in those who perceived their degree of social support and community- and social economic status as poor (Kelly et al., 2015).

Elevated scores on measures of the personality traits affective lability and conduct problems, also predicted an adverse course of anxiety disorders. This supports the idea that neuroticism and introversion/ extroversion related personality traits, are likely to be associated with mechanisms contributing to both the development and maintenance of anxiety disorders (Zinbarg et al., 2008). Interestingly, elevated scores on cluster B and C personality traits also emerged as correlates of higher self-reported relative to observed anxiety severity in chapter six. This may indicate that elevated scores on these personality traits increase distress in a manner that is not readily noticeable, even to trained observers. It must be noted that our findings pertain to a measure of personality traits and not to personality disorders. Also, as in ROM personality traits were measured during psychiatric episodes, observations should be interpreted accordingly. As elevated scores on personality measures may be state dependent, personality traits measured during an Axis I episode are likely to display synchronicity with psychiatric symptoms, resulting in inflated scores which may return to lower post-morbid levels (Karsten et al., 2012; Ormel et al., 2004). Together, these findings point at the importance of taking personality traits into account when studying anxiety, as they may be associated with higher unobserved anxiety severity as well as chronic course.

In those individuals in whom psychiatric disorders take a chronic course, the risk of complications like suicidal ideation is increased (Nock et al., 2008). A general population study demonstrated that among those who met diagnostic criteria for anxiety disorders, risk of

suicidal ideation was elevated relative to those without a psychiatric disorder (Sareen et al., 2005). A recent study among primary care patients with anxiety disorders who had been selected for an RCT, showed that suicidal ideation occurred in 26% of participants (Bomyea et al., 2013). In our sample of anxious and/or depressed outpatients with baseline suicidal ideation (chapter five), suicidal ideation and anxiety disorders coexisted in 51.5% of patients; 9.7% of patients expressing suicidal ideation had pure anxiety disorder(s) and no mood comorbidity. Together, these findings demonstrate that suicidal ideation is common in outpatients with anxiety disorders, and deserves attention in research. Although prognostic factors in suicidal ideation had been identified in previous studies, they had not been evaluated simultaneously in a large clinical sample. Results from chapter five demonstrate that low education level, depression severity, self-harm, and subjective general health independently predicted persistence of suicidal ideation among outpatients.

7.3.2 Relevance to clinical practice

Findings from the different chapters of this thesis were predominantly based on a large naturalistic dataset. The inclusion in the Leiden ROM study has been estimated to be around 80% (De Beurs, 2011). While it must be noted that for the study period, no data were available that allow comparing patients treated in Rivierduinen and at the Leiden University Medical Centre with patients treated in other secondary mental healthcare facilities, findings could be considered to be generalizable to outpatients seen in secondary mental healthcare in The Netherlands. As such, findings may hold relevance for clinical practice. Results from chapter two provide clear definitions of what could be considered as early onset of each disorder. However, routinely and retrospectively assessed early/late onset did not differentiate patients with regard to psychiatric comorbidity or general wellbeing. We therefore suggest clinicians do not heedlessly regard patients who have reported an early onset as being more likely to have more comorbidity or less wellbeing than those who reported late onset. As disease duration (defined as the total time during which the disorder was present) has been hypothesised to be a relevant patient characteristic (Batelaan et al., 2014) that might be thought to play a mediating role in the proposed clinical relevance of age of onset (Tibi et al., 2013), clinicians might discuss onset in relation to the subsequent course of anxiety disorders. Chapters three and four illustrate the differences between patients in separate age groups and the correspondingly different needs they may have. This demonstrates that it is important to be aware of life phases and environmental factors that may come with distinct stressors, but could also provide unique opportunities for support. Chapters four and five further provide indicators of patients that could be at elevated risk of both chronic anxiety and sustained suicidal ideation. It must be noted though, that as data were purely observational, correlates of

7

the course of anxiety and suicidal ideation in a naturalistic treatment setting should not be regarded as moderators of treatment effect. In addition, the predictive power of the models constructed in chapter four and five should be taken into account. Both models performed poorly as indicated by measures of the amount of variance in the data accounted for, and discriminatory power respectively. This implies that although the identified patient characteristics may hold relevance to outcome, clinicians should not regard those without these characteristics as "safe" for adverse outcome. However, the patient characteristics identified in chapter four and five can provide a first step towards the detection of patients who are at increased risk of poor outcome.

As becomes evident from chapters four, five, and six of this thesis, the use of ROM as a method for extensive assessment of patients at intake can provide clinically relevant information. In Rivierduinen and at the department of psychiatry of the Leiden University Medical Centre, ROM was implemented primarily to improve patient care, not only through the assessment of the current status of the patient, but also by monitoring progress and providing feedback to clinicians and patients (De Beurs, 2011). Although the majority of previous studies on the effectiveness of ROM feedback has serious limitations (Davidson et al., 2015), two recent studies demonstrated small to moderate positive effects on treatment results of using ROM to monitor treatment and provide feedback (De Jong et al., 2014; Connolly Gibbons et al., 2015). Furthermore, ROM has been suggested as a tool to evaluate healthcare and stimulate improvement of psychiatric care (Black, 2013). Therefore, as ROM has in recent years been implemented as a mandatory component of mental healthcare in mental healthcare facilities across The Netherlands, and the routine assessment of patients has become an integrated part of care, this should provide opportunities to improve care.

However, in order for ROM to be beneficial to clinical practice on a broad scale, several requirements need to be met. In order to minimise the burden on patients and clinicians, data collection should be facilitated, for example through the use of computerised administration (Boyce et al., 2014). If feedback is introduced, reports should be easily interpretable and clinicians should receive adequate support with regard to the communication of outcomes (Boyce et al., 2014). Instruments should be appropriate for the targeted population: they should be acceptable to patients, be reliable, validated for use in the target population, and sensitive to change (Dawson et al., 2010). The use of a structured diagnostic instrument has been suggested to be of vital importance, as patients often seek treatment for multiple disorders that may not be related to their main complaint (Zimmerman & Chelminski, 2003). Our findings in chapter four underpin the importance of assessment of AP and alcohol comorbidity as both were relevant for the course of anxiety. Although diagnostic assessment could be performed through a clinical interview, the use of a standardised instrument has been suggested to be superior to clinical interviewing, especially with regard to

assessing comorbid disorders (Pinninti et al., 2003; Zimmerman & Chelminski, 2003). In addition, our results demonstrate the potential value of assessing personality traits, as they were associated both with course of anxiety, as well as a higher experienced relative to observed level of anxiety severity (chapter four and six). Finally, in order to be useful for evaluation or benchmarking, data collection in ROM should not only be carried out with validated instruments, suited for the target population, have a high inclusion, and be collected in an unbiased manner, it should also include variables relevant for case mix (Meehan et al., 2007).

During the study period, the ROM procedure within Rivierduinen and at the department of psychiatry of the LUMC has been relatively extensive, encompassing a diagnostic instrument, generic and disorder specific measures of symptom severity, and assessments of demographic variables, personality traits, and functioning. In recent years however, due to budgetary constraints, ROM in Leiden has been down sized significantly: the MINI International Neuropsychiatric Interview-Plus (MINI-Plus; Sheehan et al., 1998; Van Vliet & De Beurs, 2007) has been removed, as has the Dimensional Assessment of Personality Pathology-short form (DAPP-SF; Livesley & Jackson, 2006). Although implementation of a ROM procedure has become mandatory across The Netherlands, the minimal dataset that institutions for mental healthcare are required to report has been deemed limited, focusing on uniform data collection and not on useful clinical evaluation of individual patients (Morrens, 2015). Therefore, the ROM procedures that have been implemented throughout the Netherlands in recent years may fail to meet requirements for clinical, as well as benchmarking purposes (Morrens, 2015). While budget cuts have been stifling, it must be noted that although a minimal ROM may cost less than a comprehensive ROM, it may chiefly serve administrative purposes, and fail to live up to its potential.

7.3.3 Research with clinical data

The different chapters of this thesis illustrate how data collected in clinical practice can be used to study various aspects of anxiety disorders in outpatients. Observational research is sometimes undeservedly regarded as inferior to research conducted in clinical trials (Black, 1996; Vandenbroucke, 2008). While it is true that selection bias and confounding cannot be ruled out in observational data (Rochon et al., 2005; Rothwell, 2005), trials are often expensive, complicated to carry out in clinical practice, have short term follow-up periods and, although they have high internal validity, they have low generalizability (Black, 1996; van der Lem et al., 2011; Rothwell, 2005; Vandenbroucke, 2008; Rochon et al., 2005), RCT's are ultimately suited to address topics like treatment effect and moderation of effect, especially in those cases in which allocation of treatment is likely to be connected to patient characteristics that hold

7

prognostic relevance (Vandenbroucke, 2008). However, observational studies include broader populations in more realistic settings, which allows for higher external validity and the study of effectiveness in practice (see table 7.1; Rochon et al., 2005). As in addition, they typically include larger samples and longer follow-up periods, observational studies are better suited for the study of rare or adverse events (Vandenbroucke, 2008; Rochon et al., 2005; Black, 1996). With regard to generalizability, the population in which research is carried out is paramount. The potential for clinical relevance is highest in studies undertaken in clinical practice (Kessler, 2007). Clinical epidemiological studies are therefore uniquely suited to describe patient characteristics and their clinical relevance, effectiveness of treatment in naturalistic treatment settings and the phenomenology of anxiety disorders in outpatients.

However, although routinely collected data has great potential for research purposes as demonstrated by the chapters in this thesis, not all data collected through ROM is unequivocally usable in research. For ROM data to be useable in research, and live up to claims of high external validity, data collection needs to meet a number of requirements. In addition, the level to which the data meets these requirements needs to be objectively determinable. Guidelines for reporting as postulated in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement aim to improve the quality of reporting on observational studies (Von Elm et al., 2007; Rothwell, 2005). For data collected in routine clinical practice to be suited for research purposes, it is preferable that the level of inclusion is high and is evaluated at regular intervals. This will provide an estimate of the level of selectiveness, and therefore generalizability of findings. In addition, general reasons for referral of patients, as well as the use of a diagnostic instrument provide further information as to the level of generalizability. Instruments used should be validated and appropriate for the sample. If specific instruments are administered by indication (e.g. disorder specific questionnaires or assessment of suicidality risk exclusively in depressed patients), this should be specified. Within a single database, it is important that data collection is uniform across institutions and over time, any changes in the data collection process must be logged. If observer rated measures are used, raters should be trained. If follow-up data is collected, ideally, follow-up intervals should be standardised, and reasons for loss to follow-up registered. Data should be extractable and anonymised. Finally it has been noted that data collection in ROM should primarily serve clinical practice, as the collection of excess data purely for research purposes in a clinical setting would be unethical and requires patients to explicitly participate and consent to taking part in research (Hoenders et al., 2014; Morrens, 2015).

Table 7.1 Characteristics of cohort studies and randomised trials

	Cohort studies	Randomised clinical trails
Populations studied	Diverse populations of patients who are served in a range of settings	Highly selected populations recruited on the basis of detailed criteria and treated at selected sites
Allocation to the intervention	Based on decisions made by providers or patients	Based on chance and controlled by investigators
Outcomes	Can be defined after the intervention and can include rare or unexpected events	Primary outcomes are determined before patients are entered into study and are focused on predicted benefits and risks
Follow-up	Many cohort studies rely on existing experience (retrospective studies) and can provide an opportunity for long follow-up	Prospective studies; often have short follow-up because of costs and pressure to produce timely evidence
Analysis	Sophisticated multivariable techniques may be required to deal with confounding	Analysis is straightforward

Source: Based on Education and Debate: Reader's guide to critical appraisal of cohort studies: 1. Role and design. Rochon PA et al., (2005) British Medical Journal, 330, 895-897.Copyright (2005) by BMJ/ Rochon.

7.3.4 Limitations

Findings discussed in this thesis should be regarded in light of several limitations that have been discussed in detail in the individual chapters. In general, it must be noted that data collected in our study, although less selective than those collected in RCT's (van der Lem et al., 2011; Hoertel et al., 2012), may be subject to selection bias (Rothwell, 2005). Although inclusion has been estimated at 80%, this estimate stems from 2009 (De Beurs, 2011), no repeated assessment of inclusion has taken place for later years. In addition, we do not have information on the patients who were not included in ROM and they might differ from included patients. In chapters four and five it became evident that attrition was high. Although this may in part be due to treatment completion, drop-out from treatment, or referral, we have no information regarding the reasons for loss to follow-up. Although our data reflect

clinical practice and, as stated before, could be thought to be generalizable to secondary mental healthcare facilities in The Netherlands, secondary mental healthcare populations in other countries might differ. In addition, data do not generalise to inpatient settings, to general practice, or to the general population. Also, patients in our study were referred for mood, anxiety, and/or somatoform disorders. As we have no information on clinical or primary diagnosis, part of our population may not have presented primarily with anxiety disorders, but instead reflect anxiety comorbidity in mood or somatoform disorders. Although the use of an instrument for standardised diagnostic assessment has been suggested to be superior to clinical diagnosis (Zimmerman et al., 2003; Pinninti et al., 2003), knowing the primary focus of treatment would be informative. Furthermore, treatment data were unavailable although previous studies in our ROM cohort did demonstrate that treatment for anxiety disorders is generally delivered according to guidelines, and exists of pharmacotherapy (23%), psychotherapy (59%) or combination therapy (16%) (Van Fenema et al., 2012). Finally, in our study, no information regarding psychiatric history, duration of episode(s), somatic comorbidity, cultural background or family history were available.

7.3.5 Future research

The starting point for this thesis differed markedly from the end-product. We originally set out in 2011 to study the continuity between child and adolescent psychiatry and adult psychiatry, using data collected in ROM. Based on the observation of a "treatment gap", with considerable differences in diagnostic and treatment approaches to child and adolescent psychiatry and adult psychiatry, we aimed to identify elements of continuity and contrast. However, this goal proved to be unattainable at the time: data collection using ROM in child and adolescent care had only just started, and, although several institutions for youth mental healthcare were willing to share data, no useable datasets were found. In addition to failing to meet the requirements stated in paragraph 7.3.3, data collected in child and adolescent mental healthcare differed from that collected in adult mental healthcare as often multiple informants were assessed: data was collected with children and adolescents, but also with parents, grandparents, teachers and temporary caregivers who alternated in taking part in child and adolescent ROM. This set unique challenges to working with the data as caregiver ratings were hardly ever performed by the same person. Although we did not succeed in achieving our original goal, the topic remains highly relevant as becomes evident from numerous publications in recent years (Lamb & Murphy, 2013; McGorry et al., 2013; Paul et al., 2013; Singh et al., 2010). At present, implementation of ROM in child and adolescent psychiatry may have evolved to a stage where the data that have been collected can be of use in research. As bridging the gap between child and adolescent psychiatry and adult psychiatry remains an

important area of research, future studies using data collected in ROM, but also in the general population like GenerationR (Jaddoe et al., 2006) and the Tracking Adolescents' Individual Lives Survey (TRAILS; De Winter et al., 2005) may provide valuable contributions. Prognostic studies following large general population samples from infancy to adulthood may also shed more light on the findings from chapter two: prospectively sampling the onset of psychiatric disorders in large samples, and tracking their development may clarify the relevance of age of onset of individual disorders and of psychiatric morbidity in general and may shed light on the role of disease duration and comorbidity.

Research with ROM may prove specifically valuable to deducing expectations regarding prognosis and the guidance of treatment. This thought has received a fair amount of attention in recent years. Based on the observation that psychiatric diagnoses according to the DSM or the International Classification of Disease (ICD) fail to capture disorders and predict course (McGorry et al., 2006), an alternative system for describing psychiatric morbidity has been proposed. The idea of clinical staging (Fava & Kellner, 1993) has analogies with the process followed in oncology. It proposes a patient's status is described in terms of the extent of disease progression along a continuum, in terms of dimensions, duration, severity, and level of functioning (McGorry et al., 2006; Batelaan et al., 2014). Clinical profiling comprises the prediction of the course of the disorder based on individual patient characteristics. The identification of disease stages may aid clinicians in the selection of optimal treatment modalities (Beekman et al., 2012), with adequate risk-benefit considerations (McGorry et al., 2006). Data collected in a large comprehensive ROM procedure, including diagnostic assessment, collection of patient background variables, and multimodal assessment, could be used to contribute to staging and profiling (Zitman, 2012). Although general population data are required to derive descriptions of pre-clinical stages, data collected in ROM may be uniquely suited to describe variations in the phenomenology of anxiety disorders in clinical practice. In addition, although clinical observational data do not lend themselves for studying how patient characteristics interact with different types of treatment towards treatment effect, it may be possible to identify course trajectories associated with patient characteristics. Furthermore, ROM provides an infrastructure that may be uniquely suited to conducting large ecologically valid clinical trials that may help answer questions relevant to staging and profiling (Arfken & Balon, 2014). The research discussed in this thesis could be seen as a first step towards staging. Future studies including large patient groups can provide insights that will help clinicians identify disease stages and provide treatment tailored to the individual patient (van Balkom et al., 2012).

7

Reference List

Anholt, G. E., Aderka, I. M., van Balkom, A. J. L. M., Smit, J. H., Schruers, K., van der Wee, N. J. A. et al. (2014). Age of onset in obsessive-compulsive disorder: admixture analysis with a large sample. *Psychological Medicine, 44,* 185-194.

Arfken, C. L. & Balon, R. (2014). Another look at outcomes and outcome measures in psychiatry: cui bono? *Psychother.Psychosom., 83,* 6-9.

Batelaan, N. M., Rhebergen, D., Spinhoven, P., van Balkom, A. J., & Penninx, B. W. (2014). Two-year course trajectories of anxiety disorders: do DSM classifications matter? *J.Clin.Psychiatry, 75,* 985-993.

Bauer, M., Glenn, T., Rasgon, N., Marsh, W., Sagduyu, K., Munoz, R. et al. (2010). Association between age of onset and mood in bipolar disorder: Comparison of subgroups identified by cluster analysis and clinical observation. *Journal of Psychiatric Research, 44,* 1170-1175.

Beekman, A. T., van, O. J., van Marle, H. J., & van Harten, P. N. (2012). [Staging and profiling of psychiatric disorders]. *Tijdschr.Psychiatr, 54,* 915-920.

Beesdo, K., Knappe, S., & Pine, D. S. (2009). Anxiety and Anxiety Disorders in Children and Adolescents: Developmental Issues and Implications for DSM-V. *Psychiatric Clinics of North America, 32,* 483-+.

Bellivier, F., Golmard, J. L., Henry, C., Leboyer, M., & Schurhoff, F. (2001). Admixture analysis of age at onset in bipolar I affective disorder. *Archives of General Psychiatry, 58,* 510-512.

Black, N. (1996). Why we need observational studies to evaluate the effectiveness of health care. *BMJ, 312,* 1215-1218.

Black, N. (2013). Patient reported outcome measures could help transform healthcare. *BMJ, 346,* f167.

Bomyea, J., Lang, A. J., Craske, M. G., Chavira, D., Sherbourne, C. D., Rose, R. D. et al. (2013). Suicidal ideation and risk factors in primary care patients with anxiety disorders. *Psychiatry Res., 209,* 60-65.

Boyce, M. B., Browne, J. P., & Greenhalgh, J. (2014). The experiences of professionals with using information from patient-reported outcome measures to improve the quality of healthcare: a systematic review of qualitative research. *BMJ Qual.Saf, 23,* 508-518.

Campbell, L. A., Brown, N. A., & Grisham, J. R. (2003). The relevance of age of onset to the psychopathology of generalised anxiety disorder. *Behavior Therapy, 34,* 31-48.

Chambless, D. L. (2012). Adjunctive Couple and Family Intervention for Patients With Anxiety Disorders. *Journal of Clinical Psychology, 68,* 548-560.

Connolly Gibbons, M. B., Kurtz, J. E., Thompson, D. L., Mack, R. A., Lee, J. K., Rothbard, A. et al. (2015). The effectiveness of clinician feedback in the treatment of depression in the community mental health system. *J.Consult Clin.Psychol., 83,* 748-759.

Craske, M. G. (1999). *Anxiety disorders psychological approaches to theory and treatment*. Oxford: Westview Press.

Davidson, K., Perry, A., & Bell, L. (2015). Would continuous feedback of patient's clinical outcomes to practitioners improve NHS psychological therapy services? Critical analysis and assessment of quality of existing studies. *Psychol.Psychother., 88,* 21-37.

Dawson, J., Doll, H., Fitzpatrick, R., Jenkinson, C., & Carr, A. J. (2010). The routine use of patient reported outcome measures in healthcare settings. *BMJ, 340,* c186.

De Beurs, E., den Hollander-Gijsman, M.E., van Rood, Y.R., van der Wee, N.J.A., Giltay, E.J., van Noorden, M.S., van der Lem, R., van Fenema, E., & Zitman, F.G. (2011). Routine Outcome Monitoring in the Netherlands: Practical Experiences with a Web-Based Strategy for the Assessment of Treatment Outcome in Clinical Practice. *Clinical Psychology & Psychotherapy,* 18, 1-12.

De Graaf, R., ten Have M., van Gool, C., & van Dorsselaer, S. (2012). Prevalence of mental disorders and trends from 1996 to 2009. Results from the Netherlands Mental Health Survey and Incidence Study-2. *Soc.Psychiatry Psychiatr Epidemiol., 47,* 203-213.

De Jong, K., Timman, R., Hakkaart-Van, R. L., Vermeulen, P., Kooiman, K., Passchier, J. et al. (2014). The effect of outcome monitoring feedback to clinicians and patients in short and long-term psychotherapy: a randomised controlled trial. *Psychother.Res., 24,* 629-639.

De Winter, A. F., Oldehinkel, A. J., Veenstra, R., Brunnekreef, J. A., Verhulst, F. C., & Ormel, J. (2005). Evaluation of non-response bias in mental health determinants and outcomes in a large sample of pre-adolescents. *Eur.J.Epidemiol., 20,* 173-181.

Delorme, R., Golmard, J. L., Chabane, N., Millet, B., Krebs, M. O., Mouren-Simeoni, M. C. et al. (2005). Admixture analysis of age at onset in obsessive-compulsive disorder. *Psychological Medicine, 35,* 237-243.

Fava, G. A. & Kellner, R. (1993). Staging: a neglected dimension in psychiatric classification. *Acta Psychiatr Scand., 87,* 225-230.

Goldstein, R. B., Wickramaratne, P. J., Horwath, E., & Weissman, M. M. (1997). Familial aggregation and phenomenology of 'early'-onset (at or before age 20 years) panic disorder. *Archives of General Psychiatry, 54,* 271-278.

Goodwin, R., Lipsitz, J. D., Chapman, T. F., Mannuzza, S., & Fyer, A. J. (2001). Obsessive-compulsive disorder and separation anxiety co-morbidity in early onset panic disorder. *Psychological Medicine, 31,* 1307-1310.

Gustavsson, A., Svensson, M., Jacobi, F., Allgulander, C., Alonso, J., Beghi, E. et al. (2011). Cost of disorders of the brain in Europe 2010. *European Neuropsychopharmacology, 21,* 718-779.

Hamilton, M. (1976). Comparative value of rating scales. *Br.J.Clin.Pharmacol., 3,* 58-60.

Hamshere, M. L., Gordon-Smith, K., Forty, L., Jones, L., Caesar, S., Fraser, C. et al. (2009). Age-at-onset in bipolar-I disorder: Mixture analysis of 1369 cases identifies three distinct clinical sub-groups. *Journal of Affective Disorders, 116,* 23-29.

Hendriks, S. M., Spijker, J., Licht, C. M., Beekman, A. T., Hardeveld, F., de Graaf. R. et al. (2014). Disability in anxiety disorders. *J.Affect.Disord., 166,* 227-233.

Hendriks, S. M., Spijker, J., Licht, C. M., Beekman, A. T., & Penninx, B. W. (2013). Two-year course of anxiety disorders: different across disorders or dimensions? *Acta Psychiatr Scand., 128,* 212-221.

Hoenders, R. H., Bos, E. H., Bartels-Velthuis, A. A., Vollbehr, N. K., van der Ploeg, K., de Jong. P. et al. (2014). Pitfalls in the assessment, analysis, and interpretation of routine outcome monitoring (ROM) Data: results from an outpatient clinic for integrative mental health. *Adm Policy Ment.Health, 41,* 647-659.

Hoertel, N., Le, S. Y., Blanco, C., Lavaud, P., & Dubertret, C. (2012). Generalizability of clinical trial results for generalised anxiety disorder to community samples. *Depress.Anxiety, 29,* 614-620.

Husain, M. M., Rush, A. J., Sackeim, H. A., Wisniewski, S. R., McClintock, S. M., Craven, N. et al. (2005). Age related characteristics of depression: a preliminary STAR*D report. *Am.J.Geriatr.Psychiatry, 13,* 852-860.

7

Iketani, T., Kiriike, N., Stein, M. B., Nagao, K., Minamikawa, N., Shidao, A. et al. (2004). Patterns of axis II comorbidity in early-onset versus late-onset panic disorder in Japan. *Comprehensive Psychiatry, 45,* 114-120.

Jaddoe, V. W., Mackenbach, J. P., Moll, H. A., Steegers, E. A., Tiemeier, H., Verhulst, F. C. et al. (2006). The Generation R Study: Design and cohort profile. *Eur.J.Epidemiol., 21,* 475-484.

Karsten, J., Penninx, B. W., Riese, H., Ormel, J., Nolen, W. A., & Hartman, C. A. (2012). The state effect of depressive and anxiety disorders on big five personality traits. *J.Psychiatr Res., 46,* 644-650.

Kelly, J. M., Jakubovski, E., & Bloch, M. H. (2015). Prognostic subgroups for remission and response in the Coordinated Anxiety Learning and Management (CALM) trial. *J.Clin.Psychiatry, 76,* 267-278.

Kessler, R. C. (2007). Psychiatric epidemiology: challenges and opportunities. *Int.Rev.Psychiatry, 19,* 509-521.

Lamb, C. & Murphy, M. (2013). The divide between child and adult mental health services: points for debate. *Br.J.Psychiatry Suppl, 54,* s41-s44.

Le Roux, H., Gatz, M., & Wetherell, J. L. (2005). Age at onset of generalised anxiety disorder in older adults. *American Journal of Geriatric Psychiatry, 13,* 23-30.

Livesley, W. J. & Jackson, D. N. (2006). *Manual for the dimensional assessment of personality problems - basic questionnaire*. Port Huron, Michigan: Sigma.

McGorry, P., Bates, T., & Birchwood, M. (2013). Designing youth mental health services for the 21st century: examples from Australia, Ireland and the UK. *Br.J.Psychiatry Suppl, 54,* s30-s35.

McGorry, P. D., Hickie, I. B., Yung, A. R., Pantelis, C., & Jackson, H. J. (2006). Clinical staging of psychiatric disorders: a heuristic framework for choosing earlier, safer and more effective interventions. *Aust.N.Z.J.Psychiatry, 40,* 616-622.

Meehan, T. J., Stedman, T. J., Neuendorf, K. E., Francisco, I. D., & Neilson, M. G. (2007). Benchmarking Australia's mental health services: is it possible and useful? *Aust.Health Rev., 31,* 623-627.

Moller, H. J. (2000). Rating depressed patients: observer- vs self-assessment. *Eur.Psychiatry, 15,* 160-172.

Montgomery, S. A. & Åsberg, M. (1979). New Depression Scale Designed to be Sensitive to Change. *British Journal of Psychiatry, 134,* 382-389.

Morrens, M. (2015). [Routine outcome monitoring in Flanders: are we learning the right lessons from the Dutch experience?]. *Tijdschr.Psychiatr, 57,* 392-394.

Nock, M. K., Borges, G., Bromet, E. J., Alonso, J., Angermeyer, M., Beautrais, A. et al. (2008). Cross-national prevalence and risk factors for suicidal ideation, plans and attempts. *Br.J.Psychiatry, 192,* 98-105.

Ormel, J., Oldehinkel, A. J., & Vollebergh, W. (2004). Vulnerability before, during, and after a major depressive episode: a 3-wave population-based study. *Arch.Gen.Psychiatry, 61,* 990-996.

Ortiz, A., Bradler, K., Slaney, C., Garnham, J., Ruzickova, M., O'Donovan, C. et al. (2011). An admixture analysis of the age at index episodes in bipolar disorder. *Psychiatry Research, 188,* 34-39.

Panariello, F., O'Driscoll, L., de Souza, R. P., Tiwari, A., Manchia, M., Kennedy, J. et al. (2010). Age at onset in Canadian Schizophrenia patients: Admixture analysis. *Schizophrenia Research, 122,* 278-279.

Paul, M., Ford, T., Kramer, T., Islam, Z., Harley, K., & Singh, S. P. (2013). Transfers and transitions between child and adult mental health services. *Br.J.Psychiatry Suppl, 54,* s36-s40.

Penninx, B. W. J. H., Beekman, A. T. F., Smit, J. H., Zitman, F. G., Nolen, W. A., Spinhoven, P. et al. (2008). The Netherlands Study of Depression and Anxiety (NESDA): rationale, objectives and methods. *International Journal of Methods in Psychiatric Research, 17,* 121-140.

Penninx, B. W. J. H., Nolen, W. A., Lamers, F., Zitman, F. G., Smit, J. H., Spinhoven, P. et al. (2011). Two-year course of depressive and anxiety disorders: Results from the Netherlands Study of Depression and Anxiety (NESDA). *Journal of Affective Disorders, 133,* 76-85.

Perroud, N., Aitchison, K. J., Uher, R., Smith, R., Huezo-Diaz, P., Marusic, A. et al. (2009a). Genetic predictors of increase in suicidal ideation during antidepressant treatment in the GENDEP project. *Neuropsychopharmacology, 34,* 2517-2528.

Perroud, N., Uher, R., Marusic, A., Rietschel, M., Mors, O., Henigsberg, N. et al. (2009b). Suicidal ideation during treatment of depression with escitalopram and nortriptyline in Genome-Based Therapeutic Drugs for Depression (GENDEP): a clinical trial. *Bmc Medicine, 7.*

Pinninti, N. R., Madison, H., Musser, E., & Rissmiller, D. (2003). MINI International Neuropsychiatric Schedule: clinical utility and patient acceptance. *Eur.Psychiatry, 18,* 361-364.

Ramsawh, H. J., Weisberg, R. B., Dyck, I., Stout, R., & Keller, M. B. (2011). Age of onset, clinical characteristics, and 15-year course of anxiety disorders in a prospective, longitudinal, observational study. *Journal of Affective Disorders, 132,* 260-264.

Rochon, P. A., Gurwitz, J. H., Sykora, K., Mamdani, M., Streiner, D. L., Garfinkel, S. et al. (2005). Reader's guide to critical appraisal of cohort studies: 1. Role and design. *BMJ, 330,* 895-897.

Rothwell, P. M. (2005). Treating Individuals 1 - External validity of randomised controlled trials: "To whom do the results of this trial apply?"'. *Lancet, 365,* 82-93.

Sareen, J., Houlahan, T., Cox, B. J., & Asmundson, G. J. (2005). Anxiety disorders associated with suicidal ideation and suicide attempts in the National Comorbidity Survey. *J.Nerv.Ment.Dis., 193,* 450-454.

Segui, J., Marquez, M., Garcia, L., Canet, J., Salvador-Carulla, L., & Ortiz, M. (1999). Differential clinical features of early-onset panic disorder. *Journal of Affective Disorders, 54,* 109-117.

Segui, J., Salvador-Carulla, L., Marquez, M., Garcia, L., Canet, J., & Ortiz, M. (2000). Differential clinical features of late-onset panic disorder. *Journal of Affective Disorders, 57,* 115-124.

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E. et al. (1998). The Mini-International Neuropsychiatric Interview (MINI): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry, 59,* 22-33.

Singh, S. P., Paul, M., Ford, T., Kramer, T., Weaver, T., McLaren, S. et al. (2010). Process, outcome and experience of transition from child to adult mental healthcare: multiperspective study. *Br.J.Psychiatry, 197,* 305-312.

ten Have, M., de Graaf, R., van Dorsselaer, S., Verdurmen, J., van't Land, H., Vollebergh, W. et al. (2009). Incidence and Course of Suicidal Ideation and Suicide Attempts in the General Population. *Canadian Journal of Psychiatry-Revue Canadienne de Psychiatrie, 54,* 824-833.

Tibi, L., van Oppen, P., Aderka, I. M., van Balkom, A. J. L. M., Batelaan, N. M., Spinhoven, P. et al. (2013a). Examining determinants of early and late age at onset in panic disorder: An admixture analysis. *Journal of Psychiatric Research, 47,* 1870-1875.

Tibi, L., van, O. P., Aderka, I. M., van Balkom, A. J., Batelaan, N. M., Spinhoven, P. et al. (2015a). An admixture analysis of age of onset in agoraphobia. *J.Affect.Disord., 180,* 112-115.

7

Tozzi, F., Manchia, M., Galwey, N. W., Severino, G., Del Zompo, M., Day, R. et al. (2011). Admixture analysis of age at onset in bipolar disorder. *Psychiatry Research, 185,* 27-32.

Van Ameringen, M., Oakman, J., Mancini, C., Pipe, B., & Chung, H. (2004). Predictors of response in generalised social phobia: Effect of age of onset. *Journal of Clinical Psychopharmacology, 24,* 42-48.

Van Balkom, A. J., Oosterbaan, D. B., Batelaan, N., Cath, D. C., Hendriks, G. J., van Megen, H. J. et al. (2012). [The characterisation of anxiety disorders: staging and profiling based on common sense]. *Tijdschr.Psychiatr, 54,* 935-940.

Van der Lem, R., van der Wee, N. J. A., van Veen, T., & Zitman, F. G. (2011a). The generalizability of antidepressant efficacy trials to routine psychiatric out-patient practice. *Psychological Medicine, 41,* 1353-1363.

Van Fenema, E., van der Wee, N. J. A., Bauer, M., Witte, C. J., & Zitman, F. G. (2012). Assessing adherence to guidelines for common mental disorders in routine clinical practice. *International Journal for Quality in Health Care, 24,* 72-79.

Van Noorden, M. S., Giltay, E. J., den Hollander-Gijsman, M. E., van der Wee, N. J. A., van Veen, T., & Zitman, F. G. (2010). Gender differences in clinical characteristics in a naturalistic sample of depressive outpatients: The Leiden Routine Outcome Monitoring Study. *Journal of Affective Disorders, 125,* 116-123.

Van Vliet, I. M. & De Beurs, E. (2007). Het MINI Internationaal Neuropsychiatrisch Interview (MINI) een kort gestructureerd diagnostisch psychiatrisch inerview voor DSM-IV- en ICD-10-stoornissen. *tijdschrift voor psychiatrie, 49,* 393-397.

Vandenbroucke, J. P. (2008). Observational research, randomised trials, and two views of medical science. *PLoS Med., 5,* e67.

Von Elm, E., Altman, D. G., Egger, M., Pocock, S. J., Gotzsche, P. C., & Vandenbroucke, J. P. (2007). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet, 370,* 1453-1457.

Wilkowska-Chmielewska, J., Szelenberger, W., & Wojnar, M. (2013). Age-dependent symptomatology of depression in hospitalized patients and its implications for DSM-5. *J.Affect.Disord., 150,* 142-145.

Wittchen, H. U., Jacobi, F., Rehm, J., Gustavsson, A., Svensson, M., Jonsson, B. et al. (2011). The size and burden of mental disorders and other disorders of the brain in Europe 2010. *European Neuropsychopharmacology, 21,* 655-679.

Zhu, T. N., De Luca, V., Gallaugher, L. A., Woldeyohannes, H. O., Soczynska, J. K., Szymkowicz, S. et al. (2012). Admixture analysis of age at onset in major depressive disorder. *General Hospital Psychiatry, 34,* 686-691.

Zimmerman, M. & Chelminski, I. (2003). Clinician recognition of anxiety disorders in depressed outpatients. *Journal of Psychiatric Research, 37,* 325-333.

Zinbarg, R. E., Uliaszek, A. A., & Adler, J. M. (2008). The role of personality in psychotherapy for anxiety and depression. *J.Pers., 76,* 1649-1688.

Zitman, F. G. (2012). [Staging, profiling and routine outcome monitoring]. *Tijdschr.Psychiatr, 54,* 979-984.

Addendum

English summary

Nederlandse samenvatting

List of publications

Curriculum Vitae

Dankwoord

English summary

This thesis describes the characteristics of outpatients who were diagnosed with four common anxiety disorders. Panic disorder (PD/A), agoraphobia without panic (AP), social phobia (SP), and generalised anxiety disorder (GAD) incur severe suffering and functional impairment, they often have a detrimental course and are associated with significant societal costs. Chapter one describes how previous research on these disorders typically involved subjects from the general population, or alternatively, patients who met strict eligibility criteria for clinical trials, or who were willing to take part in (very) long running studies. As these subjects may differ from outpatients, it is unclear if previous findings can be generalised to patients seen in everyday clinical practice. Studies using clinical data gathered in naturalistic settings are needed to describe the phenomenology of anxiety in clinical practice. Therefore, in the studies described in this thesis, we used data that had been collected in clinical practice through Routine Outcome Monitoring (ROM). As ROM is a part of normal clinical practice and as such is offered to patients, these data offer a unique opportunity to study anxiety disorders in outpatients.

Chapter two focused on the age of onset of anxiety disorders. Generally, an earlier onset is thought to be associated with higher severity and a more detrimental course. However, previous findings diverged markedly. This divergence could have resulted from a lack of consensus on a cut-off age for early onset. Therefore, in this study a data-driven technique (cluster analysis) was applied to retrospectively reported age of onset data gathered in the general population to define early onset. PD/A with an onset at or before age 31 qualified as early, whereas early onset AP started at or before age 21. The cut-off for early onset SP was at or before age 22, and early onset GAD started at or before age 27. Subsequently, subjects with early and late onset were compared with regard to clinical characteristics. This was done in a general population sample as well as in a clinical sample. Although we expected to find that those with early onset would have more comorbid psychiatric disorders and were more likely to score below cut-offs for general wellbeing than those with late onset, few differences emerged. As such, results did not support our hypothesis of more psychiatric comorbidity and less wellbeing in early onset.

Chapter three continued with an exploration of age related differences in outpatients aged 18 through 65. Outpatients diagnosed with PD/A, AP, SP, and/or GAD were divided in three age groups: young adult (18-25), mid-adult (26-40), and older adult (41-65). These three age groups were compared with regard to social demographic characteristics, psychiatric diagnostic characteristics, anxiety symptom profile, general psychiatric symptom profile, and generic health status. In addition to more obvious differences with regard to vitality and social demographic characteristics related to life phases, we expected to find differences with regard

to clinical characteristics, like comorbidities or symptom profiles. Several associations with age emerged, as expected, older patients had higher levels of physical- and sleep problems, and a relative lack of vitality. However, we also found higher prevalence of SP in younger patients, and more feelings of interpersonal sensitivity and hostility in younger and mid-adult patients compared to older patients. Older patients more often had AP, and had an increased risk of mood comorbidity. These findings demonstrate that patients from different age groups present with differences in symptomatology that may be relevant in research as well as clinical practice.

Chapter four presents an exploration of factors relevant to the course of anxiety disorders. Data of outpatients diagnosed with PD/A, AP, SP, and/or GAD were analysed to identify predictors of response during the course of treatment with a maximum of two-years of follow-up. Several socio-demographic and clinical variables predicted response: having a non-Dutch ethnicity, having no daily occupation, and having a low education level, were associated with reductions in chances of response of 29%, 24%, and 24% respectively. Patients who lived with family had a 41% better chance of response, although further analyses demonstrated that this association was specific to younger patients. Having a diagnosis of AP was associated with a 33% smaller chance of responding during follow-up, and alcohol abuse or dependence reduced chances of response with 46%. Personality traits were also associated with response: a single standard deviation increase on a continuous measure of affective lability was associated with 20% smaller chances of response; one standard deviation increase on a continuous measure of conduct problems was associated with a 16% smaller chance of response. These results do not only show what patient characteristics are associated with a detrimental course of anxiety in an outpatient setting, they also demonstrate how an extensive assessment process at intake, such as in ROM, may aid clinicians in the identification of patients who are at risk of chronicity.

In chapter five, the course of suicidal ideation in outpatients with anxiety and/or depression was examined. Suicidal ideation is a common complicating factor in both mood and anxiety disorders that can persist during the course of treatment. The identification of characteristics that help clarify which patients are at risk of sustained suicidal ideation may aid clinicians and, ultimately, help prevent suicide. Remission of suicidal ideation over a follow-up period of up to two years was associated with education level, baseline depression severity, self-harm, and general health perception. Patients with low education levels had a 14% lower chance of remission of suicidal ideation; a single standard deviation increase in baseline depression scores and self-harm severity, corresponded to 16% and 23% lower chances of remission of suicidal ideation. Finally, a single standard deviation decrease in general health perception scores, corresponded to an 8% reduced chance of remission of suicidal ideation. These results underpin addressing the needs of patients with suicidal ideation who have low

education levels, severe depression, severe self-harm, and poor general health perception, as they are at increased risk of sustained suicidal ideation.

Chapter six focused on the observer-rated versus self-reported assessment of anxiety severity. Although both types of measures usually concur, in some individuals they do not. It is important to know in which patients these measures are likely to diverge, as this knowledge may help identify patients in whom reliance on either self-report or observer-rated measure may not suffice. In this study, standardised scores on a self-report measure of anxiety severity by outpatients diagnosed with PD/A, AP, SP, and GAD, were compared to standardised anxiety severity ratings made by trained psychiatric research nurses. Overall correlation between self-reported and observer-rated anxiety severity was positive and strong but discordance occurred in 23.6% of patients, with higher scores on the observer-rated relative to the self-report measure in 12.4% of patients, and lower observer-rated relative to self-reported anxiety severity in 11.2% of patients. Patients with higher observer-rated than self-reported anxiety severity did not differ from patients for whom both measures were concordant. However, patients with lower observed- than self-reported anxiety severity more often had PD/A and less often had SP than concordant patients. In addition, they scored higher on cluster B (dramatic) and C (anxious) personality characteristics than concordant patients. The general level of concordance in our sample demonstrates that on a group level, the use of either a self-reported or an observer-rated measure gives a good indication of severity. On an individual level however, our results demonstrate that when a single instrument is used, anxiety severity may be overlooked in a group of patients. Specifically, trained observers may not adequately assess anxiety severity in those patients who have higher scores on measures of cluster B and C personality traits. Therefore, when determining anxiety severity for clinical purposes, a multi-method approach, encompassing both self-report- and observer-rated measures of anxiety severity as well as assessments of personality traits, is preferable. This will allow for assessment across different domains, and through multiple sources of information. As such, a multi-method approach may provide clinicians with more relevant information than the use of a single instrument would.

In the final chapter of this thesis, findings are summarised and discussed in light of recent literature and clinical implications. The use of routinely collected clinical data in care as well as in research is critically discussed, as are limitations of the presented work. It is suggested that future studies focus on bridging the gap between child and adolescent psychiatry and adult psychiatry. A prospective approach to the study of onset of anxiety is proposed. Finally, it is suggested that studies based in a ROM infrastructure could contribute significantly towards the development of clinical staging and profiling models of anxiety disorders.

Nederlandse samenvatting

In dit proefschrift worden kenmerken van poliklinisch behandelde patiënten met vier veelvoorkomende angststoornissen beschreven. Paniekstoornis, agorafobie zonder paniek, sociale fobie en gegeneraliseerde angststoornis zorgen voor ernstig lijden en beperkingen in het functioneren, ze kennen vaak een ongunstig beloop en zijn geassocieerd met aanzienlijke maatschappelijke kosten. In het eerste hoofdstuk wordt beschreven hoe eerder onderzoek op het gebied van deze aandoeningen in de hoofdzaak betrekking had op mensen met angst in de algemene bevolking, op mensen die voldeden aan de strenge inclusiecriteria van klinische trials of op patiënten die bereid waren tot deelname aan (zeer) langlopende studies. Omdat deze onderzoeksdeelnemers mogelijk verschillen van poliklinisch behandelde patiënten is het onduidelijk of bevindingen uit eerder onderzoek kunnen worden gegeneraliseerd naar de klinische praktijk. Studies die gebruik maken van klinische data die zijn verzameld in een naturalistische setting zijn nodig om de fenomenologie van angst in de klinische praktijk te beschrijven. De studies die in dit proefschrift worden beschreven zijn dan ook uitgevoerd met data die zijn verzameld in de klinische praktijk met behulp van Routine Outcome Monitoring (ROM). Omdat ROM in principe onderdeel is van de behandeling en dus standaard aan patiënten wordt aangeboden, biedt het gebruik van deze data een unieke kans om angststoornissen in poliklinisch behandelde patiënten te bestuderen.

Hoofdstuk twee beschrijft de ontstaansleeftijd van angststoornissen. Over het algemeen geldt dat een vroeger ontstaan van angststoornissen geassocieerd is met hogere ernst en een ongunstiger beloop. De resultaten van eerder onderzoek lopen echter sterk uiteen. De discrepantie tussen bevindingen kan mogelijk worden verklaard door het ontbreken van een eenduidige definitie van vroeg ontstaan. Daarom is er in deze studie voor gekozen om met behulp van een data-gestuurde methode (cluster analyse) vroeg ontstaan te definiëren. Cluster analyse werd toegepast op retrospectief door een sample uit de algemene bevolking gerapporteerde ontstaansleeftijden. Een paniekstoornis die in of voor het 31e levensjaar is ontstaan kan worden geclassificeerd als vroeg, vroeg ontstane agorafobie treedt op in of voor het 21e levensjaar. De grens voor vroege sociale fobie was in of voor het 22e jaar en vroege gegeneraliseerde angst ontstaat in of voor het 27e jaar. Vervolgens werden degenen met een vroeg ontstane angststoornis vergeleken met degenen met een laat ontstane angststoornis. Deze vergelijking werd zowel in een sample uit de algemene bevolking als in een sample van poliklinisch behandelde patiënten gemaakt. Hoewel de verwachting was dat een vroeg ontstane angststoornis gekenmerkt zou worden door meer psychiatrische comorbiditeit en een lager niveau van algemeen welbevinden, bleken de twee groepen slechts op een klein aantal kenmerken te verschillen. Hiermee steunden de resultaten de hypothese van meer comorbiditeit en minder welbevinden in vroeg ontstane angst niet.

In het derde hoofdstuk werden leeftijdsgerelateerde kenmerken van poliklinisch behandelde patiënten met angst in de leeftijd van 18 tot 65 jaar verkend. Patiënten met paniekstoornis, agorafobie, sociale fobie en/of gegeneraliseerde angst werden verdeeld in drie groepen: jong volwassen (18-25), mid-volwassen (26-40) en ouder volwassen (41-65). Deze drie groepen werden vergeleken op sociaal demografische kenmerken, psychiatrische diagnostische kenmerken, angst-symptoomprofiel en algemene gezondheidsbeleving. Naast meer voor de hand liggende verschillen met betrekking tot bijvoorbeeld vitaliteit en sociaal demografische kenmerken gerelateerd aan levensfase, verwachtten we ook verschillen met betrekking tot klinische kenmerken zoals comorbiditeit en symptoomprofielen. Verschillende associaties met leeftijd kwamen naar voren, zoals verwacht hadden oudere volwassenen meer fysieke problemen en slaapproblemen en een lager niveau van vitaliteit. Daarnaast bleek echter ook de prevalentie van sociale fobie hoger onder jongere patiënten en kwamen in de jonge en mid-volwassen groep meer gevoelens van interpersoonlijke gevoeligheid en vijandigheid voor. Oudere patiënten hadden juist vaker agorafobie en hadden een verhoogd risico op een comorbide stemmingsstoornis. Deze bevindingen laten zien dat patiënten uit verschillende leeftijdsgroepen zich presenteren met verschillen in symptomatologie die zowel relevant kunnen zijn voor de klinische praktijk als in onderzoek.

Hoofdstuk vier betreft een verkenning van factoren die relevant kunnen zijn voor het beloop van angststoornissen. Gegevens van poliklinisch behandelde patiënten met paniekstoornis, agorafobie, sociale fobie en/of gegeneraliseerde angststoornis werden geanalyseerd om voorspellers van het beloop van de angststoornis over een periode van maximaal 2 jaar te identificeren. Verschillende sociaal demografische en klinische kenmerken voorspelden beloop: een niet Nederlandse afkomst, het ontbreken van dagbesteding en een laag opleidingsniveau waren geassocieerd met een vermindering van respectievelijk 26%, 24% en 24% in de kans op behandelrespons. Patiënten die bij familie woonden hadden 41% meer kans op behandelrespons, al bleek uit verdere analyses dat deze associatie uitsluitend gold voor jongvolwassen patiënten. Een agorafobie diagnose ging gepaard met een 33% lagere kans op respons en alcoholmisbruik of -afhankelijkheid met een 46% lagere kans op respons. Verschillende persoonlijkheidskenmerken waren geassocieerd met respons: een 1 standaard deviatie hogere score op een continue maat van affectlabiliteit was geassocieerd met 20% minder kans op respons; een 1 standaard deviatie hogere score op een continue maat voor gedragsproblemen was geassocieerd met een 16% lagere kans op respons. Deze resultaten laten niet alleen zien welke patiëntkenmerken geassocieerd zijn met het beloop van angststoornissen in een poliklinische setting, ze tonen ook aan hoe een uitgebreide screeningsprocedure bij intake zoals in ROM het geval is, clinici kan helpen bij het identificeren van patiënten die een verhoogde kans op chroniciteit hebben.

In hoofdstuk vijf werd het beloop van suïcidale gedachten onder poliklinisch behandelde patiënten met angst en/of depressie onderzocht. Suïcidale gedachten vormen een veelvoorkomende complicatie zowel onder mensen met angst- als met stemmingsstoornissen, die soms blijft bestaan tijdens behandeling. Het identificeren van kenmerken die duidelijk maken welke patiënten een verhoogd risico hebben op aanhoudende suïcidale gedachten kan clinici helpen en kan mogelijk bijdragen aan het voorkomen van suïcide. Remissie van suïcidale gedachten over een periode van maximaal twee jaar was geassocieerd met opleidingsniveau, ernst van de depressie op baseline, zelfbeschadiging en algemene gezondheidsbeleving. Patiënten met een laag opleidingsniveau hadden 14% minder kans op remissie; een 1 standaard deviatie hogere score op depressie en zelfbeschadiging was geassocieerd met respectievelijk 16% en 23% minder kans op remissie van suïcidale gedachten. Tot slot ging een 1 standaard deviatie lagere score op een maat voor algemene gezondheidsbeleving gepaard met 8% vermindering van de kans op remissie. Deze resultaten onderschrijven de noodzaak om aandacht te besteden aan patiënten met suïcidale gedachten met een laag opleidingsniveau, ernstige depressie, zelfbeschadiging, en slechte algemene gezondheidsbeleving, aangezien zij een verhoogd risico lopen op aanhoudende suïcidale gedachten.

Hoofdstuk zes gaat in op zelf-gerapporteerde versus geobserveerde maten van angst ernst. Hoewel tussen beide types instrumenten over het algemeen een hoge mate van overeenstemming bestaat, is dit soms niet het geval. Inzicht in kenmerken van patiënten bij wie geen sprake is van overeenstemming is belangrijk omdat het exclusieve gebruik van zelf-rapportage dan wel observatielijsten bij deze patiënten een vertekend beeld op kan leveren. In deze studie werden gestandaardiseerde scores van poliklinisch behandelde patiënten met paniekstoornis, agorafobie, sociale fobie en/of gegeneraliseerde angst op een zelfrapportage- en een observatielijst voor het meten van de ernst van angstklachten vergeleken. Over het algemeen was er sprake va een sterke en positieve correlatie tussen de twee maten. Bij een aanzienlijke groep (23.6%) was echter geen sprake van overeenstemming. In 12.4% was sprake van een hogere geobserveerde dan zelf gerapporteerde angst, in 11.2% was sprake van een lagere geobserveerde dan zelf gerapporteerde angst. Patenten met hogere geobserveerde dan zelf gerapporteerde angst verschilden niet van patiënten waarbij de maten overeenstemden. Patiënten met lagere geobserveerd dan zelf gerapporteerde angst daarentegen hadden vaker een paniekstoornis en minder vaak sociale fobie dan patiënten waarbij overeenstemming bestond. Daarnaast scoorde deze groep hoger op cluster B (dramatische cluster) en C (angstige cluster) persoonlijkheidstrekken dan patiënten waarbij overeenstemming bestond. Het algemene niveau van overeenstemming tussen de twee lijsten laat zien dat op groepsniveau gebruik van 1 van de twee lijsten volstaat om de ernst van de angststoornis te meten. De resultaten laten echter ook zien dat op individueel niveau het gebruik van 1 instrument kan zorgen voor een vertekend beeld. Getrainde observators schatten de ervaren ernst van angst

mogelijk niet adequaat in, met name bij patiënten met hoge scores op cluster B en C persoonlijkheidskenmerken. Daarom verdient het de voorkeur om bij het bepalen van de ernst van angststoornissen voor klinische doeleinden gebruik te maken van verschillende methodes en zowel zelfrapportage als observatiematen van ernst te gebruiken, als ook persoonlijkheidskenmerken in kaart te brengen. Op deze manier kan worden gemeten op verschillende domeinen en met behulp van verschillende informatiebronnen. Op die manier geeft een multi-method benadering clinici meer relevante informatie dan het gebruik van slechts een instrument zou doen.

In het laatste hoofdstuk van dit proefschrift worden bevindingen samengevat en besproken in het licht van recente literatuur en klinische implicaties. Het gebruik van routinematig verzamelde informatie in zorg en in onderzoek wordt kritisch besproken, evenals de beperkingen van het gepresenteerde onderzoek. Mogelijke onderwerpen voor toekomstige studies worden besproken, zoals het gat tussen de kinder- en jeugdpsychiatrie en de volwassenenpsychiatrie, het verder onderzoeken van de ontstaansleeftijd van angst in prospectieve studies. Tot slot wordt voorgesteld dat onderzoek dat binnen de ROM infrastructuur wordt uitgevoerd mogelijk een belangrijke bijdrage kan leveren aan het ontwikkelen van klinische modellen voor stagering en profilering van angststoornissen.

List of publications

This thesis:

Schat A, Van Noorden MS, Noom MJ, Giltay EJ, Van der Wee NJA, De Graaf R, Ten Have M, Vermeiren RRJM, Zitman FG. Correlates of age of onset in anxiety disorders, results of the Netherlands Mental Health and Incidence Study-II and the Leiden Routine Outcome Monitoring Study. Submitted

Schat A, Van Noorden MS, Noom MJ, Giltay EJ, Van der Wee NJA, Van Amelsvoort T, Vermeiren RRJM, Zitman FG. Age related characteristics of outpatients with anxiety and depression: The Leiden Routine Outcome Monitoring Study. Submitted

Schat A, Van Noorden MS, Noom MJ, Giltay EJ, Van der Wee NJA, Vermeiren RRJM, Zitman FG. Predictors of outcome in outpatients with anxiety disorders: the Leiden Routine Outcome Monitoring Study. J Psychiatr Res. 2013 Dec;47(12):1876-85.

Schat A, Hubers AAM, Van Noorden MS, Willems SJM, Fiocco M, Noom MJ, Giltay EJ, Vermeiren RRJM, Zitman FG. Predictors of remission of suicidal ideation in outpatients with anxiety and depression: the Leiden Routine Outcome Monitoring Study. Submitted

Schat A, Van Noorden MS, Noom MJ, Giltay EJ, Vermeiren RRJM, Zitman FG. Concordance between self-reported and observer-rated anxiety severity in naturalistic outpatients with anxiety disorders: The Leiden Routine Outcome Monitoring Study. Submitted

Other:

Schat A, Van den Broek WW, Mulder PG, Birkenhager TK, Van Tuijl R, Murre J. Changes in everyday memory function after ECT. J ECT. 2007 Sep;23(3):153-7.

Willems SJM, Schat A, Van Noorden MS, Fiocco M. Correcting for informative censoring using Inverse Probability Censoring Weights. Stat Methods Med Res. 2016 Mar 17. pii: 0962280216628900.

Recourt K, Schat A, Bogers JPAM, Mouton C, Van Hees N, De Goede J, Geleijnse JM, Giltay EJ. Dietary intake of psychiatric inpatients in closed wards. Submitted

Wieland J,* Schat A,* Van Noorden MS, Zitman FG. Predictors of outcome in psychiatric outpatients with intellectual disabilities. *the first two authors contributed equally to this manuscript. Submitted

Hazewinkel AWP, Schat A, Hubers AAM, Bogers JPAM, Morshuis MPA, Mouton C, Van den Hout WB, Giltay EJ. Economic costs of aggression in closed long-stay psychiatric wards. Submitted

Setroikromo SNW, Schat A, Rodenburg- Vandenbussche S, Van Bodegom-Vos L, Giltay EJ. Barriers to and facilitators for the acceptance of dietary supplements among psychiatric inpatients at closed wards: a qualitative study. Submitted

Curriculum Vitae

Anke Schat was born on September 6th 1979. She attended OSG Huygenwaard in Heerhugowaard where she completed her pre-master education in 1997. She enrolled with the department of Psychology of the University of Amsterdam, where she completed a clinical internship in neuropsychology at the Reinier de Graaf Gasthuis in Delft and performed both a research thesis on everyday memory function in patients treated for unipolar depression with electroconvulsive therapy, and a literature thesis on hippocampal involvement in long term memory following observations of memory function in different forms of dementia. She received her Master of Science degree in clinical neuropsychology at the department of cognitive psychology at the University of Amsterdam in 2006. After working for several years as a research executive, she started her PhD project at the Curium department of child and adolescent psychiatry and the department of psychiatry of the Leiden University Medical Center, supervised by emeritus Professor F.G. Zitman and Professor R.R.J.M. Vermeiren. Alongside her PhD she has taken part in various courses focused on quantitative techniques and research methodology. She teaches courses in biomedical sciences, psychiatry and epidemiology, and has supervised several internships. She attended and presented at various national and international meetings and conferences. In 2014 she was project leader of a successful grant application for a four-year study on reducing aggression among chronic psychiatric inpatients through nutritional supplements with ZonMW. In March 2015 she started working as a post-doctoral researcher on this project.

Dankwoord

Eindelijk is het af! Daar wil ik een aantal mensen voor bedanken.

Te beginnen bij mijn promotoren, professor Frans Zitman, en professor Robert Vermeiren, bedankt voor jullie niet aflatende steun bij het uitvoeren van het oorspronkelijke plan, maar ook bij het vormgeven van het uiteindelijke proefschrift waarbij ik heb kunnen bogen op jullie expertise wat betreft onderzoek in het algemeen, maar ook zeker op het gebied van ROM. Dr. Martijn van Noorden, ik heb heel veel gehad aan je kennis en ervaring met het doen van onderzoek met de ROM-data en aan je hulp bij het bepalen van de koers van het proefschrift. Je maakte tijd om met me mee te denken over het proefschrift maar ook over andere dingen, dankjewel. Dr. Erik Giltay, onze samenwerking is nu eigenlijk pas echt begonnen maar je hebt ook bij het uitwerken van dit proefschrift steeds met grenzeloos enthousiasme meegedacht en gediscussieerd over met name de onderzoeksmethode en de statistische aanpak. Dr. Marc Noom, bedankt voor je steun bij de start van het project en dat je altijd betrokken bent gebleven bij het proefschrift. Professor Nic van der Wee, jouw rol in een proefschrift over angststoornissen was natuurlijk onontbeerlijk, bedankt dat ik altijd aan kon kloppen voor advies. Dr. Ron de Graaf, dr. Margreet te Have, professor Jeanine Houwing en professor Therese van Amelsvoort, ook jullie wil ik bedanken voor de prettige en zeer leerzame samenwerking. Professor Bert van Hemert, bedankt voor je goede raad en je steun, of het nu ging om congresbezoeken, subsidieaanvragen of het opzetten van een onderzoeksbijeenkomst. Dr. Marta Fiocco en Sanne, ik vond het heel leuk om met jullie mee te kijken en ik ben benieuwd naar de toekomstige resultaten. Vivian en Danielle, jullie hebben het onmogelijke mogelijk gemaakt en steeds weer ruimte gevonden voor gezamenlijke afspraken in de goedgevulde agenda's van Frans en Robert.

Alle kantoortuinders en J9's, Marloes, Denise, Jessica, Justine, Steven, Nienke, Luisa, Nathaly, Anne-Suzanne, Cesare, Sumayah, Viktoria en Liora bedankt voor het goede gezelschap, de thee, de Lebkov, de support en het meedenken! Denise, Marloes, met jullie heb ik het heel gezellig gehad maar ook heel veel over onderzoek gepraat, jullie maakten het LUMC een stuk leuker en ik vind het erg jammer dat jullie niet meer op de kantoortuin zijn. En Marloes, ik hoop dat we in de toekomst nog vaker samen kunnen werken, dankjewel dat je mijn paranimf wil zijn. Nienke, je was een goede buur en nu een verre vriend en dat is eigenlijk allebei heel leuk. Jessica, Justine, Sumayah en Steven, ook met jullie heb ik het heel gezellig, ik ben blij dat dat nog even zo blijft! Luisa, Alberto and Cesare, I am happy to have met what must be the nicest researchers in Italy! Suus, Yulan, Rosan, Rebecca, Danielle, Christy, Gaby, Nathalie, Janne, Jenneke, Tim, Ard, Sharita, Sophie, Linda, Michelle, Gelare, Tineke... Dank jullie wel voor heel veel gezelligheid en luisterende oren. Ellen & Remco, Erik & Erika en Loes & Daan, dank jullie wel dat jullie me hebben aangemoedigd maar alles ook hebben gerelativeerd.

Erik, ik ben blij dat mijn grote broer me bij de verdediging bijstaat. Ellen, dankjewel dat ik altijd bij je terecht kan voor grootzusterlijke goede raad en Loes, we hebben allebei ons ei gelegd, hoera! Lieve papa en mama, dank jullie wel! En lieve Joost, zelfs een proefschrift schrijven is leuker met jou!