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# **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

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

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

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

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

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

|                                | <b>Cohort studies</b>                                                                                                     | <b>Randomised clinical trials</b>                                                                                      |
|--------------------------------|---------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|
| 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).

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