Chapter 8

General Discussion
People at ultra high risk for psychosis

The work presented in this thesis aims to contribute to improvement of the early detection of psychosis by the search for risk factors and characteristics of the ultra high-risk (UHR) population, especially the sub-clinical psychotic symptoms and the development of non-psychotic psychopathology. We searched for these risk factors in the general population (using the NEMESIS data), retrospectively in a first-episode cohort (The Hague psychiatric case register), and in the UHR sample of the EDIE-NL study.

This chapter summarizes the main findings, which are compared with other relevant studies. In addition, the important methodological strengths and limitations are addressed, and the implications for clinical practice are discussed.

The main findings of this work are:

1) Social phobia and paranoid ideation are associated in the general population (Chapter 2);
2) Psychotic-like experiences are highly prevalent in the help-seeking patients entering the secondary mental health care (Chapter 4);
3) More than 50% of the psychotic patients sought help in secondary mental healthcare services for mental disorders prior to the onset of psychosis (Chapter 5);
4) Screening a consecutive help-seeking population found a high-risk population with ARMS symptoms comparable to those in the referred population, but with more severe non-psychotic psychopathology (Chapter 6); and
5) UHR patients scored high on depression and anxiety, and experienced multiple sub-clinical psychotic symptoms.

Main findings and previous research

Prevalence of psychotic-like experiences in the general and help-seeking populations

This work shows that the presence of psychotic-like experiences (PLEs) is associated with non-psychotic mental disorders in both the general and the help-seeking population. In the general population (Chapter 2), a lifetime association was found between symptoms of social phobia and paranoid ideation (OR=3.08; 95% CI=2.49-3.82, \(p<0.001\)), with a dose-response effect. Further examination showed that sub-clinical paranoid symptoms preceded the onset of social phobia (OR=4.07; 95% CI=2.50, \(p<0.001\)). Again, a dose-response effect was found: ORs increased from 3.22 (one paranoid symptom) to 7.62 (three symptoms). This is in line with previous research reporting that psychological mechanisms in patients with paranoia and patients with social phobia overlap (e.g. heightened awareness of the self, scanning the environment), but that they act on different motives.
PLEs were also highly prevalent in help-seeking patients entering the secondary mental healthcare services: at least 96% (n=3,581/3,694) of the patients reported PLEs on the Prodromal Questionnaire (Chapter 4). We found no associations between distinct mental disorders and PLEs; psychotic symptoms were prevalent in several Axis I and II disorders (Eaton, Hall, MacDonald & McKibben, 2007).

**ARMS and mental disorders**

Sub-clinical psychotic symptoms are associated with help-seeking behaviour (Murphy, Shevlin, Houston & Adamson, 2010). Persons who reported sub-clinical paranoia, unusual thought content or perceptual abnormalities, were twice more likely to attend the mental healthcare services and general practitioners than those who reported no symptoms. Therefore, entering the secondary mental health services for non-psychotic disorders might be an important pathway to psychosis. Of the 1,753 patients that developed a first-episode psychosis as registered in the case register of the Parnassia Psychiatric Institute (The Hague), 56.2% of the patients (n=985) had sought help in secondary mental health service prior to the onset of psychosis (Chapter 5). The most prevalent disorders in this group were mood and anxiety disorders, substance use disorders and adjustment disorders. It took on average 127 months from the first contact with the mental health services until the first diagnosis of a psychotic disorder. Patients with mood and anxiety disorders developed psychosis significantly earlier than those who sought help for personality disorders. The average time to diagnosis of a first psychotic disorder included a (probably long) duration of untreated psychosis.

Making the transition into psychosis while receiving treatment in secondary mental healthcare services resulted in a remarkably longer duration of untreated psychosis (Boonstra, Wunderink, Sytema & Wiersma, 2008; Brunet, Birchwood, Lester & Thornhill, 2007). Although in most studies the most prevalent disorders in the prodromal phase appeared to be mood and anxiety disorders (Addington, Van Mastrigt, Hutchinson & Addington, 2002; Bota, Munro & Sagduyu, 2005; Häfner, et al., 2003; Häfner, Maurer, Trendler, An der Heiden & Schmidt, 2005), the current study found no distinct pathways to psychosis. The higher rate of mood and anxiety disorders reflects the epidemiology, with mood and anxiety disorders being highly prevalent in the general population (De Graaf, Ten Have & Van Dorsselaer, 2010). In line with Eaton et al. (2007), we found psychotic symptoms to be highly prevalent in several Axis I and II disorders and that they interacted with non-psychotic symptoms until they crossed the threshold of frank...
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psychosis. The idea that psychopathology is generally associated with psychotic onset is also confirmed by the results presented in Chapters 6 and 7: patients with ARMS experienced several Axis I and II disorders. In addition, all included patients reported high scores on depression and anxiety scales, meaning that patients diagnosed with other disorders showed levels of depressive symptoms comparable to those diagnosed with a mood disorder. Another study found that the rates of depression and daily stress were higher in the ARMS population than in the first-episode population (Pruessner, Iyer, Faridi, Joober & Malla, 2011).

Screening versus referral as an early detection strategy
Because many psychotic patients have been help-seeking for non-psychotic disorders prior to the onset of psychosis, patients entering the secondary mental healthcare services may be eligible for screening. To explore whether it is possible to detect prodromal patients in the secondary mental healthcare, and whether this group yield the same conversion rates to psychosis, the EDIE-NL study (Chapter 3) implemented a two-stage screening method in one site and the traditional referral method in another site (Chapter 6). Screening in a consecutive help-seeking population accessing the secondary mental healthcare, resulted in a higher proportion per capita of at-risk mental states (prevalence rate 0.024) compared to the traditional referral method to the tertiary research settings (prevalence rate 0.008). Screening also revealed 52 patients who already showed frank psychosis, without being noticed at intake at the secondary mental health. Compared to the traditional referral strategy, the screening strategy included slightly older patients and more women. Compared to the referred population, the screened population reported higher scores on psychopathology, and converted to psychosis more often than the referred group: $X^2$ (1, n=110)=4.1, $p=0.043$). These findings indeed confirm the idea that screening in a help-seeking population entering the secondary mental healthcare services for non-psychotic problems would detect a group of patients who are in a late prodromal stage. However, these results are explorative and certainly not conclusive, because the institutions were not randomly assigned to the two recruitment conditions.

Sex and age bias
In this thesis the populations differed in age and gender profile from other populations reported in earlier studies on psychosis (Addington et al., 2002; Bota et al., 2005; Mason, Harrison, Glazebrook, Medley & Croudace, 1996) and in high-risk populations (McGlashan et al., 2007; Morrison et al., 2011; Yung et al., 2008). The
subjects included in the EDIE-NL were older than those included in other studies (McGlashan et al., 2007; Morrison et al., 2011; Yung et al., 2008). This is probably a selection phenomenon resulting from the age range in which recruitment was conducted. Most research programs recruit in the age range of 14-30 years, as this population is reported to have the highest risk of developing psychosis (DeLisi, 1992). This resulted in reported average ages of 17-19 years (McGlashan et al., 2006; Morrison et al., 2011; Phillips et al., 2009). However, studies conducted in adult cohorts found mean ages of 25 (Koutsouleris et al., 2011) and 26 years (Allen et al., 2011) or even 29 years (Häfner, Maurer, Löffler & Riecher-Rossler, 1993).

The study described in Chapter 5 used the range of 18-35 years at intake for non-psychotic disorders, but had no restricted age criteria for the onset of psychosis. This means that also late onsets are present in that study, resulting in a higher mean age of the cohort.

Our study populations also differed from others on gender profile (McGlashan et al., 2006; Morrison et al., 2011). The studies in this dissertation found a higher percentage of women who developed psychosis (Chapter 5) or who meet the criteria of an at-risk mental state of developing psychosis (Chapters 6 and 7). This might be the result of including the affective psychotic disorders in the analyses, which are more prevalent in women than the non-affective psychotic disorders.

Analyses showed no sex differences for psychotic symptoms, but the scores on general psychopathology did show sex differences. Multivariate analyses of variance showed that the differences in psychopathology between the populations recruited by different methods were influenced by site (F (7)=2.68, p=0.013) and age (F (7)=4.58, p<0.0001) and not by sex (F (7)=0.282, p=0.96) or the interaction site*sex (F (7)=0.73, p=0.643). These results support previous research, which found that females fell ill three to four years later but that the core symptoms of schizophrenia were comparable for both sexes (Häfner et al., 1993).

The results of the present study suggest that the selected populations of previous research may be biased, as a result of the inclusion criteria of the early psychosis projects. The emphasis on adolescence and young adulthood as the characteristic period of onset of schizophrenia and related disorders, has led to an overrepresentation of young men in clinical research settings. Community healthcare professionals overlook other patients, who do not fulfil the traditional criteria for a schizophrenic development. Screening in addition to referral might overcome this problem.
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High-risk profiles
To filter out a sub-sample of patients with a high psychosis proneness, it would be helpful to establish psychotic-like experiences (PLEs) that predict psychosis with the highest reliability and validity. A latent class analysis exploring the underlying latent structure of the reported PLEs revealed a four-class solution as the best fitting model. The classes were labelled as ‘severe’, ‘moderate’, ‘mild’ and ‘normative’. However, no classes with distinct profiles of PLEs were found; the four classes show a consistent increase in the probability of endorsing any item, which suggests a continuum of psychosis or an extended psychosis phenotype (Howes & Kapur, 2009; Stip & Letourneau, 2009; Van Os, Hanssen, Bijl & Ravelli, 2000). This supports the reported findings with latent class analyses conducted in general and high-risk populations (Murphy, Shevlin & Adamson, 2007; Shevlin, Murphy, Dorahy & Adamson, 2007; Valmaggia, et al., 2011).

A cross-sectional exploration of the ARMS population found high-risk symptoms to be associated with each other (Chapter 7). More than 50% (n=102) of the patients scored ARMS on two or more positive symptom scales of the CAARMS. In this latter study, although it is unknown whether perceptual abnormalities precede delusions or whether it is a result of delusions, it is suggested that hallucinations precede the onset of psychosis (Tone, Goulding & Compton, 2011). Also, high scores for depression accompany the presence of high-risk symptoms on the Beck Depression Inventory. The final common pathway to psychosis is largely based on catastrophizing the psychotic-like symptoms. Following this theory, delusions are formed as an incorrect explanation for unusual experiences (Garety & Hemsley, 1991). Future research should elucidate whether certain combinations of high-risk symptoms predict psychosis with a higher validity than other high-risk profiles.

Clinical implications of the screening method
Screening the help-seeking population in the secondary mental healthcare leads to the early detection of patients who are otherwise overlooked. The screened sample had a higher transition rate than the referred sample, suggesting that screening did not lead to more false- positive cases. However, we realise that screening the symptoms of psychosis does not detect those with a genetic risk (i.e. one of the three groups described as being at risk). Also, screening does not detect UHR patients who have been in care for a longer period of time before the onset of PLEs. Therefore, we suggest that both the screening and referral options be applied within the general secondary mental healthcare.
In addition, the screening method found patients who already had full-blown psychosis, without anybody noticing. Therefore, screening might be useful not only for the prevention of psychosis, but might also result in a decrease in the duration of untreated illness. The risks of being treated for another disorder without noticing psychosis has also been documented; a longer duration of untreated psychosis was reported in patients who were treated in the secondary mental healthcare for non-psychotic disorders (Boonstra, Wunderink, Sytema & Wiersma, 2008; Brunet, Lester, Birchwood & Thornhill, 2007) and in patients visiting the general practitioner for psychological problems (Lester, Birchwood, Freemantle, Michail & Tait, 2009).

When evaluating the screening method in the secondary mental healthcare services, some disadvantages have to be taken into account. The most important one concerns the greater amount of staff time required due to a lower specificity compared to the referral strategy. Of the 420 Prodromal Questionnaire (PQ) positives, 52 were diagnosed as being psychotic (12%) and 147 were diagnosed with an at-risk mental state with the CAARMS (35%); this means a total PQ true-positive rate of 47% and a false-positive rate of 53%. At the same time, out of 193 referred patients there was a total true-positive rate of 68% and a false-positive rate of 32%. As a result, the screening method required more interview time, i.e. it took about two full-time equivalent research assistants to do the interviews. In addition, there was some burden for the patient; they had to fill in the PQ and a CAARMS interview of about (on average) one hour.

As a result of the higher false-positive rates in the secondary mental healthcare services, there is the risk of stigmatizing patients who were - with hindsight - not at ultra high risk of developing psychosis. In order to prevent stigma in the people with ARMS, they were told to meet the criteria for a risk profile to develop future psychiatric problems, without mentioning psychosis, and that we might be able to prevent these future problems with an add-on intervention. Offering help was not stigmatizing, as this group of people were help-seeking from the start.

**Methodological considerations**

The strengths and limitations of the studies presented in this thesis have been described in the different chapters. Here we present a brief overview of the main methodological considerations.

The first limitation concerns the measurement of symptoms. The EDIE-NL study used self-report questionnaires to measure PLEs, mood, anxiety, quality of life and
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personal beliefs about illness. This could have resulted in several biases, e.g. over-reporting of symptoms. On the other hand, self-reporting can be reliable in help-seeking and general populations (Eaton, Romanoski, Anthony, & Nestadt, 1991; Hanssen, Bak, Bijl, Volleberg & Van Os, 2005) and the questionnaires used reported good reliability and validity (Brooks & EuroQol-Group, 1996; Loewy, Bearden, Johnson, Raine & Cannon, 2005; Mattick & Clarke, 1998; Priebe, Huxley, Knight & Evans, 1999; Van der Does, 2002). Moreover, with regard to the PLEs we did not collect data on the frequency, severity and persistence of the symptoms, nor on the distress caused by PLEs reported on the Prodromal Questionnaire and the CIDI. The presence of paranoia in the general population was difficult to reliably assess in a structured interview (the CIDI; Andrews & Peters, 1998; Wittchen, 1994) conducted by trained research assistants. Subjects were only re-interviewed when they were suspected of having psychotic symptoms, which might result in false-negative cases in the NEMESIS database. Especially paranoid individuals could withhold information in interviews held with people unknown to them, causing underreporting of the paranoid symptoms.

Second, we did not collect data on treatments. The final common pathway from prodromal stage to psychosis is characterized by catastrophising interpretations of psychotic-like symptoms and end in highly emotional secondary delusion on, for example, the origin and purpose of voices (Garety, Kuipers, Fowler, Freeman & Bebbington, 2001). Cognitive behaviour therapy, anti-psychotic medication or anti-depressive medication might have reduced the emotional arousal from the sub-clinical psychotic symptoms (French et al., 2003; French & Morrison, 2004). This might, in particular, have influenced the mean time to transition into psychosis in the study exploring the help-seeking pathways.

Third, the results of the screening method versus the referral method are not inclusive, but have to be considered as preliminary because the institutes were not randomly assigned to one of the recruitment conditions. In addition, the number of patients in the referred population was very small and the transition rate in this population was very low. As a consequence, it was not possible to explore whether the screening method did indeed find a different population that converted to other kinds of psychotic disorders compared to the referred population.

The main strength of the work presented in this thesis is that it has strong internal and external validity. The studies described in Chapters 3 to 7 were conducted in routine care and therefore have an immediate and positive effect on clinical practice. All raters who interviewed the patients with the CAARMS had an extensive two-day training by Alison Yung, who was the principle investigator and
developer of this instrument. Fidelity checks were done every three months. Another strength concerns the samples included in the studies. The sample in Chapter 5 is based on the data of all the consecutive cases of psychotic disorder in the catchment area within a five-year time frame. The samples in Chapters 4, 6 and 7 are based on all consecutive help-seeking individuals entering the secondary mental healthcare services between February 2008 and February 2010.

**Future research**

Many challenges remain in the early detection and prevention of psychosis, and a few are briefly addressed here. First, this thesis included an explorative study on two recruitment strategies and our results have not yet been replicated. We suggest to examine the effectiveness of different recruitment strategies in randomized controlled trials. Such a study should also include a cost benefit/effectiveness analysis. This would also give the opportunity to test whether shifting from the tertiary research setting to the secondary mental healthcare would indeed not lead to the detection of more false-positive cases. A second challenge concerns the different age and gender profiles of our study population compared to other populations. In order to improve the early detection and prevention of psychosis, we have to explore whether our data, or the data of other studies, is biased in age and gender profile. Furthermore, we would like to explore whether women and men differ on high-risk profiles and whether different symptoms are predictive for transition into psychosis for both sexes. Third, more research is needed on the Axis I and II disorders not included in the EDIE-NL study. For instance, the institutions participating in the EDIE-NL did not provide care related to substance use. Thus, the persons who did seek help for substance use disorders were not screened for high-risk symptoms. However, Chapter 5 shows that many first-episode patients did seek help for substance use disorders prior to the onset of psychosis. Fourth, it would be interesting to explore which risk factors and symptoms best predict psychosis. For instance, a combination of high scores on unusual thought content in combination with low functioning and a genetic trait were particularly associated with transition into psychosis (Thompson, Nelson & Yung, 2011). In Chapter 7 we found various groups of patients that had overlap in the high-risk criteria. Future research needs to reveal which groups have the highest risk of developing psychosis.
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Conclusions

The work in this thesis allows us to conclude that psychotic-like experiences and at-risk mental states are associated with help-seeking behaviour. In addition, many psychotic patients did seek help for several mental disorders prior to the onset of psychosis. The screening of a consecutive help-seeking population entering the secondary mental healthcare services on top of the traditional referral strategy might prove to be a successful recruitment strategy in the early detection and prevention of psychosis. When compared to the traditional referral strategy, screening found a threefold higher incidence of psychosis proneness and a threefold higher conversion rate. This suggests that help-seeking patients, who were at high risk of developing psychosis, were not recognized as having an ARMS by non-trained community mental health caretakers (i.e., false-negative cases), who should be one of the important referrers to specialized clinical research settings. Implementation of the screening method in the secondary mental healthcare setting will hopefully help detect more women and young adults who do not fulfil the traditional criteria for schizophrenic development.
Reference List


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General discussion


