Summary
People at ultra high risk for psychosis

Schizophrenia and related disorders have a major impact on social functioning, psychological and physical health. The early detection of psychosis might prevent, delay or improve the outcome of psychosis. This is only effective in a group of patients with high incidences of psychotic onsets. Defining reliable criteria for high risk states in order to filter out a group at high risk of developing psychosis is one of the challenging scopes of the current intervention studies. Recently, researchers discussed whether the ultra high risk-criteria should be included as a diagnosis in the DSM-V. When this becomes reality, early detection probably will shift from the tertiary mental health care services to the secondary mental health care services. Field testing outside the tertiary expert centres is necessary in order to explore whether such a diagnosis would be valid and reliable when used in other settings. The Dutch Early Detection and Intervention Evaluation (EDIE-NL) is the first study to screen in the help-seeking population entering the secondary mental health care settings in the Netherlands. The study examines whether cognitive behaviour therapy (CBT) targeting the high risk symptoms could prevent, delay or improve the outcome of psychosis in high risk patients. The current dissertation is part of the EDIE-NL-study and aims to contribute to the improvement of the early detection of psychosis by the search for risk factors and characteristics of the ultra high-risk (UHR) population 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. Especially the sub-clinical psychotic symptoms and the development of non-psychotic psychopathology were explored.

Chapter 1 presents the general introduction to the contents of this thesis. The clinical description, aetiology and main risk factors of psychosis were given. The use, purpose of and research of early detection was mentioned, as well as criteria to be assessed for introducing the high risk phase in the DSM-V. The outline and scope of this thesis was highlighted.

Chapter 2 describes the association between social phobia and paranoid symptoms in the general population. A total of 7,076 adults from the general population were assessed for symptoms of social phobia and paranoia using the Composite International Diagnostic Interview at baseline, one and three years. Lifetime social phobia and paranoid symptoms were found to be associated, with a dose response. Further analyses revealed that paranoid symptoms precede social phobia with a dose response. Paranoid symptoms emerging after social phobia was not significant.

Chapter 3 gives the research protocol of the Dutch Early Detection and Intervention
Evaluation (EDIE.NL). The aim of this study was to explore the effectiveness of cognitive behaviour therapy (CBT) in targeting the biases that are involved in the development of psychosis in patients with an ultra high risk of developing psychosis who were help-seeking for non-psychotic disorders. Patients included in this study were help-seeking patients aged between 14 and 35 years who were referred to the mental health services between February 2008 and February 2010 in three regions in The Netherlands. They were pre-screened with the Prodromal questionnaire and individuals who scored above the cut-off score of 18 on the positive symptoms scale (45 items in total), were assessed with the Comprehensive Assessment of At Risk Mental States (CAARMS). In a different pathway to care, all referrals from the mental health services in Amsterdam area to the specialized psychosis clinic of the Academic Medical Centre in Amsterdam, were also assessed with the CAARMS. Patients at high risk of developing psychosis were randomly assigned to the CBT or CBT + treatment as usual condition. It was hypothesized that the psycho-educational CBT approach may prove to be a successful strategy in preventing people from becoming psychotic as most people at high risk were distressed by their unusual experiences.

The presence of psychotic-like experiences (PLEs) is considered to be a risk factor for developing psychosis. As PLEs are quite common in the patient population, it is important to explore the differences between those patients with PLEs who will develop psychosis and those who will not. Analyses that focus on underlying latent classes will contribute to an understanding of the aetiology (why some psychotic-like experiences precede psychosis, whereas others do not) and the development of screening tools with higher sensitivity and specificity. In chapter 4, latent class analyses were used to explore the underlying latent structure of psychotic-like experiences (PLEs) reported by the consecutive help-seeking population that entered the secondary mental health care of The Hague. PLEs were associated with various mental disorders. Latent class analyses resulted in four classes. No distinct sub-types of PLEs were found: the subjects in the different classes gradually endorsed PLEs.

In chapter 5, the prodromal help-seeking behavior of first episode patients is described. The psychiatric case register in The Hague was used to identify a cohort of 1,753 persons in the age range of 18-35 at first contact, who developed a psychotic disorder in the period from January 1st 2005 to December 31st 2009. More than half of the patients (n= 985, 56.2%) had been treated in the secondary mental health services prior to the onset of psychosis. Although the most prevalent disorders were mood, anxiety and substance use disorders, several other disorders
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were prevalent in the prodromal phase. This suggests that there are no distinct pathways to care: prodromal patients are help-seeking for various disorders. The interval between first contact and first diagnosis of psychosis was approximately 69 months in cases presenting with mood and anxiety disorders and 127 months in cases presenting with personality disorders.

Chapter 6 explores the effectiveness of the two recruitment strategies used in EDIE. NL: a two-stage screening method in a consecutively help-seeking population entering the secondary mental health services for non-psychotic disorders versus a population that was referred to the Diagnostic Center of an early psychosis clinic due to suspicion of a schizophrenic development. The screening detected a threefold higher incidence of at risk mental states (0.025) compared to the referral strategy (0.008). Screened subjects were older, more often female, made the transition three times more often and reported significantly higher scores on depression, social anxiety, distress with positive symptoms. Statistically these differences were significantly influenced by site and age, but not by sex.

Chapter 7 reports the baseline characteristics of the patients included in the EDIE.NL-study (N=201). The sample in this study was older and included a higher proportion of women compared to the populations found in other studies. MANOVA revealed that these differences had no effect on the high risk symptoms. The differences of population characteristics could be attributed to the populations in which the recruitment was conducted. All patients scored high on the BDI, which implies that the presence of depressive symptoms is independent of the diagnosis of mood disorder.

The final chapter, summarized and discussed the importance of the main findings. The limitations and ideas for further research are considered.

When the at risk mental state becomes a diagnosis in the DSM-V, early detection probably will shift from the tertiary mental health care services to the secondary mental health care services. The results of this thesis show psychotic symptoms to be very prevalent in several Axis I and II disorders and that they interacted with non-psychotic symptoms, until they crossed the threshold of full-blown psychosis. More than half of the patients that developed a first episode psychosis, were help-seeking for several mental disorders in the prodromal phase. Screening a consecutive help-seeking population entering the secondary mental health services compared to a referred population to tertiary services, did lead to the detection of a threefold higher incidence of at risk mental states with a threefold higher conversion rate to psychosis. The higher transition rate suggests that screening does not lead to the detection of more false positives.
Summary

The patients included in the studies differed from other studies on age and sex. This was mainly the result of the age-range in which the recruitment was conducted. Screening in adolescent population will find young patients, whereas screening in adult populations will find a population with a higher mean age. It is known that women develop psychosis four years later than men. These women are detected more often when using a wide age range.