Chapter 1

General Introduction
Psychotic disorders

Psychotic disorders are a serious mental health problem with, in particular, schizophrenia being notorious for its poor prognosis. Moreover, this severe mental disorder is ranked in the top-ten causes of long-term disability worldwide (Üstün et al., 1999). Schizophrenia becomes manifest mainly during adolescence or early adulthood and has a chronic course in 20-30% of patients. Despite improvements in treatment, at least 75% of patients relapse at least once in their lifetime (Mason, Harrison, Glazebrook, Medley & Croudace, 1996; Wiersma, Nienhuis, Slooff & Giel, 1998). Psychotic disorders have many comorbid conditions, including mood disorders, personality disorders, substance use disorders, physical illnesses and posttraumatic stress disorders (McGorry, Killackey & Yung 2008). Schizophrenia has a major impact on social functioning, psychological wellbeing and physical health. Patients have problems with keeping a job, finishing school and study, and maintaining relationships with friends and partners. Finally, about 10% of patients die by suicide (Wiersma et al., 1998).

The consequences of psychotic disorders for society are also substantial. Although the incidence is low, in the Netherlands the yearly incidence rates of schizophrenia spectrum disorders, psychosis not otherwise specified (NOS) and affective psychotic disorders (e.g. mood disorders with psychotic features, bipolar disorder) are estimated at around 0.021%, 0.014% and 0.008%, respectively (De Graaf, Ten Have & Van Dorsselaer, 2010; Selten et al., 2007), indicating that the costs and burden on society are high. Clinical costs within the Dutch healthcare system for schizophrenia alone are about 517,000,000 Euros per annum (Poos, Smit, Groen, Kommer & Slobbe, 2005). In addition, indirect costs for the society are also high; for instance, in the Netherlands about 80-90% of people with schizophrenia is unemployed and receives a state disability pension (Michon, Van Erp, Giesen & Kroon, 2003; Michon & Van Weeghel, 2008). In the future, the costs of psychotic disorders and the burden on healthcare will probably increase, as there will be fewer caretakers due to the aging of the population and to the increasing numbers of patients.

Clinical description

Psychotic patients are extremely variable in their symptom presentations, suggesting a broad array of psychopathological phenomena. Schizophrenia
(and related psychotic disorders) has no pathognomonic symptoms (Eaton, Hall, MacDonald & McKibben, 2007). All symptoms and signs of schizophrenia can be seen in patients suffering from other disorders (e.g. the negative symptoms of schizophrenia, such as lack of initiative or social contacts, can also be observed in depression) and subclinical ‘prodromal’ symptoms of schizophrenia can even be found in the general population (Hanssen, Bak, Bijl, Vollenberg & Van Os, 2005; Tien & Eaton, 1992). In the absence of characteristic symptoms, the diagnosis of schizophrenia depends on other criteria, such as the duration of symptoms and signs, psychosocial decline and exclusion of primary affective disorder, somatic diseases, and substance and alcohol abuse disorders (DSM IV; Table 1.1) (Eaton et al., 2007). Schizophrenia is characterised by three clusters of symptoms: positive symptoms, negative symptoms and disorganized symptoms. Positive symptoms include delusions (bizarre and non-bizarre/paranoid), hallucinations, and formal thought disorders. Delusions are defined as false personal beliefs that are not part of cultural or religious concepts. Hallucinations are perceptual experiences that are not shared by others. Perceptual hallucinations include the five senses: visual, auditory, olfactory, taste and touch. Negative symptoms are also a marker of schizophrenia; these symptoms are defined as anhedonia, apathy, alogia and flat affect. The disorganization cluster is characterised by formal thought disorder, i.e. by a loss of associations between thought processes that mostly result in incoherent reasoning and disorganized speech, by inadequate affect and disorganized behaviour. Symptoms and signs of schizophrenia are accompanied in most cases by cognitive impairments, such as problems in attention and concentration, problems in executive functioning, impairment in learning abilities, and memory impairments.

**Early detection**

While the facts of psychosis are sobering, there is hope that these disorders may be preventable in the future. Intervention in the very early stages might prevent, delay or improve the outcome of the first-episode psychosis. However, to get to this point, reliable methods of early detection and accurate risk assessments are needed. To develop reliable methods of early detection, we need to identify risk factors which predict psychosis with a high level of accuracy (Heckers, 2009). Although a variety of environmental and genetic risk factors have been implicated in the aetiology of psychosis, the exact aetiology itself remains unknown. In addition, the
### Table 1.1: DSM IV-TR criteria Schizophrenia.

<table>
<thead>
<tr>
<th>A. Characteristic symptoms: Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated):</th>
</tr>
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<tbody>
<tr>
<td>• delusions</td>
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<tr>
<td>• hallucinations</td>
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<tr>
<td>• disorganized speech (e.g., frequent derailment or incoherence)</td>
</tr>
<tr>
<td>• grossly disorganized or catatonic behaviour</td>
</tr>
<tr>
<td>• negative symptoms, i.e., affective flattening, alogia, or avolition</td>
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Note: Only one Criterion A symptom is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person's behaviour or thoughts, or two or more voices conversing with each other.

| B. Social/occupational dysfunction: For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care are markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic, or occupational achievement). |

| C. Duration: Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences). |

| D. Schizoaffective and Mood Disorder exclusion: Schizoaffective Disorder and Mood Disorder With Psychotic Features have been ruled out because either (1) no Major Depressive Episode, Manic Episode, or Mixed Episode have occurred concurrently with the active-phase symptoms; or (2) if mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods. |

| E. Substance/general medical condition exclusion: The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition. |

| F. Relationship to a Pervasive Developmental Disorder: If there is a history of Autistic Disorder or another Pervasive Developmental Disorder, the additional diagnosis of Schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month (or less if successfully treated). |

Source: Diagnostic and Statistical Manual of Mental Disorders, 4th ed., text revision (DSM-IV-TR).

Known risk factors are non-specific, and make only minor individual contributions to the development of psychosis. The main risk factors are, for instance, a genetic risk (e.g. the offspring of people with schizophrenia have a 10% lifetime risk for psychosis, in comparison with a population-level risk of 0.021%), minority status, smoking cannabis, exposure to an urban environment, prenatal factors (e.g. infection or stress of the mother during pregnancy) and developmental trauma (Tandon, Keshavan & Nasrallah, 2008). General psychopathology is also reported to be a precursor for the development of psychosis in many cases (Corcoran et al., 2011; Van Rossum, Dominguez, Lieb, Wittchen & Van Os, 2011). These risk factors are highly prevalent, whereas the incidence of psychosis is very low. Therefore, because screening based on risk factors results in the detection of too many false-positive cases, we still need to identify risk factors that predict psychosis with a high specificity.
In addition to the identification of risk factors, diagnostic criteria are needed to reliably separate the risk stage from the onset of schizophrenia, other disorders and normality (Heckers, 2009). Prodromal symptoms could, for instance, be wrongly interpreted by parents as signs of puberty (Linszen et al., 2011). These symptoms could also be indicators for other severe mental illnesses (Linszen et al., 2011). Therefore, differential diagnosis of the risk phase is very important.

As mentioned above, schizophrenia has no pathognomonic symptoms (making prediction difficult) and risk factors for a first psychotic episode are non-specific. For instance, patients in the prodromal phase of schizophrenia share 8 out of 10 symptoms with patients in the prodromal phase of major depression (Häfner et al., 2005a; Häfner et al., 2005b). Retrospectively, psychotic-like experiences (PLEs; referring to the sub-clinical positive psychotic symptoms) almost always precede frank psychosis, but only 8% of new cases with PLEs develop psychosis prospectively within 24 months, and 8% experience persistent PLEs with no conversion to psychosis. In 84% of people, PLEs spontaneously disappear within two years (Hanssen et al., 2005). There seems to be a blurring of the boundaries between normal experience and prodromal symptoms on the one hand, and between these prodromal symptoms and other mental disorders on the other (Yung, Nelson, Thompson & Wood, 2011a). Examples of these other psychiatric syndromes are schizotypal personality disorders, borderline personality disorders, post-traumatic stress disorders and obsessive-compulsive disorder (Linszen et al., 2011). In particular, depressive symptoms are associated with the at-risk phase. However, these symptoms generally do not meet the criteria for mood disorders. Patients diagnosed with a post-traumatic stress disorder could also report hallucinations; however, these hallucinations are related to the trauma (Jessop, Scott & Nurcombe, 2008). In addition, the non-psychiatric disorders (which have signs comparable to the psychotic syndromes) have to be excluded (e.g. epileptic disorders). As a result, recognizing those patients that will develop psychosis is problematic.

**Operational definition of the ultra high-risk group**

Alison Yung (from the PACE clinic Melbourne, Australia) was the first to define operational criteria for the detection of ultra high-risk patients (Yung & McGorry, 1996). These patients were referred to as being at ultra high-risk (UHR) contrasting this group of individuals with persons with a high-risk (HR) for psychosis with a parent suffering from schizophrenia-like disorders. The UHR patients have an at-risk
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mental state (ARMS) for developing psychosis in prospective studies. Throughout this thesis we use the term ARMS to refer to the high-risk condition and UHR to refer to a group of people at high risk. McGorry and colleagues conceptualised ARMS as a mixture of social decline, mild-positive psychotic symptoms, mood and anxiety disorders, sleep problems, cognitive impairments and comorbid disorders (Häfner, 2000; Häfner et al., 2003; Klosterkötter, Hellmich, Steinmeyer & Schultze-Lutter, 2001; Krabbendam & van Os, 2005; Yung & McGorry, 1996). Three subgroups of ARMS patients have been identified: 1) those with a genetic vulnerability; 2) those patients with attenuated psychotic symptoms; and 3) those that experience a brief limited intermittent psychotic syndrome (BLIPS; psychosis shorter than one week that resolves spontaneously).

Yung and colleagues (2005) developed the Comprehensive Assessment of At-Risk Mental States (CAARMS) for the assessment of ARMS. The CAARMS is a semi-structured interview that assesses sub-clinical psychotic symptoms over the preceding 12 months. Both the intensity and frequency of these symptoms are measured separately allowing to differentiate (based on arbitrary criteria) between ARMS (Tables 1.2 and 1.3), psychosis (Table 1.4), or neither of these: sensitivity (86%), specificity (91%), positive predictive value (80%) and negative predictive value (94%) (Yung et al., 2005). Attenuated symptoms are measured on four subscales: unusual thought content, non-bizarre ideas (persecutory ideas), perceptual abnormalities and disorganized speech. Two kinds of attenuated symptoms exist: those with sub-threshold intensity occurring frequently, i.e. subgroup intensity, and those with an intensity comparable to a frank psychotic symptom occurring at a low frequency, i.e. subgroup frequency. (See Chapter 3 for a comprehensive description of the CAARMS and ARMS criteria).

To be successful in detecting high-risk patients, one has to use enrichment strategies to create a sample with a high prevalence of psychosis proneness. A strategy that combines several risk factors (a close-in strategy) decreases the number of false-positives and increases false-negatives (McGorry, Yung & Phillips, 2003; Van Os & Delespaul, 2005). The current early detection teams use a close-in strategy: the case recruitment strategy of most early detection teams relies on referral of people suspected of psychosis. The referrals are generally made to tertiary medical research centres. The problem is, however, that referrers have difficulty in recognising a high risk for developing psychosis. For instance, it took McGlashan and colleagues (2003) four years to recruit 60 high-risk patients by referral in a recruitment area with a yearly prodromal incidence rate of 600 individuals (as ascertained following epidemiological research). In addition, the
transition rates in these early detection studies subsequently declined to only 7% (Yung et al., 2007). This suggests that even referring those suspected of psychotic development leads to too many false-positive cases.

**Table 1.2:** Group 2a Attenuated symptoms subgroup intensity (Comprehensive Assessment of At Risk Mental States: CAARMS)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Intensity score</th>
<th>Frequency score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unusual thought content</td>
<td>3-5</td>
<td>3-6</td>
</tr>
<tr>
<td>Non-bizarre ideas</td>
<td>3-5</td>
<td>3-6</td>
</tr>
<tr>
<td>Perceptual abnormalities (hallucinations)</td>
<td>3-4</td>
<td>3-6</td>
</tr>
<tr>
<td>Disorganised speech</td>
<td>4-5</td>
<td>3-6</td>
</tr>
</tbody>
</table>

**Table 1.3:** Group 2b Attenuated symptoms subgroup frequency (Comprehensive Assessment of At Risk Mental States: CAARMS)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Intensity score</th>
<th>Frequency score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unusual thought content</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Non-bizarre ideas</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Perceptual abnormalities (hallucinations)</td>
<td>5-6</td>
<td>3</td>
</tr>
<tr>
<td>Disorganised speech</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>

**Table 1.4:** Psychosis threshold

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Intensity score</th>
<th>Frequency score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unusual thought content</td>
<td>6</td>
<td>4-6</td>
</tr>
<tr>
<td>Non-bizarre ideas</td>
<td>6</td>
<td>4-6</td>
</tr>
<tr>
<td>Perceptual abnormalities (hallucinations)</td>
<td>5-6</td>
<td>4-6</td>
</tr>
<tr>
<td>Disorganised speech</td>
<td>6</td>
<td>4-6</td>
</tr>
</tbody>
</table>

*Symptoms have to be present for more than one week; if a symptom is present for less than one week, the patient scores in group 3 (BLIPS)*
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Vignette Ryan

Ryan entered the secondary mental health service because of problems in functioning at school. He complains about fatigue and disturbances in concentration. He is in his last year of college and has to find a work experience placement where he can undertake his Bachelor research and thesis. He is unsuccessful in this task because he feels very nervous when talking to other people. He has spoken with a dean at school who advised him to seek help within PsyQ Haaglanden. Ryan has a couple of school friends, but he never sees them in leisure time. He plays computer games for at least 10 hours a day and watches American television. Ryan has the feeling something odd is going on. For instance, last week he called in sick to school. When he was at home, he had the feeling that people at school would act differently when he was not around. It felt like they were acting in a play when he was at school. He can’t exactly explain what is going on. Twice a week he has the feeling that the school is different to how it used to be. He sees that the furniture is the same, but it doesn’t feel that way. He also has the experience three times a week that something said on television is actually a message for him. At that moment, he is 90% sure that the people from the broadcast station know what he is thinking. These thoughts interrupt his normal functioning. Ryan reports feelings of suspiciousness four days a week. When he walks around the living room, he feels like he is being spied upon, but he does not know by whom. During the intake assessment interview, he identifies it is an illogical thought. (N.B Ryan is a fictitious name)

ARMS as DSM-V diagnosis?

The inclusion of the ARMS diagnosis (proposed to be named Attenuated Psychotic Syndrome; APS) in the DSM-V that will be introduced in the near future, is the subject of an ongoing and challenging debate in the field of schizophrenia (Carpenter & Van Os, 2011).

Before inclusion of the APS in the DSM-V certain criteria must be met (Heckers, 2009). The first requirement is a valid diagnosis. Studies assessing the applicability of high-risk criteria initially showed that about 40% of patients who fulfil the ARMS criteria developed psychosis within 12 months (McGlashan et al., 2006; Yung et al., 2005). More recent evidence, however, has indicated transition rates of only
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7% (Yung et al., 2007; Yung et al., 2011b). These declining transition rates might be explained by a greater awareness of caretakers and healthcare professionals, resulting in earlier detection and earlier intervention. Intervention might be more effective in this early stage of illness, as is the case in breast cancer where early intervention results in a better prognosis (Yung et al., 2007).

In comparison to the incidence of 0.02% in the general population, the transition rate of 7% in UHR populations within a relatively short period is still relatively high. Although many individuals identified as UHR patients did not make the transition to psychosis, they still experienced poor functional outcome and low quality of life (Lin et al., 2010). The false positives found by early detection clinics appeared to develop other severe psychopathology later on, such as severe depression (McGorry, Hickie, Yung, Pantelis & Jackson, 2006). This implies that the ARMS criteria measure an integral vulnerability with different phenotypes: the UHR group is at risk for multiple severe illnesses besides psychotic disorders.

The second requirement for the APS as a DSM diagnosis is its feasibility and reliability in clinical practice. One of the counter-arguments in this discussion is that this diagnosis has been made only in research settings attracting ill persons at rates disproportionate to the general population (Carpenter & Van Os, 2011). The criteria used in these studies are not tested outside these specialized clinics, for instance in secondary mental healthcare services. It is not clear whether field testing outside these clinics would result in the detection of an ARMS population with comparable transition rates into psychosis.

Third, the social, legal and medical consequences of the diagnosis need to be examined (Heckers, 2009). The assessment of risks for developing psychosis carries its own risks. Risks include stigmatization, induction of anxiety and inappropriate treatment (e.g. antipsychotic medication in false-positives) (Heckers, 2009). Besides the fact that not all criteria are met, early detection of UHR patients is only useful when appropriate treatments are available to prevent people from becoming psychotic. This raises the question: are there in fact appropriate treatments? A review of studies examining both anti-psychotic medications (AP) and/or cognitive behavioural therapy (CBT) targeting risk symptoms in (tertiary psychosis) patients referred for suspected psychotic development, concluded that improvement of clinical outcomes has not yet been adequately demonstrated (De Koning et al., 2009). There is some evidence that AP may delay the onset of psychosis for one year (McGorry et al., 2002), and others have shown that CBT (Morrison et al., 2007) and omega-3 fatty acids delayed psychosis by at least one year (Amminger et al., 2010). In all follow-up studies, except for one (Velthorst et
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al. 2010), the functioning of high-risk patients remained poor (De Koning et al., 2009). Furthermore, the side-effects of AP present in the high-risk group result in a relatively low rate of medication compliance. Although these results are still inconclusive, they are encouraging.

EDIE-NL

As mentioned before, ARMS is determined by a combination of risk factors, including genetic susceptibility as well as symptomatology (Bell, 1992). The presence of non-psychotic mental disorders might be a risk factor for developing psychosis. For example, the presence of two or more sub-clinical psychotic symptoms in a specific age group of patients (i.e. 14-35 years) referred to a specialized clinic in combination with a depressed mood, resulted in a 40% chance of developing a psychosis within two years (Hanssen et al., 2005). The Dutch Early Detection and Intervention Evaluation (EDIE-NL, see Chapter 3) is the first study to screen in the help-seeking population entering secondary mental health care settings in the Netherlands. The study examines whether CBT targeting the high-risk symptoms could prevent, delay or improve the outcome of psychosis in patients with an ARMS who enter the secondary mental health care.

The aim of the EDIE-NL is to prevent a broader concept of first-episode psychosis. Therefore, the study not only targeted the high-risk symptoms of non-affective psychosis (i.e. schizophrenia spectrum and psychosis NOS), but also the first episode of affective psychotic syndromes (e.g. depression with psychotic features and bipolar disorder).

Outline and scope of this thesis

If the APS is eventually included as a diagnosis in the DSM, the early detection and prevention of psychosis will shift from tertiary specialized research centres to the secondary (community) mental healthcare settings. However, the ARMS criteria have not yet been tested in secondary mental health care. In addition, we need to identify risk factors which predict psychosis with a high level of accuracy in order to reduce the detection of false-positive cases.

The work presented in this thesis aims to contribute to the improvement of early detection by the search for risk factors, especially the sub-clinical psychotic symptoms, decline in social function, and the development of non-psychotic psychopathology. We have searched for these risk factors in the general population
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(NEMESIS), retrospectively in a first-episode cohort (The Hague psychiatric case register), and in the ARMS sample of the EDIE-NL. In addition this work aims to assess psychosis proneness within the general help-seeking population entering the secondary mental healthcare services, as well as the association between ARMS and mental disorders. Furthermore, it examines whether a close-in strategy conducted within secondary mental healthcare settings results in the detection of a UHR population with a high prevalence of psychosis proneness.

Specifically, the following topics and research questions are investigated, addressed and discussed:

In Chapter 2 the NEMESIS data are used to explore the aetiology of paranoia and the association with social phobia in the general population.

Chapter 3 describes the protocol of the EDIE-NL, including a comprehensive description of the study, its aims, sample procedure, diagnostic instruments, randomization protocol, quality control procedures and data analysis.

Chapter 4 explores the prevalence and structure of self-reported psychotic-like experiences (PLEs) in members of the general population who seek help from mental health services, using latent class analysis. Investigated are: whether all PLEs provoke the same risk for developing psychosis, and whether the transient nature of PLEs imply that some PLEs are innocent phenomena not associated with psychosis, while others might be associated with an ultrahigh risk for developing psychosis.

The EDIE-NL implemented the screening for UHR patients in the secondary mental health services. However, it is not yet known whether patients enter the secondary mental health services before developing a first-episode psychosis. Data from the The Hague psychiatric case register (Chapter 5) were used to examine the help-seeking behaviour for mental health problems in the prodromal phase of all patients that had a first episode of psychosis registered between 2005 and 2009, in order to explore whether it is feasible to detect such cases within secondary mental healthcare.

Chapter 6 explores whether screening in a secondary mental healthcare setting is able to detect UHR patients. In addition, differences and similarities were assessed between a population identified by the two-stage screening method and a population that was referred to the Diagnostic Centre of the specialized psychosis clinic in Amsterdam.

Chapter 7 describes the characteristics of the patients included in the EDIE-NL study. Baseline characteristics of these subjects were used to test five hypotheses: 1) the presence of ARMS is associated with help-seeking for mood and anxiety...
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disorders; 2) ARMS symptoms are accompanied by high scores for depression and anxiety; 3) the presence of more than one ARMS symptom is associated with increased scores for depression and anxiety; 4) ARMS in men is associated with negative symptoms and cognitive impairment; and 5) ARMS in women is characterised by affective symptoms.

In the final chapter (Chapter 8), the main findings are summarized and compared with other studies, important methodological limitations and strengths are considered, and implications for clinical practice are presented and discussed.
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