CHAPTER 1

General Introduction
Psychotic disorders
Psychotic disorders are characterized by a distortion in reality testing. In most cases psychotic disorders first emerge in adolescence, and the illness often has a chronic course [1]. The lifetime prevalence of psychotic disorders is around 2-3% [2]. According to the latest version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [3] psychotic disorders are defined when two or more of the following symptoms are present: (1) delusions, (2) hallucinations, (3) disorganized speech, (4) disorganized or catatonic behavior or (5) negative symptoms of which one symptom is from the first three mentioned. The psychotic symptoms are ‘positive symptoms’, because they refer to symptoms, which are present in patients and are generally not present in healthy people. Positive symptoms are distinguished from so called ‘negative symptoms’. Negative symptoms refer to symptoms that are usually present in healthy people, but are absent in patients with psychotic disorders (i.e. reduced social functioning, affective flattening and avolition). Schizophrenia is being diagnosed when the illness is present for more than six months.

The ultra-high risk stage of psychotic disorders
In the last decades an increasing amount of research has been conducted on the prodromal stage of psychotic disorders. The prodromal stage is the period that precedes the onset of a first episode of psychosis (FEP) and is characterized by subtle behavioral changes and a decline in social functioning, 1 to 5 years prior to a FEP. Because the prodromal stage can only be determined retrospectively, Yung and colleagues [4] introduced criteria that could identify individuals experiencing these early signs of psychosis. They identified the three following groups, of which at least one has to be present to fulfill the now widely applied ‘Ultra High Risk’ (UHR) or ‘At Risk Mental State (ARMS) criteria: (1) Attenuated Psychotic Symptoms (APS) criterion: attenuated positive symptoms during the past year; (2) Brief Limited Intermittent Psychotic Symptoms (BLIPS) criterion: an episode of frank psychotic symptoms that have not lasted longer than a week and have been abated spontaneously; and (3) Familial Risk Factor criterion: having a first-degree relative with a psychotic disorder or having a schizotypal personality disorder in addition to a significant decrease in functioning in the past year. ‘UHR’ criteria are usually assessed with the Structured Interview for Prodromal Syndromes (SIPS) [5] or the Comprehensive Assessment of At Risk Mental State (CAARMS) [6]; the criteria are broadly congruent. For consistency reasons, throughout this thesis the term UHR will be used.
Of individuals in the UHR stage only a subset will eventually transition to a first episode of psychosis. Initially, transition rates ranging from 15% to 54% were reported across different settings around the world, with an average of approximately 40% within 12 months [7-10]. However, three reviews have reported a decline in transition rates [10-12]. An explanation for this drop in transition rate is that because of increasing awareness of the UHR stage of psychosis, patients experiencing these early signs of psychosis might present to clinical services in an earlier stage.

Research on prevention of psychosis in the UHR stage has shown promising results. In the Dutch Early Detection and Intervention trial (EDIE-NL) [13] the effect of cognitive behavioral therapy (CBT) in UHR individuals was evaluated. In line with a recent meta-analysis [14], the EDIE-NL trial showed that CBT was associated with a risk reduction of around 50% at 18 months follow-up [15]. These findings indicate that it is important to offer CBT in an early stage, because it could prevent or even delay the development of a FEP in the UHR stage. Furthermore, early intervention is important because the duration of untreated psychosis is associated with worse prognosis of the disease [16].

**Risk factors of psychotic disorders**

For many years the etiology of psychotic disorders has been subject of investigation. In previous research several genetic variations have been linked to schizophrenia [17, 18]. Overall, these genetic studies have shown modest contributions to the pathogenesis of schizophrenia. Therefore, research in the last decades has led to the understanding that genetic and environmental risk factors most likely interact in the onset of psychotic disorders (gene-environment interaction) [19-21]. In other words, genetic risk factors may operate by sensitizing the vulnerability for environmental factors. For example, susceptibility of the functional polymorphism in the catechol-O-methyltransferase (COMT) gene has been suggested to operate on cannabis use in adolescence; an environmental risk factor that has often been related to psychotic symptoms [22, 23]. The gene-environment interaction hypothesis has led to the EUropean network of national schizophrenia networks studying Gene-Environment Interactions (EU-GEI). EU-GEI is a naturalistic prospective multicenter study that aimed to identify the interactive genetic, clinical and environmental determinants of schizophrenia.
The most important environmental risk factors of psychotic disorders are urban environment (OR = 1.4) [24, 25], neuroticism (OR = 1.2) [26], perceived discrimination (OR = 1.2 – 4.0) [27, 28], no breast-feeding (OR = 1.7) [29], bullying (OR = 2.5) [30], low social economic status (OR = 2.7) [31], cannabis use (OR = 2.8) [32], migration (OR = 2.9) [33], deafness (OR = 3.0) [34], negative ethnic identity (OR = 3.3) [35], second generation immigrants (OR = 5.8) [36] and childhood sexual abuse (OR = 7.3) [37].

In particular the effect of childhood abuse and cannabis use in the onset of psychosis has received much attention in recent years. Childhood abuse is typically broken down into the following sub domains: physical abuse, sexual abuse, emotional abuse, emotional neglect, physical neglect [38] and bullying before the age of 18 years [39]. For all these sub domains of childhood abuse, increased odds for psychosis have been found [40, 41]. In addition, previous research showed that individuals being exposed to early sexual traumatic events are more likely to being re-exposed to sexual abuse in adulthood [42-44]. To date, little is known about underlying pathways of the association between childhood abuse and psychosis. Studies examining these pathways focused on specific associations between sub domains of abuse and specific types of psychotic symptoms. These studies found that in particular childhood sexual abuse was associated with hallucinations, while childhood neglect was associated with paranoia [45, 46]. These findings suggest that there might be different pathways in the association between forms of childhood abuse and different psychotic symptoms.

In recent years, there is also growing evidence that recent stressful life events play a role in the pathway to psychosis [47]. Recent life events are defined as events in the last months prior to the onset of psychosis that usually involve danger and that cause a substantial change in one’s positive or negative personal circumstances [48]. Examples of stressful life events are: divorce, death of a close relative or a severe financial crisis. A meta-analytical overview showed that life events in the months prior to the onset of psychosis increases the risk for psychosis by threefold [47].

Reviews on the association between cannabis use and psychosis risk show that cannabis use is associated with roughly a twofold increased risk of developing psychosis [49, 50]. The risk increases to almost threefold when individuals use high potency cannabis (skunk) [51]. Also the age of onset of cannabis use has been associated with psychosis, with greater risk for early-onset of cannabis use. A possible explanation is that cannabis use during adolescence, a period in which
the brain is still developing, might disrupt normal neurodevelopmental processes and subsequently enhance psychosis risk [52].

**Childhood abuse and cannabis use in UHR research**

In UHR studies to date, the effect of childhood abuse and cannabis use on transition to psychosis in prospective designs is relatively unexplored. With the declining transition rates in UHR studies, it has become increasingly important to search for additional factors that might contribute to prediction of psychosis in the UHR stage. Despite substantial research effort in the last decades, it is still unclear which subset of UHR individuals has highest chances of developing a FEP. Examining important risk factors of psychosis like childhood abuse and cannabis use in the UHR stage might help in better prediction of transition to psychosis.

However, while the UHR stage was originally designed as a risk stage for psychotic disorders, recent research suggests that the UHR stage should be considered as a transdiagnostic stage [53]. In other words, the UHR stage should be considered a risk stage for overall distress, functional impairment and psychopathology instead of a risk stage for solely psychosis. Although most UHR studies mainly focused on transition to psychosis outcome, UHR studies increasingly focus on other outcome measures beside transition to FEP. The experience of childhood abuse, a risk factor that has been associated with a wide range of psychopathology [54], may play an important role in the effect on differential outcomes in the UHR stage.

**Aims and outline of this thesis**

The main objective of this thesis was to increase our knowledge on the role of childhood abuse and cannabis use on transition to psychosis and other clinical and functional outcome measures in individuals at UHR for psychosis. Answering the following questions may contribute to our knowledge on risk factors for psychosis in the UHR stage and may help to better predict transition to FEP. Therefore, the present thesis will address the following key questions:

1. Is childhood abuse predictive of transition to psychosis in subjects fulfilling UHR criteria?
2. Is cannabis use predictive of transition to psychosis in subjects fulfilling UHR criteria?
3. Is childhood abuse associated with other clinical and functional outcomes in subjects fulfilling UHR criteria?
This thesis starts with two separate reviews. In **chapter 2** a review of all available studies examining childhood abuse and recent stressful life events in UHR individuals is presented. Using meta-analysis the mean prevalence rate of childhood abuse in UHR individuals will be evaluated. In addition, the effect of recent stressful life events on transition to psychosis in UHR studies will be examined.

Subsequently, **chapter 3** presents a review of all available studies examining the effect of cannabis use in UHR individuals. Using meta-analytical techniques, we examine the effect of (1) lifetime cannabis use and (2) cannabis abuse or dependence according to DSM-IV criteria [55] on transition to psychosis in prospective UHR studies.

**Chapter 4** addresses the efficacy of the EDIE-NL trial at 4-year follow-up. In this study, the effect of an add-on CBT aimed at the prevention of psychosis is compared to treatment as usual over a 4-year follow-up period. Moreover, in this study UHR subjects that transitioned to psychosis are compared to UHR subjects that did not transition to psychosis on clinical and functional outcome measures. In chapter 5-7, the effect of childhood abuse on transition to psychosis and other clinical and functional outcome measures will be evaluated in three separate UHR populations. Firstly, **chapter 5** describes the effect of childhood abuse on transition to psychosis in participants of the EDIE-NL trial. This study presents data of UHR individuals with 4-year follow-up data. Apart from the association between childhood abuse and transition to psychosis the effect of childhood abuse on depression, anxiety and global functioning will be examined. In addition, the effect of childhood abuse on health care costs will be discussed.

In **chapter 6**, childhood abuse will be investigated in UHR individuals of the Dutch Prediction of Psychosis Study (DUPS) with 24-month follow-up data. DUPS was the Dutch part of the larger European Prediction of Psychosis Study [56]. DUPS was a naturalistic longitudinal UHR study. We evaluate the effect of childhood abuse on transition to psychosis in this UHR cohort. Also, the effect of childhood abuse on baseline symptoms and symptoms at 24-month follow-up will be discussed. In addition, the effect of childhood abuse on the course of symptoms between baseline and 24-month follow-up will be presented.

**Chapter 7** will present a study on associations between childhood abuse and various clinical and functional outcome measures in UHR individuals of the EU-GEI study. We will address the effect of childhood abuse on transition to psychosis.
in this UHR cohort, and we will examine the effect of childhood abuse on other clinical and functional outcome measures.

To conclude, in chapter 8 a summary and general discussion of this thesis will be presented, and further clinical implications will be discussed.
References


