Background
Schizophrenia is one of the leading causes of disease burden worldwide (1). In addition, the severity of schizophrenia (and psychotic disorders) leads to substantial economic costs, mainly due to hospitalization and unemployment (2). Research into the developmental stages of schizophrenia shows that a first episode of psychosis generally manifests itself in early adulthood, and is preceded in most patients by a period with an ultra-high risk (UHR) of developing a first-episode psychosis. Without a targeted intervention, 36% of all people at UHR go on to develop a psychotic disorder within three years (3).

Objectives
The aim of the work in this thesis was to identify the UHR group in routine mental health care, to offer them (add-on) proactive/preventive cognitive behavior therapy for UHR (CBTuhr) and to guide them through a critical period of their lives with the aim to prevent the
transition to a first episode of psychosis, preferably in an effective and cost-effective manner. This chapter presents the key findings of the studies described in Chapters 2-9 together with their strengths and limitations. In addition, implications emerging from the results are addressed and some suggestions are made for further research.

**Main findings**

Chapter 1 presents an outline of this thesis. In Chapter 2 the research protocol of the Dutch Early Detection and Intervention Evaluation (EDIE-NL) trial is presented (data from the trial are presented in subsequent chapters). Chapter 3 describes the development of a brief version of the Prodromal Questionnaire (i.e. the PQ-16) to facilitate routine screening for psychosis risk in a general help-seeking population. The PQ-16 had a high sensitivity (87%) and specificity (87%) and a positive predictive value (PPV) of 44%. In Chapter 4 we report the baseline characteristics of the patients included in the EDIE-NL study. In this study, the sample was older and included a higher proportion of women compared to the populations found in other UHR studies. The majority of our UHR patients had a depressive disorder (58%) or social phobia (42%). In women especially anxiety, and not depression, was associated with the level of subclinical psychotic symptoms. No differences were found between men and women in the subclinical psychotic symptoms. Chapter 5 discusses the longer-term effects of CBT for psychosis. At 4-years post-baseline, the incidence of psychosis was lower in the CBTuhr group (12 patients) compared with the treatment-as-usual group (22 patients), and more patients remitted from their UHR status in the group that received CBTuhr (76.3% vs. 58.7%). Transition to frank psychosis was associated with more severe psychopathology and lower levels of social functioning. In Chapter 6 the cost-effectiveness of CBTuhr was evaluated at 18-months post-baseline. It was demonstrated that the CBTuhr intervention had a probability of 63.7% of being ‘dominant’ from a cost-effectiveness perspective, because it was less costly than routine care per prevented psychosis. CBTuhr was also the preferred treatment because it was successful in generating more quality-adjusted life years (QALYs) for costs that were lower compared with those of routine care. The longer-term cost-effectiveness and cost-utility is addressed in Chapter 7. The cost-effectiveness of the intervention was sustained and even improved at 4 years post-baseline: there was a 83.0% likelihood that CBTuhr would be successful in reducing the incidence of psychosis for lower costs. Similarly, there was a 75.0% likelihood that the intervention would result in more QALY gains for lower costs. These favorable outcomes were mainly driven by reduced healthcare costs (in particular, fewer hospital re-admissions) in the experimental condition. Chapter 8 examines the association between a history of childhood abuse and clinical and functional outcome at 4-year follow-up. It is shown that childhood abuse is predictive of more depression and lower social functioning. In line with these findings, although it is not surprising that healthcare costs are higher in the group that experienced childhood trauma, trauma was not asso-
associated with a greater risk of making a transition to psychosis. This may indicate that childhood abuse increases the chance to present at mental health services with a non-psychotic mental disorder. Finally, in Chapter 9, a stage-dependent prognostic model was developed for individuals recognized as UHR patients that were seeking treatment for comorbid (non-psychotic) psychopathology. The predictor model included the following variables: observed blunted affect, subjective complaints of impaired motor function, beliefs about social marginalization, decline in social functioning, and distress associated with suspiciousness. The positive predictive value of the model was 80.0%. Based on the prognostic scores of the five variables, we identified three statistically distinct risk classes that were able to further classify the magnitude of the psychosis risk in selected risk groups. The instantaneous incidence rate in the highest class was almost 26 times higher than that in the lowest class, and more than 9 times higher than that in class II. Furthermore, the time to transition differed markedly between class III and the other classes; the mean difference compared with the lowest class was more than 8 months. Therefore, the different risk classes may be useful to help healthcare professionals to stratify and personalize treatment.

Conclusions
The main aim of this thesis was to contribute to the development, evaluation and implementation of early detection and treatment of young people at ultra-high risk of psychosis and severe psychopathology in routine mental health care, in the context of the Early Detection and Intervention Evaluation (EDIE-NL) trial. In this setting, we aimed to identify the ultra-high risk (UHR) group in routine mental health care, to offer them proactive/preventive cognitive behavior therapy for UHR (CBTuhr), and to guide them through a critical phase of their lives whereby the transition to a first episode of psychosis is prevented, in an adequate and (cost-) effective manner. We conclude that it was possible to identify those at UHR in routine care and that the prognosis of UHR patients appears to improve substantially by intervening with CBTuhr during a critical period; this effect was shown to be sustained over a 4-year period. Furthermore, the intervention was shown to be (cost-) effective and even cost-saving.