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Contents

Abstract

Psychosis is usually preceded by a prodromal period. This phase is characterized by psychotic-like symptoms, attenuated positive symptoms not severe enough to reach a psychotic level, preceding the onset of full-blown psychotic symptoms. For example, a person may hear voices that are not real. However, psychotic-like symptoms are common among adolescents, especially among those with other psychiatric symptoms, and they are not necessarily indicative of the psychosis prodrome.

This study addresses symptoms that based on previous research may be associated with a heightened risk for psychosis. By finding which symptoms predict transition to a severe psychiatric illness during the following months or years, these risk symptoms can be identified early, and effective interventions can attenuate, delay or even prevent the onset of a psychotic disorder.

The objective of the study was to investigate whether it is possible and useful to screen for psychosis risk in an unselected clinical adolescent population seeking help for psychiatric symptoms. The study wanted to gain information on the character and prevalence of psychotic-like symptoms and to investigate which symptoms predict psychosis and hospitalizations among adolescents in general psychiatric care. In addition, the associations between psychosis risk symptoms, cognitive functioning, and suicidal ideation and behavior were investigated.

This study collected data on adolescent psychiatric patients aged 15–18 years in Helsinki during the years of 2003–2004 and 2007–2008. The participants were screened using the Prodromal Questionnaire (PQ) for prepsychotic symptoms, which was completed by 731 adolescents. The Structured Interview for Prodromal Syndromes (SIPS) was administered to 174 adolescents to ascertain their psychosis risk status, and broad cognitive testing was done. The participants were followed via patient files and the national hospital discharge register.

The adolescents with high-risk symptoms had deficits in their cognitive functioning which were associated with stronger negative symptoms. Particularly poorer verbal performance was associated with stronger negative symptoms among adolescent patients, regardless of the psychosis risk status. Visuospatial performance was poorer among the adolescents with a psychosis risk compared to other patients.

A third of the participants in general adolescent psychiatric services were identified as psychosis risk patients, but psychosis incidence during follow-up was low, and the psychosis risk status was not specifically predictive of psychosis. Hospital admissions for psychotic disorder were predicted by the depersonalization symptom intensity of the questionnaire and the positive symptom intensity of the interview. In addition, psychosis risk status predicted psychiatric hospitalizations overall during the following years.

Psychotic-like experiences were associated with suicidal ideation among the adolescent psychiatric patients, but they did not predict an increased risk of severe, hospital-treated self-harm during follow-up. The best predictor of intentional self-harm was emotional inexpressivity.

Psychotic-like symptoms are common among adolescent psychiatric patients, but the development of psychosis is rare, and predicting psychosis with psychotic-like symptoms is not possible in the clinical environment. However, identifying and treating psychotic-like symptoms is important, as not only are they often distracting experiences in themselves, they can also be associated with cognitive deficits and suicidality, predict hospitalizations, and thus indicate a more serious disorder.

Tiivistelmä

Maija Lindgren: Psychotic-like symptoms and psychosis prediction in adolescent psychiatric patients [Psykoottisenkaltaiset oireet ja psykoosin ennustaminen nuorisopsykiatrisilla potilailla]

Psykoosia edeltää tavallisesti niin sanottu prodromaali- eli esioirevaihe. Tälle vaiheelle ovat ominaisia psykoottisenkaltaiset oireet, vaimentuneet psykoottistasoisia oireita lievemmät positiiviset oireet, jotka edeltävät täysimittaisten psykoottisten oireiden alkamista. Henkilö voi esimerkiksi kuulla ääniä, jotka eivät ole todellisia. Psykoottisenkaltaiset oireet ovat kuitenkin tavallisia nuorilla, erityisesti muuten psykiatrisesti oireilevilla nuorilla, eivätkä ne välttämättä ole oire alkavasta psykoosista.

Tässä tutkimuksessa tutkitaan oireita, jotka aikaisempien tutkimusten mukaan voivat liittyä kohonneeseen riskiin sairastua psykoosiin. Kun saadaan tietää mitkä oireet ennustavat henkilön sairastumista vakavaan mielenterveyden häiriöön lähikuukausina tai -vuosina, voidaan näiden riskioireiden tehokkaalla hoidolla viivästyttää tai jopa ennaltaehkäistä psykoottisen häiriön puhkeamista tai lieventää kehittyvää häiriötä.

Tutkimuksen tarkoitus oli selvittää, onko psykoosiriskiä mahdollista ja hyödyllistä seuloa valikoitumattomassa aineistossa sellaisten nuorten parissa, jotka ovat hakeneet apua mielenterveyden oireisiin. Tutkimuksessa haluttiin kartoittaa nuorisopsykiatristen potilaiden psykoottisenkaltaisia oireita, niiden luonnetta ja yleisyyttä, ja selvittää mitkä oireet ennustavat psykooseja ja sairaalahoitoja. Myös psykoosiriskioireiden yhteyttä kognitiiviseen suoriutumiseen sekä itsemurha-ajatuksiin ja itsetuhoiseen käyttäytymiseen tutkittiin.

Aineisto kerättiin nuorisopsykiatrisilta 15–18-vuotiailta potilailta Helsingissä vuosina 2003–2004 ja 2007–2008. Tutkittavat seulottiin käyttäen esipsykoottisia oireita mittaavaa PQ-itseraportointilomaketta (suom. NKK), jonka täytti 731 nuorta. 174 nuoren psykoosiriskiä tutkittiin srukturoidulla SIPS-haastattelulla ja tutkittaville tehtiin laaja kognitiivinen testaus. Potilaita seurattiin sairaskertomusten ja hoitoilmoitusrekisterin avulla.

Riskioireilevilla nuorilla oli kognitiivisen suoriutumisen vaikeuksia, jotka olivat yhteydessä vaikempiin negatiivisiin oireisiin. Erityisesti nuorisopotilaiden heikentynyt kielellinen suoriutuminen oli yhteydessä voimakkaampiin negatiivisiin oireisiin

riippumatta siitä, täyttyivätkö psykoosiriskikriteerit. Visuospatiaalinen suoriutuminen oli heikompaa psykoosiriskikriteerit täyttävillä nuorilla kuin muilla potilailla.

Valikoitumattoman nuorisopykiatrisen aineiston tutkittavista kolmasosa täytti psykoosiriskikriteerit, mutta psykoosiin sairastumiset seuranta-aikana olivat harvinaisia ja psykoosiriskistatus ei ennustanut spesifisti psykoosia. Sairaalahoitoja psykoosin vuoksi ennustivat kyselylomakkeen mittaamat depersonalisaatio-oireet ja haastattelun mittaamat positiiviset oireet. Psykoosiriskistatus taas ennusti ylipäänsä lähivuosien psykiatrisia sairaalahoitoja.

Psykoottisenkaltaiset kokemukset olivat yhteydessä itsetuhoisiin ajatuksiin nuorisopsykiatrisilla potilailla. Psykoottisenkaltaiset oireet eivät kuitenkaan ennustaneet seuranta-ajan vakavia, sairaalahoitoa vaativia tahallisia itsensä vahingoittamisia. Parhaiten itsetuhoista käyttäytymistä ennusti vähentynyt tunteiden ilmaisu.

Psykoottisenkaltaiset oireet ovat nuorisopsykiatrisilla potilailla yleisiä mutta psykoosiin sairastuminen harvinaista, eikä sairastumisen ennustaminen psykoottisenkaltaisten oireiden perusteella ole kliinisessä työssä mahdollista. Psykoottisenkaltaisten oireiden tunnistaminen ja hoitaminen on kuitenkin tärkeää, sillä sen lisäksi että ne usein ovat itsessään häiritseviä kokemuksia, ne voivat olla yhteydessä kognitiivisiin puutoksiin ja itsetuhoisuuteen, ennustaa sairaalahoitoja, ja siten kertoa vakavammasta sairaudesta.

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List of original papers

The thesis is based on the following original articles, which are referred to in the text by Roman numerals (I-IV).

I Lindgren, M., Manninen, M., Laajasalo, T., Mustonen, U., Kalska, H., Suvisaari, J., Moilanen, K., Cannon, T. D., Huttunen, M., Therman, S. (2010). The relationship between psychotic-like symptoms and neurocognitive performance in a general adolescent psychiatric sample. *Schizophrenia Research* 123(1): 77–85.

II Lindgren, M., Manninen, M., Kalska, H., Mustonen, U., Laajasalo, T., Moilanen, K., Huttunen, M., Cannon, T. D., Suvisaari, J., Therman, S. (2014). Predicting psychosis in a general adolescent psychiatric sample. *Schizophrenia Research* 158(1–3):1–6.

III Therman, S., Lindgren, M., Manninen, M., Loewy, R.L., Huttunen, M.O., Cannon, T.D., Suvisaari, J. (2014). Predicting psychosis and psychiatric hospital care among adolescent psychiatric patients with the Prodromal Questionnaire. *Schizophrenia Research* 158(1–3):7–10.

IV Lindgren, M., Manninen, M., Kalska, H., Mustonen, U., Laajasalo, T., Moilanen, K., Huttunen, M., Cannon, T. D., Suvisaari, J., Therman, S. (2015). Suicidality, self-harm, and psychotic-like symptoms in a general adolescent psychiatric sample. *Early Intervention in Psychiatry*, Jan 13. doi: 10.1111/eip.12218. [Epub ahead of print]

Abbreviations

APS	Attenuated Positive Prodromal Syndrome (in SIPS); Attenuated Psychosis Syndrome (in DSM-5)
BAI	Beck Anxiety Inventory
BDI	Beck Depression Inventory
BHS	Beck Hopelessness Scale
BLIPS	Brief Limited Intermittent Psychotic Symptoms
BPRS	Brief Psychiatric Rating Scale
BSABS	Bonn Scale for the Assessment of Basic Symptoms
CAARMS	Comprehensive Assessment of At-Risk Mental States
CASH	Comprehensive Assessment of Symptoms and History
CBT	Cognitive Behavioral Therapy
CHR	Clinical High-Risk
CI	Confidence Interval
CVLT	California Verbal Learning Test
COPS	Criteria of Prodromal Syndromes
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
ERIraos	Early Recognition Inventory
GRD	Genetic Risk and Deterioration syndrome
HR	Hazard Ratio
HILMO	Finnish Hospital Discharge Register (Care Register for Health Care, Finnish: Hoitoilmoitusrekisteri, HILMO)
ICD-10	International Classification of Diseases, 10th edition
IQ	Intelligence Quotient
MRI	Magnetic Resonance Imaging
n	Number of participants
NAPLS	North American Prodrome Longitudinal Study
PACE	Personal Assessment and Crisis Evaluation
PQ	Prodromal Questionnaire (Finnish: Nuoruusiän kokemuskysely, NKK)
RAP	Recognition and Prevention program
SCID	Structured Clinical Interview for the DSM-IV

SD	Standard Deviation
SIPS	Structured Interview for Prodromal Syndromes
SOPS	Scale of Prodromal Symptoms
SPI-A	Schizophrenia Proneness Instrument, Adult version
SPSS	Statistical Package for the Social Sciences
UHR	Ultra High-Risk
WAIS-III	Wechsler Adult Intelligence Scale – third edition
WAIS-R	Wechsler Adult Intelligence Scale – revised
WHO	World Health Organization
WMS-III	Wechsler Memory Scale – third edition
WMS-R	Wechsler Memory Scale – revised

1 Introduction

Early recognition of emerging mental health disorders has become a priority in the field of psychiatry (Coughlan et al., 2013). First signs of many psychiatric illnesses can already be detected during the premorbid period, enabling early intervention. The earlier the problems are treated, the greater the chance of a successful recovery (van der Gaag et al., 2013). The World Health Organization (WHO, 2004; 2013) states the prevention of mental disorders as a public health priority.

Severe psychiatric disorders usually develop gradually and are often preceded by *a prodromal phase* (Häfner et al., 2005; McGlashan, 1996; Yung & McGorry, 1996). The symptoms of this phase not only include general symptoms, such as sleeping problems, depressive mood, social withdrawal, and problems in school or work, but also include attenuated positive symptoms, such as suspiciousness and perceptual abnormalities. The prodromal symptoms cause distress and suffering a long time before the actual illness, and psychosocial functioning often declines years before the first psychotic symptoms and the initiation of treatment (Addington, Penn, Woods, Addington, & Perkins, 2008; Häfner, Loffler, Maurer, Hambrecht, & an der Heiden, 1999). The *clinical high-risk* approach aims to predict transition to psychosis by clinically significant risk symptoms that do not meet the threshold of psychotic disorder (Addington & Heinssen, 2012).

The delay between the onset of symptoms and treatment onset is linked with poorer outcome (Penttilä, Jääskeläinen, Hirvonen, Isohanni, & Miettunen, 2014), and hence, one goal of early treatment is to shorten the duration of untreated psychosis (Häfner & Maurer, 2006; Larsen et al., 2001). Early recognition and treatment are emphasized in the Finnish recommendations for schizophrenia care (Schizophrenia: Current Care Guidelines). Further, the clinical high-risk approach aims to detect and effectively treat risk symptoms early in order to prevent or delay the onset of psychosis, and to reduce the severity of the prodromal symptoms (McGorry et al., 2002; Morrison et al., 2012; van der Gaag et al., 2013; Walker et al., 2009). Even postponing the transition to psychosis in adolescence is valuable, because of the leaps in maturation of the brain and the development of social relationships and academic skills. Psychosis risk symptoms also cause distress themselves, thus reliable methods to detect vulnerability to psychosis are needed (Salokangas & McGlashan, 2008).

1.1 Psychosis

Psychotic disorders are severe mental disorders characterized by behaviors and experiences that make it difficult to understand reality. These include delusions (false beliefs), hallucinations (perceiving things that are not real), and disorganization (including disturbed and confused thoughts, speech, or behavior). These symptoms, which most individuals do not normally experience but are present in a psychotic disorder, are called *positive symptoms*. Also common in psychotic illnesses are *negative symptoms*, functions normally found in healthy persons, but diminished or absent in affected persons. These symptoms include withdrawal from friends and family, impoverishment of thoughts and speech, and flattening of affect. In the latest update of the Diagnostic and Statistical Manual of Mental Disorders, DSM-5 (American Psychiatric Association, 2013), the dimensional assessment of psychosis includes hallucinations, delusions, disorganized speech, abnormal psychomotor behavior, and negative symptoms. As novel dimensions, depression, mania and impaired cognition are also assessed as part of psychotic illnesses (Barch et al., 2013).

Psychotic disorders cause great suffering and affect relationships, education and work, and quality of life. Psychotic disorders classified in DSM-5 are listed in Table 1. The most common psychotic disorder is schizophrenia, the prevalence being approximately 1% in Finland (Perälä et al., 2007). Schizophrenia is characterized by delusions and hallucinations, as well as disorganized speech and behavior, causing social or occupational dysfunction. For a diagnosis, symptoms and functional impairment must have been present for six months. Schizophrenia is often associated with significant deficits and need for help in everyday functioning (Viertiö et al., 2012).

Other psychotic disorders include schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, and other specified schizophrenia spectrum and other psychotic disorder. In addition, schizotypal personality disorder is classified as a schizophrenia spectrum disorder. Bipolar disorder and depressive disorder, categorized in mood disorders, can also occur with psychotic features.

Table 1. Psychotic disorders according to DSM-5

Disorder	Specifiers
Schizophrenia	Delusions, hallucinations, disorganized speech and behavior, for six months, causing social or occupational dysfunction
Brief psychotic disorder	Delusions, hallucinations, disorganized speech and behavior, for less than one month
Schizophreniform disorder	Delusions, hallucinations, disorganized speech and behavior, for more than one month but less than six months
Delusional disorder	Delusions for one month, hallucinations not prominent, functioning not markedly impaired
Schizoaffective disorder	Features of both schizophrenia and a mood disorder, either bipolar disorder or depression
Substance or medication induced psychotic disorder, Psychotic disorder due to another medical condition	Psychotic disorder explained with substance use, medication, or a medical condition
Catatonic disorder	Psychomotor disturbance; associated with another disorder or medical condition, or unspecified catatonia
Other specified schizophrenia spectrum and other psychotic disorder	Psychotic disorder not specified
Unspecified schizophrenia spectrum and other psychotic disorder	Psychotic disorder, with insufficient information for a specific diagnosis

1.1.1 Epidemiology of psychotic disorders

In a study of the whole population of Denmark, 3.7% of women and 3.8% of men were estimated to have received treatment for schizophrenia and related disorders over their lifetime (Pedersen et al., 2014). Similarly, in a comprehensive study using multiple information sources, the lifetime prevalence of psychosis was over 3% in the general population in Finland (Perälä et al., 2007).

As for adolescents, the cumulative incidence of schizophrenia spectrum disorders (International Classification of Diseases, 10th edition, ICD-10 codes F20–F29) by the age of 20 in Denmark was 0.73% (95% CI 0.70–0.75) for women and 0.65% (95% CI 0.63–0.68) for men (Pedersen et al., 2014). The corresponding rates for schizophrenia (ICD-10 F20) were 0.29% (95% CI 0.28–0.31) for women and 0.33% (95% CI 0.31–0.35) for men. By the end of 25 years of age, the cumulative incidence of schizophrenia spectrum disorders rose to 1.33% (95% CI 1.30–1.37) in women and to 1.48% (95% CI 1.44–1.51) in men, the corresponding rates for schizophrenia being 0.66% (95% CI 0.64–0.69) for women and 0.80% (95% CI 0.78–0.83) for men.

Although there are no gender differences in the incidence of schizophrenia during childhood and adolescence, in adulthood the incidence per 10 000 person-years is higher for men until at age 50, when the women's incidence becomes higher (Pedersen et al., 2014).

These rates are consistent with results of cohort studies in Finland. In the Northern Finland 1986 birth cohort study, adolescents between ages 17 and 23 years, who had completed the PROD-screen (a screen for prodromal symptoms of psychosis) at age 15 to 16, were followed via the Finnish Hospital Discharge Register (Mäki et al., 2014). 0.4% of the sample was diagnosed with psychosis during follow-up, out of which 0.3% were non-affective psychoses (Mäki et al., 2014). In the Finnish 1981 birth cohort study, 1.5% of the males and 0.8% of the females were treated for psychosis between the ages of 13 to 24 years according to the Finnish Hospital Discharge Register (Gyllenberg et al., 2010). The cumulative incidence for non-affective psychoses was 1.3% for males and 0.5% for females (Gyllenberg et al., 2010).

Compared to first-episode psychosis patients with onset after 18 years, adolescent onset patients tend to have a slower onset of symptoms and experience a longer delay in access to treatment (Joa et al., 2009). This group may have worse premorbid functioning. Teen onset of psychosis may also be associated with higher levels of depression and suicidal ideation and suicide attempts (Joa et al., 2009).

1.2 The prodromal phase of psychosis and psychotic-like symptoms

The prodromal phase, which often precedes psychosis 1–2 years before the first admission (Salokangas & McGlashan, 2008), provides an opportunity to detect a disease course, predict psychosis and to possibly intervene before frank disease (Addington & Heinssen, 2012; Mees, Zdanowicz, Reynaert, & Jacques, 2011). The prodromal phase of psychosis is characterized by *psychotic-like symptoms*, which are attenuated positive symptoms not severe enough to reach a psychotic level (Rietdijk et al., 2014; Yung et al., 2009).

As an example of these mild positive symptoms, a person may occasionally have perceptual distortions, for example hear voices, but realizes that they are not real. Or a

person may be distracted by the feeling that others can read his or her mind but is not sure if it is really happening or if it is imaginary, so the delusional idea does not reach the psychotic level. The difference between psychotic and psychotic-like symptoms lies in reality testing and conviction of the experience being real. Typically, in a psychotic disease course, psychotic-like symptoms gradually get stronger, finally reaching the psychotic level. However, the predictive value of single psychotic-like experiences is low.

Table 2 presents the basic concepts of psychosis risk research. It has to be noted that the term prodrome can be misleading, as it can only be correctly used retrospectively; not all patients classified as being at psychosis risk ever develop psychosis.

A current controversy is the boundary between normal experience and psychosis risk symptoms (Yung & Nelson, 2013). Psychotic experiences can be seen as a continuum, with full clinical psychosis representing the extreme (Linscott & van Os, 2010; van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009). From this perspective, psychotic symptoms are not qualitatively different from normal experiences. People with psychosis and healthy people can therefore have the same experiences, but to a different degree.

As normal variation in the psychosis continuum, mild psychotic-like experiences, such as perceptual abnormalities of a healthy person, are not clinically relevant if they come and go and do not interfere with functioning in everyday life. In stressful situations associated with sleep deprivation, trauma, drugs, or bereavement following

Table 2. Concepts of psychosis risk research

Concept	Specifiers
Psychotic-like symptoms	Attenuated positive symptoms under psychotic threshold
Prodrome / prodromal phase	Retrospective concept of the symptomatic phase before onset of frank psychosis; phase of prodromal symptoms
Psychosis risk	Heightened risk for psychosis, either symptomatic risk (psychosis risk symptoms) or genetic (familial) risk
Basic symptoms	Early prodromal phase; subtle, self-experienced anomalities in cognition and perception
Psychosis risk syndromes: • clinical high-risk (CHR) • ultra high-risk (UHR)	Late prodromal phase, symptomatic approach; operationalizations of psychosis risk: • attenuated positive symptoms (APS) OR • brief limited intermittent psychotic symptoms (BLIPS) OR • lowered functioning in addition to schizotypal personality or familial risk to psychosis (GRD)
Genetic high-risk	Heightened risk for a psychosis in case of family history of psychosis

the loss of a loved one, anyone can have transitory psychotic experiences at some stage in their lives. Psychotic-like symptoms that are milder than in clinical psychotic disorders are common in the general population (Rössler et al., 2007; Schultze-Lutter, Michel, Ruhrmann, & Schimmelmann, 2014; van Os et al., 2009; Werbeloff et al., 2012), especially among children and adolescents (McGorry et al., 1995; Yung et al., 2009), the prevalence declining from childhood into adolescence (Brandizzi et al., 2014). In the Northern Finland 1986 birth cohort, psychotic-like experiences were commonly reported in the PROD-Screen questionnaire by 15–16-year-old adolescents from the population, with endorsement frequencies up to 35% (Mäki et al., 2014; Therman et al., 2011). In an Australian study, 8.4% of the adolescents in the population had hallucinations, as assessed with questionnaire and clinical evaluation of a written description of the experience (Scott et al., 2009). According to a meta-analysis, the median prevalence of psychotic(like) symptoms in 13–18-year-old adolescents in the community was 7.5% (Kelleher et al., 2012).

From adolescence to adulthood, the experiences get rarer (Schultze-Lutter et al., 2014), and the association between them and psychiatric disorders strengthens (Kelleher et al., 2012). Further, among adults there is a negative correlation between age and number of psychotic-like experiences reported (Rietdijk et al., 2014). The gender differences in reporting psychotic-like experiences have been controversial. Females have reported more psychotic-like experiences than males among adult psychiatric patients (Rietdijk et al., 2014) and adolescents in the community (Yung et al., 2009), whereas in a few other population studies, the prevalence was higher in males (Kelleher et al., 2012; van Os et al., 2009).

1.3 Psychosis risk and predictors of psychosis

Psychotic-like symptoms are usually transitory and disappear over time (Simon et al., 2009; van Os et al., 2009; Ziermans, Schothorst, Sprong, & van Engeland, 2011). Subclinical psychotic symptoms that are persistent (Dominguez, Wichers, Lieb, Wittchen, & van Os, 2011) or linked to negative symptoms and poor global functioning (Addington & Heinssen, 2012) are more likely to be predictive of later psychosis. In a meta-analysis of prospective population-based studies, psychotic-like experiences in

non-help-seeking healthy people were predictive of a 3.5 times higher risk of transition to psychosis, and there was a dose-response relation between severity and persistence of psychotic-like experiences and conversion to psychosis (Kaymaz et al., 2012).

Psychotic-like experiences are not only specifically linked to psychosis but are also common among non-psychotic disorders (Gaudiano & Zimmerman, 2013; Rietdijk et al., 2014). In a study conducted in Italy, practically all (98%) help-seeking adolescents reported at least one attenuated psychotic-like experience in the Prodromal Questionnaire (Brandizzi et al., 2014). In the population, psychotic-like symptoms are associated with an increased risk for the development of other mental disorders, help-seeking and psychiatric hospitalizations (Fisher et al., 2013; Murphy, Shevlin, Houston, & Adamson, 2012; Rössler et al., 2011; Werbeloff et al., 2012), even when they had been considered to be false-positive ratings (van Nierop et al., 2012). In other words, psychotic-like experiences are clinically relevant as they are associated with various forms of mental disorder and distress.

The unspecificity of the symptoms of the prodromal period makes it difficult to separate psychosis from depression in the early course of illness (Häfner, an der Heiden, & Maurer, 2008; Häfner et al., 2005; Simon, Ferrero, & Merlo, 2001). They both have the same kind of early prodromal phase and depressed mood is one of the most common first symptoms of the psychosis prodrome. Comorbidity of positive symptoms, with anxiety and depression, has been found among risk patients in several studies (Fusar-Poli, Nelson, Valmaggia, Yung, & McGuire, 2014; Salokangas et al., 2012). Psychotic-like symptoms co-occurring with anxiety and depression can be a sign of illness severity and poorer treatment prognosis (Krabbendam et al., 2005; Wigman et al., 2012). The psychosis prodrome can also reflect other diagnoses, indicated by findings of non-psychotic diagnoses being predictive of later schizophrenia in longitudinal cohort studies in Sweden and Denmark (Lewis, David, Malmberg, & Allebeck, 2000; Maibing et al., 2014).

Besides the symptomatic risk approach, the genetic risk approach emphasizes a heightened risk for psychosis in cases of a family history of psychosis (Cannon, 2005). One of the strongest single indicators of individual schizophrenia risk is a family history of schizophrenia (Sørensen et al., 2014). In a large Danish cohort study, the relative risk of schizophrenia for persons with a mother with schizophrenia was 9 compared with

persons with a mother without the disease (Mortensen et al., 1999). Relative risks for persons with an affected father or sibling were 7 (Mortensen et al., 1999). Another Danish cohort study reported a 27% risk (relative risk 32) for schizophrenia when a person had two affected parents and a 7% risk (relative risk 8) with one affected parent, compared to a 1% risk when neither parent had been treated for schizophrenia (Gottesman, Laursen, Bertelsen, & Mortensen, 2010). Other psychiatric disorders of first-degree relatives also increase the risk of schizophrenia (Mortensen, Pedersen, & Pedersen, 2010). A meta-analysis of twin studies estimated the heritability of schizophrenia at 81%, meaning that 81% of the variation in liability to schizophrenia is due to genetic factors (Sullivan, Kendler, & Neale, 2003).

Subtle neuroanatomical abnormalities have also been found to predict psychosis. They can be studied with various brain imaging techniques, most often with magnetic resonance imaging (MRI) of the brain (Cannon, 2005). Several neuroanatomical abnormalities are associated with both cognitive deficits and functional outcome in psychosis risk patients (Niendam, Jalbrzikowski, & Bearden, 2009). In a recent study, MRI-based predictors provided a 36% increase of prognostic certainty among high-risk persons recruited at two early recognition centers (Koutsouleris et al., 2014).

There are also certain developmental and environmental variables associated with vulnerability to develop subpsychotic symptoms or a psychotic disorder, such as family background and early experiences. Involvement in bullying and family adversity predicted psychotic-like symptoms in a population sample (Singh, Winsper, Wolke, & Bryson, 2014). In another study, being a victim of bullying was associated with psychotic-like symptoms in unaffected controls (Trotta et al., 2013). Comparing psychosis cases and controls, bullying victimization was reported twice as likely among those with psychosis (Trotta et al., 2013).

Further, an association between childhood trauma and psychosis has been suggested (Bebbington et al., 2004). The prevalence of history of trauma in a psychosis risk population is high (Bechdolf et al., 2010) and childhood sexual abuse has been found to be one contributing factor in conversion to psychosis (Thompson et al., 2014). Overall, according to a meta-analysis, childhood adversities seem to be associated with a high risk of psychosis (Varese et al., 2012) and the risk is higher with more violent traumatic experiences (Cutajar et al., 2010).

Table 3 presents risk factors of schizophrenia based on a meta-analysis by Clarke, Kelleher, Clancy, and Cannon (2012). However, the risk factors overlap and may interact with each other (e.g. the gene-environment interaction), making it challenging to assess the risks separately (Clarke et al., 2012).

The stress vulnerability model of psychosis emphasizes heightened genetic and/or developmental predisposing risk factors, and in addition, triggering events, such as stress or substance use, at the onset of the disease (Schizophrenia: Current Care Guidelines). In addition to this traditional model, Howes and Murray (2014) have recently suggested in their review that the excessively sensitive dopamine system in schizophrenia is associated with cognitive misinterpretations, such as paranoid thoughts and viewing internal stimuli as externally driven. Psychosis patients show increased sensitivity to stress and a greater dopamine release as a response to stress. Negative life events affect both the dopamine system and cognitive schema, maintaining a vicious cycle of dopamine dysfunction and stress (Howes & Murray, 2014).

Table 3. Risk factors of schizophrenia based on Clarke and colleagues (2012)

Risk factor	Specific risks
Obstetric complications	Complications of pregnancy, abnormal fetal growth and development, complications of delivery
Prenatal infection	Prenatal exposure to influenza, herpes, polio, rubella, or toxoplasmosis
Prenatal stress	Exposure to catastrophic events or loss of spouse or relative during pregnancy; unwanted pregnancy
Prenatal nutrition	Exposure to famine during pregnancy; deficiency in folate, vitamin D, iron, protein during pregnancy
Childhood trauma	Exposure to abuse or domestic violence; involvement in bullying
Cannabis use	Amount used and duration of use, strength of cannabis used
Epilepsy	Epilepsy; family history of epilepsy
Head injury	Traumatic brain injury
Encephalitis	Anti-NMDA receptor encephalitis
Genetic risk	Common low-risk and rare high-risk variants

1.3.1 Detecting psychosis risk

Various symptom criteria have been developed for detecting a psychosis risk state, with a high probability for later psychosis (Addington & Heinssen, 2012; Correll, Hauser, Auther, & Cornblatt, 2010; Olsen & Rosenbaum, 2006b), particularly schizophrenia (Fusar-Poli, Bechdolf et al., 2013). Table 4 summarizes the most widely used criteria in

assessing the risk phase of psychosis, although a recent review listed a total of 22 instruments for assessing psychosis risk (Daneault, Stip, & Refer-O-Scope Group, 2013). The evaluation tools are also being combined for more efficient identification of risk patients (Daneault et al., 2013). The different definitions and operationalizations of the risk criteria between research centers can make comparisons of the results difficult (Schultze-Lutter, Schimmelmann, Ruhrmann, & Michel, 2013), and the validity of the psychosis threshold in psychosis risk research has also been questioned (Yung, Nelson, Thompson, & Wood, 2010a).

Following a lively debate (Shrivastava et al., 2011; Yung, Nelson, Thompson, & Wood, 2010b; Yung & Nelson, 2013), Attenuated Psychosis Syndrome (APS) was defined in DSM-5 under "Other specified schizophrenia spectrum and other psychotic disorders". APS includes distressing and disabling attenuated hallucinations, delusions, or disorganized speech, with a frequency of at least once a week, not better explained by another disorder, with symptoms having begun or worsened during the last year (Tsuang et al., 2013). The onset/worsening criterion has been criticized, as the idea of the APS originally was to pay attention to the attenuated symptoms themselves, not

Table 4. The most widely used criteria in assessing psychosis risk

Approach	Diagnostic interview / rating system	Reference
Ultra High-Risk (UHR) state / At-Risk Mental States (ARMS)	CAARMS	Yung & McGorry, PACE clinic, Melbourne, Australia (Yung et al., 2005; Yung et al., 2006)
Prodromal syndromes, Clinical High-Risk (CHR)	SIPS/COPS	McGlashan & Miller, Prime clinic, New Haven, USA (Miller et al., 1999; Miller et al., 2003)
Basic symptoms	BSABS, SPI-A	Huber, Klosterkötter & Schultze-Lutter, Cologne Early Recognition project, Germany (Klosterkötter, Hellmich, Steinmeyer, & Schultze-Lutter, 2001; Schultze-Lutter et al., 2012)
Basic symptoms + high-risk symptoms	ERIraos	Häfner & Maurer, German Research Network on Schizophrenia (Häfner et al., 2004)
CHR− and CHR+	CASIS	Lencz & Cornblatt, RAP, New York, USA (Cornblatt et al., 2003; Lencz, Smith, Auther, Correll, & Cornblatt, 2004)
Attenuated Psychosis Syndrome (APS)	DSM-5	(Tsuang et al., 2013)

CAARMS, Comprehensive Assessment of At-Risk Mental States; PACE, Personal Assessment and Crisis Evaluation; SIPS, Structured Interview for Prodromal Syndromes; COPS, Criteria of Prodromal Syndromes; BSABS, Bonn Scale for the Assessment of Basic Symptoms; SPI-A, Schizophrenia Proneness Instrument, Adult version; ERIraos, Early Recognition Inventory; RAP, Recognition and Prevention; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th edition

only with respect to possible progression to psychosis. A criterion "not always having been present in its current severity" has been proposed instead, thus differentiating APS symptoms from trait-like symptoms (Schultze-Lutter et al., 2014). There is encouraging data on the reliability and validity of the APS, and currently it is stressed that multiple shifts from APS are possible; the outcomes ranging from psychosis to depression and other non-psychotic disorders, or spontaneous remission (Fusar-Poli, Carpenter, Woods, & McGlashan, 2014).

Three risk groups can be separated using the symptomatic risk approach: patients with Attenuated Psychosis Syndrome (APS) symptoms, patients who present symptoms at the psychotic level of intensity for a short time, less than a week (Brief Limited Intermittent Psychotic Symptoms, BLIPS), and patients with lowered functioning in addition to schizotypal personality or familial risk to psychosis (Genetic Risk and Deterioration syndrome, GRD). The biggest risk to psychosis appears to be associated with the BLIPS state, and this group is considered to represent the later phase of the prodrome, while individuals with GRD are considered to be at an early phase of the prodrome with a lower risk to transition compared with the other risk groups (Nelson, Yuen, & Yung, 2011).

1.3.1.1 CAARMS and SIPS interviews

Of the structured interviews developed for the identification of the above-mentioned psychosis risk states, the Comprehensive Assessment of At-Risk Mental States or CAARMS (Yung et al., 2006) was the pioneer. The criteria for the ultra high-risk (UHR) groups were operationalized in Australia using two interview methods, the Brief Psychiatric Rating Scale (BPRS) and the Comprehensive Assessment of Symptoms and History (CASH), to create a new instrument. Yung and McGorry also created a definition of frank psychosis used as the outcome measure: presence of clear threshold level psychotic symptoms occurring several times per week for at least a week. The risk criteria were then tested at the PACE clinic with an encouraging 12-month transition rate of over 40% (Yung et al., 2006). These risk criteria have been adopted and adapted internationally.

Besides the CAARMS, one of the most widely used interviews is the Structured Interview for Prodromal Syndromes, SIPS (Miller et al., 2003). The Clinical High-Risk

(CHR) approach, developed in the United States, is most often used in North America, while the UHR is used in Europe and Australia (Correll et al., 2010). However, the differences between the two high-risk approaches are scarce and both divide risk groups similarly (Miller et al., 2003). In the SIPS interview, psychotic-like and other risk symptoms are also mapped and criteria for prodromal syndromes are evaluated. For every symptom reported by the patient there are additional qualifiers to inquire into, including the degree of conviction, degree of distress, and degree to which the symptom interferes with daily life. Psychosis is defined by one or more of the positive symptoms scored at 6, a psychotic level of intensity, with a frequency of at least four days a week and duration of at least a month, or being a seriously disorganizing or dangerous symptom (Miller et al., 2003).

The prodromal risk syndrome detected by the SIPS has been suggested as a valid diagnostic entity, distinct from other psychiatric disorders (Woods et al., 2009). There is a definite need for care with persons fulfilling the risk criteria, as they present more severe symptoms and low functioning than people with established psychosis who already receive treatment (Woods et al., 2009). Psychosis risk status is also associated with long-term impairment in both social and role functioning (Addington et al., 2011) and disruptive symptoms, also found among those who do not develop psychosis during follow-up, in other words, false-positive risk individuals (Haroun, Dunn, Haroun, & Cadenhead, 2006).

Since the early years of psychosis risk research, a reduction in the psychosis transition rate has been noticed, with false positives lately outnumbering true positives (Yung et al., 2007; Yung et al., 2008). In a long-term follow-up, including studies between 1993 and 2006, it was found that risk patients recruited in the earlier years had a significantly higher transition rate than later cohorts (Nelson et al., 2013). This is consistent with significant transition rate reductions over time also found by other study groups (Fusar-Poli, Bonoldi et al., 2012; Simon et al., 2011). Possible reasons may be the better detection and treatment of risk patients (Cannon, Cornblatt, & McGorry, 2007; Simon et al., 2011). Since risk patients are identified early in the process, the transition can also take longer than previously. Hence, a long follow-up time of the risk individuals has been recommended by several researchers (Fusar-Poli, Bonoldi et al., 2012; Riecher-Rössler et al., 2009).

Still, with alternative methods to define the risk state, the psychosis risk state is associated with a 36% risk for psychosis during a three-year follow-up according to a meta-analysis (Fusar-Poli, Bonoldi et al., 2012). Similarly, in a review by Gee and Cannon (2011), it was approximated that about 1/3 of psychosis risk cases convert to psychosis, about 1/3 do not convert but remain symptomatic and functionally impaired, and about 1/3 recover symptomatically and functionally. According to their results, recovery from the risk status may be predicted by higher social functioning and lower rating of negative symptoms at baseline (Gee & Cannon, 2011).

1.3.1.2 Other approaches

Psychosis has also been predicted with basic symptoms, which are subtle, self-experienced anomalies (Klosterkötter et al., 2001). These include cognitive experiences (such as thought blockages), perceptual experiences (for example sensitivity to light), motor experiences (such as loss of automatic skills), and bodily experiences (such as electric sensations, pain, numbness, and sensations of abnormal heaviness or lightness).

Not only positive symptoms are important when predicting psychosis and concentrating solely on them may lead to false positives and false negatives, that is, missing some of the real at-risk patients (Simon & Umbricht, 2010). Various baseline variables besides positive symptoms have been found to be effective in predicting psychosis (Mees et al., 2011). For instance, impaired social and role functioning have been found to predict clinical outcome and psychosis in CHR patients (Cornblatt et al., 2012; Fusar-Poli et al., 2010).

Furthermore, negative symptoms have also been found to predict transition to psychosis along with or even better than positive, psychotic-like symptoms (Demjaha, Valmaggia, Stahl, Byrne, & McGuire, 2012; Mason et al., 2004; Piskulic et al., 2012; Schlosser et al., 2012; Velthorst et al., 2009). The RAP study group in New York differentiates CHR− and CHR+ risk groups, the former characterized by negative and non-specific symptoms, representing the early prodrome stage, and the latter characterized by attenuated positive symptoms, closer to established psychosis (Cornblatt et al., 2003; Cornblatt, 2002; Lencz et al., 2004). In this approach, attention is given to cognitive deficits, affective disturbances, social isolation, and school functioning, referred to as the CASIS cluster (Cornblatt et al., 2012).

In NAPLS, which is a large multisite longitudinal study in North America, five features were used as psychosis predictors: genetic risk with decrease in functioning, low social functioning, substance abuse, and the two positive symptom scales of unusual thought content and suspiciousness (Cannon et al., 2008). With these variables used in prediction algorithms, the positive predictive power was higher than with using the psychosis risk status alone. Some studies have used total SIPS symptom scores and highest single-item positive symptom scores to predict psychosis, instead of the CHR state (Lencz, Smith, Auther, Correll, & Cornblatt, 2003). In a long follow-up of risk patients, the best predictive value was accomplished by weighting suspiciousness, social anhedonia, and reduced cognitive speed (Riecher-Rössler et al., 2009). In another study, disorganized communication was the best predictor of transition to psychosis during a 2.5-year follow-up (DeVylder et al., 2014). Based on a large European multi-center study, using a two-step risk assessment, a risk group can first be assembled with the use of SIPS and basic symptoms, and then the risk of transition can be evaluated for each individual using the formula of a prediction model consisting of positive symptom, bizarre thinking, and sleep disturbance scores; schizotypia, highest level of functioning during the past year, and years of education (Ruhrmann et al., 2010). To summarize, along with the psychosis risk status, various combinations of symptoms have been found to be predictive of psychosis. Final consensus is still to be reached, as the significant predictors vary greatly across studies, with one possible cause being differences in participant recruitment.

1.3.1.3 Questionnaires

As interviews such as the SIPS are time consuming and require special training, questionnaires focusing on the early detection of psychoses have been developed (Daneault et al., 2013; Olsen & Rosenbaum, 2006a). The most widely used screening instruments are the PROD-screen (Heinimaa et al., 2003), the PRIME-screen (Miller, Chicchetti, Markovich, McGlashan, & Woods, 2004), the Youth Psychosis at-Risk Questionnaire (Kline et al., 2012; Ord, Myles-Worsley, Blailes, & Ngiralmau, 2004), and the Prodromal Questionnaire (Loewy, Bearden, Johnson, Raine, & Cannon, 2005). The questionnaires assessing psychotic-like experiences have been found to have good structural and criterion validity (Therman, 2014).

Screeners are validated against gold standard measures such as the SIPS or the CAARMS (Kline & Schiffman, 2014). Screening instruments are also used to estimate symptom prevalence and to screen for psychotic symptoms to select likely high-risk patients for targeted interviews. Using a two-step screening and interview procedure, CHR prevalence seems to be at 4–5% among unselected help-seeking adolescent and young adult samples (Kline & Schiffman, 2014). Comparing different recruitment strategies in psychosis risk studies, it has been found that screening reduces the number of false positives (Rietdijk et al., 2012); the increased likelihood ratio for psychosis among screen-positives has been estimated to range from 1.5 to 3.8 (Gale, Glue, & Gallagher, 2013).

1.3.1.4 Detecting psychosis risk in different samples

As the risk criteria have been developed for help-seeking individuals, psychosis risk detection in the general population does not seem advisable, the main problem being high rate of false positives. For example, in the general population-based Northern Finland Cohort 1986, the symptomatic risk group consisted of participants with functional impairment and attenuated positive symptoms reported in questionnaires. Only 5% fulfilled the psychosis risk criteria of the SIPS (Veijola et al., 2013).

It has been suggested that the choice of the study population has a significant impact on the ability of the CHR status to predict later psychosis (Yung et al., 2008). Current psychosis risk criteria have mostly been studied with highly selected patient samples in clinics specialized in treating patients with a psychosis risk (Fusar-Poli, Yung, McGorry, & van Os, 2014). These clinics use screening methods to enrich the patient samples, and referral to the clinic may be based on the referring clinician's impression of heightened psychosis risk (Addington et al., 2012; Broome et al., 2005; Cannon et al., 2008; Ruhrmann et al., 2010). As expected, the proportion of the patients who develop psychosis is high in such preselected high-risk research. Although psychosis risk defined with the current criteria predicts psychosis among those who seek help for psychosis risk symptoms (Loewy, Therman, Manninen, Huttunen, & Cannon, 2012), it is unclear if the results can be generalized to all psychiatric patients who seek help for various other symptoms (Fusar-Poli, Borgwardt et al., 2013).

Yung et al. (2006) found conversion to be low in a sample of help-seeking young people of which 41% were considered to be at risk for psychosis. Within 6 months, 10%

of the UHR patients became psychotic, the sensitivity and specificity of the risk status being 92% and 62%, respectively (Yung et al., 2006). Otherwise, the usability of the internationally used psychosis risk criteria and methods in an unselected sample of adolescent psychiatric patients has been largely unaddressed. It could be hypothesized that the CHR state also predicts psychosis among unselected psychiatric help-seekers, but with a weaker predictive value than in studies made in specialized clinics.

1.4 Other outcomes besides psychosis in psychosis risk

In psychosis risk studies, conversion to psychosis is not the only relevant outcome (Fusar-Poli, Borgwardt et al., 2013). It has even been envisioned that the high-risk state could more broadly be a general syndrome of early mental distress, with a heightened risk for a range of mental disorders; not just psychosis but, for instance, for mood disorders (Fusar-Poli, Yung et al., 2014). Soft entry for treatment of risk symptoms, regardless of diagnosis, and matching illness stage to intervention have also been proposed, and is referred to as the clinical staging model (Cross et al., 2014; McGorry & van Os, 2013; McGorry et al., 2014).

The major criticism of psychosis risk studies has been that a severe decline in functioning and negative symptoms can remain neglected if the positive symptoms of the person do not reach the limit of transition to psychosis (Broome & Fusar-Poli, 2012). Many studies have recently included functioning as an outcome of interest in itself (Cotter et al., 2014; Salokangas et al., 2013), reflecting the everyday ability to perform and quality of life better than a diagnosis number. In a review, baseline negative and disorganization symptoms predicted poor functioning during follow-up, whereas positive symptoms did not (Cotter et al., 2014).

1.5 Psychosis and cognition

1.5.1 Cognition and the assessment of cognition

Cognition means information processing, including various mental processes starting from perception of sensory input and attention to more complex processes of interpretation, memory, reasoning, problem solving, decision making, and language.

Within each class of cognitive functions, a division can be made between verbal and non-verbal functions (Lezak, Howieson, Bigler, & Tranel, 2012).

Cognitive assessment means evaluating these processes. The purposes of such assessment vary from aid in making a diagnosis, planning treatment and rehabilitation, and evaluating the effectiveness of treatment and level of functioning, to providing information for a legal matter, or doing research (Lezak et al., 2012). Taking the client's background, history and circumstances into consideration, the examiner uses observation, interview, and a selection of tests designed to examine cognitive functioning (Lezak et al., 2012). Neuropsychological tests are used to measure attention, reasoning, memory, speed, visuomotor functions, and visual and verbal functions, and the results are compared to population norms where the age of the person is taken into account. Cognition related to psychiatric disorders can be assessed using various instruments (Bakkour et al., 2014).

1.5.2 Cognitive deficits in psychosis

Psychotic disorders are associated with significant cognitive impairments to the extent that schizophrenia can be seen as a disorder of information processing (Hambrecht, Lammertink, Klosterkötter, Matuschek, & Pukrop, 2002). A recent review showed that compared to healthy controls, global cognitive impairment was already present in first-episode psychosis patients, the largest effect sizes being observed for verbal memory, executive function, and general IQ (Aas et al., 2014). Compared to schizophrenia, cognitive deficits appear to be slightly less severe but present in affective psychoses and schizoaffective disorder (Bora, Yucel, & Pantelis, 2009; Heinrichs, Ammari, McDermid Vaz, & Miles, 2008; Trotta, Murray, & MacCabe, 2014).

In the course of the psychotic illness, the cognitive deficits tend to stay preserved and not respond to changes in the clinical state or medication (Cornblatt, Obuchowski, Schnur, & O'Brien, 1997). Cognitive deficits can also be found among antipsychotic-naïve psychosis patients (Fatouros-Bergman, Cervenka, Flyckt, Edman, & Farde, 2014; Saykin et al., 1994).

1.5.3 Cognition and psychosis risk

Cognitive impairment is already present in the premorbid and prodromal phases of the psychotic illness (Bora et al., 2014; Erlenmeyer-Kimling et al., 2000; Fusar-Poli, Deste et al., 2012; Hambrecht et al., 2002; Klosterkötter, Schultze-Lutter, Gross, Huber, & Steinmeyer, 1997; Trotta et al., 2014), suggesting that at least some of these deficits are primary and not secondary to the psychotic symptoms. In a large cross-sectional study, the neurocognitive function of those children and adolescents endorsing psychotic symptoms was behind in chronological age compared with typically developing youths, with greater developmental delay among those with more significant symptoms (Gur et al., 2014).

A meta-analysis showed that individuals with subsequent schizophrenia had lower IQ at the age of 13 and impaired motor functioning at the age of 16, but there were no differences in their general academic and mathematical achievement compared to those who did not develop the disease (Dickson, Laurens, Cullen, & Hodgins, 2012).

The cognitive problems of psychosis risk patients are qualitatively similar but milder than in psychosis, performance being at a level intermediate to that displayed by first-episode psychosis and control samples (Keefe et al., 2006). Individuals who fulfill criteria for psychosis risk seem to have deficits especially in processing speed and verbal memory (Gschwandtner et al., 2003; Kelleher et al., 2013; Michel, Ruhrmann, Schimmelmann, Klosterkötter, & Schultze-Lutter, 2014; Seidman et al., 2010). However, neuropsychological impairments have not been been evident in all studies, such as in a non-help-seeking high-risk sample drawn from the Northern Finland 1986 birth cohort (Mukkala et al., 2011). Lower cognitive performance is associated with more severe depressive sympoms in psychosis risk patients, emphasizing the significance of the neurocognitive challenges (Ohmuro et al., 2015).

1.5.4 Predicting psychosis and functioning with cognition

In studies of cognition and later psychosis, various predictors of transition to psychosis have been found. Visuospatial performance has been found to predict psychosis among risk patients (Brewer et al., 2005; Wood et al., 2003) and among Finnish male conscripts (Tiihonen et al., 2005). Later conversion to psychosis has also been found to be associated with verbal deficits, especially weaker verbal memory (Fusar-Poli, Deste

et al., 2012; Valli, Tognin, Fusar-Poli, & Mechelli, 2012), although not all studies have found such an association (Tiihonen et al., 2005). More rapid conversion to psychosis was predicted by verbal memory deficits in one study (Seidman et al., 2010).

Many longitudinal studies have found childhood cognitive performance to predict psychosis. A higher risk of adult schizophrenia seems to be connected to lower verbal and non-verbal childhood cognitive functioning (Cannon et al., 2000; MacCabe, 2008). In several longitudinal studies, cognitive overall performance has been found to be weaker than average among those who later develop a psychotic disorder (Erlenmeyer-Kimling et al., 2000; Jones, Rodgers, Murray, & Marmot, 1994; Koenen et al., 2009) and among those risk patients who later convert to psychosis compared to those do not convert (Keefe et al., 2006; Niemi, Suvisaari, Tuulio-Henriksson, & Lönnqvist, 2003). Cognitive decline seems to be relatively specific to schizophrenia, as compared to, for instance, individuals with persistent depression (Meier et al., 2014). Further, high intellectual capacity has been found to be a protective factor against psychosis (Davidson et al., 1999). Interestingly, high cognitive performance has been associated with a heightened risk for bipolar disorder and mania (Koenen et al., 2009; MacCabe et al., 2013; Tiihonen et al., 2005), and in the Northern Finland 1966 birth cohort study, superior school performance was also a risk factor for schizophrenia in males (Isohanni et al., 2006).

In a longitudinal cohort study, a decline in cognitive performance in adolescence and young adulthood, particularly in verbal ability, was associated with an increased risk for psychosis in adulthood (MacCabe et al., 2013). In another study, adult psychotic symptoms were best explained by an IQ decline during early childhood (Kremen et al., 1998). Progressive cognitive impairments (Woodberry et al., 2013) or lack of cognitive improvement in follow-up testing (Keefe et al., 2006) have also been found to accompany risk for psychosis. Among psychosis risk patients, recently emerging or intensifying cognitive deficits were to some extent predictive of transition (Hambrecht et al., 2002). In a meta-analysis among high-risk participants, later transition to psychosis was associated with more severe cognitive deficits in all domains except sustained attention (Bora et al., 2014). These results imply that cognitive dysfunction may be a likely neurobiological marker of psychosis and specifically, a core feature of schizophrenia vulnerability (Cannon et al., 2000; McGorry et al., 2014). However, it has

been noted in several studies that cognitive impairment by itself has a limited capacity to actually predict the outcome of high-risk patients (Bora et al., 2014; Valli et al., 2012).

Irrespective of psychosis transition, cognitive deficits affect everyday functioning. When functional capacity has been used as an alternative outcome, cognitive deficits have predicted impaired functioning during follow-up among psychosis risk patients (Cotter et al., 2014). Lin et al. (2011) showed larger and broader differences in cognitive performance when comparing psychosis risk individuals with poor or good functional outcome, than when comparing those with and without transition to psychosis. Lowered performance on logical memory at baseline was the strongest predictor of poor functional outcome (Lin et al., 2011). In another study, baseline cognitive functioning was not associated with psychosocial outcome but the course of neurocognitive change during follow-up differentiated patients with good and poor functional outcomes (Niendam et al., 2007).

1.5.5 Cognition and symptoms domains

Across the psychosis continuum, different psychosis symptoms can be associated with different cognitive abnormalities. Cognitive dysfunction seems to have little or no association with positive symptoms among schizophrenia patients (Cameron et al., 2002; Lucas et al., 2004; O'Leary et al., 2000; Rhinewine et al., 2005; Strauss, Buchanan, & Hale, 1993; Van der Does, Dingemans, Linszen, Nugter, & Scholte, 1993) or psychosis risk patients (Niendam et al., 2006; Ohmuro et al., 2015), although some studies have discovered that positive symptoms may be linked to slower information processing speed in the general population (Simons, Jacobs, Jolles, van Os, & Krabbendam, 2007) or poorer verbal fluency in psychosis patients (Verdoux et al., 1999). In one study conducted among schizophrenia patients, positive symptoms were associated with memory and attention impairment (Talreja, Shah, & Kataria, 2013). One possible explanation for this may be symptoms occurring during the testing, leading to an inability to concentrate (Strauss, 2011).

Compared to positive symptoms, negative symptoms seem to have a stronger connection to cognitive deficits (Bilder et al., 2000; Ventura, Hellemann, Thames, Koellner, & Nuechterlein, 2009). The association between negative symptoms and both

processing speed (Cameron et al., 2002; Cuesta & Peralta, 1995; O'Leary et al., 2000; Rhinewine et al., 2005) and verbal performance (Dominguez, Viechtbauer, Simons, van Os, & Krabbendam, 2009) is well established among patients with psychosis and the latter has even been discovered in the general population (Simons et al., 2007), leading to speculation that the symptoms and cognition may be expressions of the same phenomenon, possibly a cerebral connectivity impairment (Dominguez et al., 2009). However, not all studies have found any connection between negative symptoms and cognitive deficits among psychosis patients (Cornblatt et al., 1997; Joyce et al., 2002; Lucas et al., 2004; Verdoux et al., 1999) or psychosis risk patients (Niendam et al., 2006).

The association between cognitive performance and psychosis risk symptoms needs further research. Specifically, the issue of cognitive deficits among adolescents referred to general psychiatric care, comprising non-selected help-seeking adolescents with and without psychosis risk symptoms, is an interesting area of research. By finding which areas of cognitive performance are linked to more severe psychosis risk symptoms, clinical attention can be targeted accordingly in adolescent psychiatric care.

1.6 Intentional self-harm

Intentional self-harm refers to for example poisoning or injury of bodily tissues. A dichotomous separation can be made between non-suicidal and suicidal self-injury, although the intent of self-harm is not always clear (Hasley et al., 2008). In a study among adolescents presenting with self-harm, cutting was usually coded as non-suicidal self-harm, and suicidal self-harm appeared to start at an older age, with poisoning as a common mean (Ougrin et al., 2012). Among suicide attempters admitted to medical wards in Norway, adolescents with intent to die had more serious suicide attempts and reported more severe depressive and other symptoms compared to those without such intention (Grøholt, Ekeberg, & Haldorsen, 2000). The authors also stated, however, that the need for help in the group with no intent to die may be underestimated (Grøholt et al., 2000).

Suicidality can be seen as a continuum ranging in severity from recurrent thoughts of death and suicidal ideation to suicide plans, attempts, and finally completed suicide. In a

large adolescent population sample it was found that one third of suicide ideators will make a suicide plan, about 60% of those with a plan will attempt suicide, and that these transitions between stages of suicidality usually happen during the first year of onset of ideation (Nock et al., 2013). In another study, suicidal ideation at age 15 years was associated with long-term emotional and behavioral difficulties and was a risk marker of suicide attempts at age 18 years (Reinherz et al., 1995).

While adolescents with any behavior within the suicidal spectrum are at a high risk of making a suicide attempt, it has to be noted that suicidal ideation, having thoughts about ending one's life, is common in this age group (Pearce & Martin, 1994). In the United States, 12% of adolescents between 13–18 years of age reported lifetime suicidal ideation (Nock et al., 2013). Among Australian school students the lifetime prevalence of suicidal ideation was 31% and current prevalence 16% (Delfabbro, Winefield, & Winefield, 2013). Girls had more suicidal ideation than boys, and other significant predictors included substance use and psychological distress (Delfabbro et al., 2013).

According to a review of self-harm in adolescents in the population, around 10% reported having self-harmed (Hawton, Saunders, & O'Connor, 2012). Psychiatric disorders, alcohol abuse, and smoking were associated with suicidality (Hawton et al., 2012). Lifetime suicide attempts were reported by 4% of adolescents in the United States (Nock et al., 2013).

Self-harm is a major health concern particularly among adolescents with psychiatric disorders. In a Finnish longitudinal study of adolescent psychiatric outpatients with major depressive disorder, 22% had a history of suicide attempt at baseline, 14% attempted suicide during 1-year follow-up, and 12% during follow-up from 1 to 8 years (Tuisku et al., 2014). In a sample of adolescent psychiatric inpatients aged 12–17 years, 13% of the boys and 26% of the girls had attempted suicide during their lifetime (Tikkanen et al., 2009).

1.6.1 Suicide

Suicide rates in Finland are high (Official Statistics of Finland (OSF)), and although rates of adult suicides have declined, rates of adolescent suicides have not, with the prevalence remaining high compared to other European countries (Safety Investigation Authority, 2014). Suicide is the most common cause of death among 15–19-year-old

boys in Finland. During the years 2009–2011, there were 51 suicides committed by children and adolescents under the age of 18 years in the whole country, the youngest to commit suicide being 13 years old (Safety Investigation Authority, 2014). A third of the adolescents who had committed suicide were under the influence of alcohol and the most common way to commit suicide was to jump under a train.

Three-quarters of adolescent suicides during the years 2009–2011 were committed by boys (Safety Investigation Authority, 2014). The male-to-female ratio was 3.6:1 in a study investigating all 901 suicides committed by persons under the age of 18 years during the years 1969–2008 (Lahti, Räsänen, Riala, Keränen, & Hakko, 2011). The study group noticed that whereas the rate of male adolescent suicides in Finland has decreased since 1990, the rate of female adolescent suicides has increased, and that violent, more lethal suicide methods have become more common among females (Lahti et al., 2011).

The so-called gender paradox means that while suicidal ideation and suicide attempts are more common among females than males, of the completed suicides the majority are committed by males (Delfabbro et al., 2013; Hawton et al., 2012; Qin, Agerbo, Westergard-Nielsen, Eriksson, & Mortensen, 2000; Schrijvers, Bollen, & Sabbe, 2012). Not all studies have found these differences, however, such as Suokas and colleagues in a study of suicide attempts among young Finnish adults (2011). Possible reasons for the gender paradox are various (Schrijvers et al., 2012). For instance there can be cultural factors in reporting suicidality, men use more lethal means in suicide attempts than women, and women seek help more often than men. Women also tend to rethink more often than men and men's suicidal process is shorter than women's.

A stress-diathesis model of the risk factors of suicide has been suggested (Hawton & van Heeringen, 2009). The predisposing factors can be related to family environment, hopelessness, cognitive styles, or genetic risk, while the triggering factor can be, for instance, a life event or a mood disorder (Hawton & van Heeringen, 2009). In the Northern Finland 1966 birth cohort study, daily smoking at aged 14, a single parent-family, and a family with more than five children were risk factors for suicidal behavior in the general population (Alaräisänen, 2010).

1.6.2 Positive symptoms and self-harm

Psychotic disorders are associated with a high lifetime risk for suicide (Li, Page, Martin, & Taylor, 2011; Pompili et al., 2011; Suokas et al., 2010). According to a systematic review and meta-analysis, among mental disorders, schizophrenia is associated with the highest relative risk for suicide in men and the third highest in women after substance and affective disorders (Li et al., 2011). For example, in the Northern Finland 1966 birth cohort followed prospectively until 39 years of age, 7% of schizophrenia patients committed suicide, the majority of the suicides taking place during the first three years after onset of the illness (Alaräisänen, 2010). In first-episode psychosis and other hospitalizations, the suicide rate is highest soon after discharge (Pompili et al., 2011; Qin et al., 2000).

Contradicting results have been reported concerning the association between positive symptom severity in psychosis and suicidality. In a review of schizophrenia and suicide, reduced suicide risk was found to be associated with hallucinations (Hawton, Sutton, Haw, Sinclair, & Deeks, 2005). In a study made in emergency psychiatric services, pseudohallucinations (experienced as coming from within the head) were associated with increased suicidality compared to lower suicidality among those with auditory hallucinations (experienced as coming from outside the head) or no hallucinations (Penagaluri, Walker & El-Mallakh, 2010). In a large sample of schizophrenia patients, delusional and hallucination severity and distress were associated with self-harm (Haddock, Eisner, Davies, Coupe, & Barrowclough, 2013). Further, in a sample of schizophrenia and schizoaffective disorder patients, command auditory hallucinations for suicide were somewhat associated with suicide attempts (Harkavy-Friedman et al., 2003). In a sample of both psychotic and psychosis risk patients assessed with a momentary assessment technique of mobile phone-based measures several times a day for seven days, psychotic symptoms and especially paranoia seemed to trigger self-injurious thoughts the next day (Palmier-Claus et al., 2014). Nevertheless, a meta-analysis of first-episode psychotic patients suggested that positive symptoms are unrelated to deliberate self-harm (Challis, Nielssen, Harris, & Large, 2013).

Many of the suicide risk factors among psychosis patients, such as depression, hopelessness, suspiciousness, social isolation, and substance use, may also be risk factors for suicidality among psychosis risk patients (Hutton, Bowe, Parker, & Ford,

2011). Self-harm may also serve as a maladaptive coping mechanism from stress and negative emotions caused by the confusing positive symptoms (Palmier-Claus et al., 2014). On the other hand, risk patients may not yet have been exposed to some of the factors that may be linked to increased suicide risk in people with established psychosis, such as stigma, social exclusion, and trauma of being admitted to hospital (Hutton et al., 2011). Nevertheless, suicidal ideation has been reported to be high among patients at high risk for psychosis (DeVylder et al., 2012; Granö et al., 2013; Hutton et al., 2011; Taylor, Hutton, & Wood, 2015).

In a study conducted among school children aged 13 to 15 years with psychiatric disorder, psychotic-like symptoms were associated with 5-fold increased odds of suicidal behavior (Kelleher et al., 2012). In young people aged 12–16 referred to mental health services, psychotic experiences were strong markers of risk for suicide plans and attempts, highlighting that a report of psychotic experiences in a young person with psychopathology should alert clinicians to the risk for suicidal behavior (Kelleher et al., 2014).

Further, among adult psychiatric outpatients, attenuated psychotic symptoms were associated with more severe suicidal ideation and suicide attempts (Gaudiano & Zimmerman, 2013). In a longitudinal study, childhood psychotic symptoms at age 11 predicted suicide attempts by age 38 (Fisher et al., 2013). Retrospectively viewed, a large number of schizophrenia patients were suicidal in the prodromal phase and patients with suicidal behavior experienced a greater number of positive prodromal symptoms (Andriopoulos, Ellul, Skokou, & Beratis, 2011). Suicide attempts were associated with an earlier onset of prodromal symptoms and frank psychosis (Andriopoulos et al., 2011).

Psychotic-like experiences have been found to be associated with suicidal ideation and behavior even in a general adolescent population (Jang et al., 2014; Kelleher et al., 2012). Among Japanese school children, especially hearing voices and a feeling of being followed increased the risk of suicidal feelings and deliberate self-harm (Nishida et al., 2010). In adult populations, delusional-like experiences (Saha et al., 2011) and psychotic-like symptoms (Suokas et al., 2011) have also been found to be markers of vulnerability to suicide.

The association between suicidality and psychotic-like symptoms in a general adolescent psychiatric sample is an area needing further research, with the aim of more efficient detection of the risks of self-destructive behavior among young psychiatric patients.

1.7 Adolescence and adolescent psychiatric care

Adolescense is a distinct life stage with specific developmental tasks and challenges, beginning with biological changes related to puberty and lasting roughly from the age of 12 to 22 (Marttunen & Kaltiala-Heino, 2014). The developmental tasks of adolescence include forming an adult identity and separation from the childhood home. Development is intense in adolescence in many areas; there are physical as well as psychosocial changes, and adolescents have to cope with major changes in their bodies as well as psychological changes (Turk, Graham, & Verhulst, 2007). The young person has a growing need for independence and belonging to a peer group, but at the same time, still needs a lot of support from the family. Interest in intimate releationships also gradually increases during adolescence. Areas of school work, hobbies, and future plans are all psychosocial factors influencing the life of the adolescent person. With maturation in brain structure and activity, there are also major cognitive changes during the adolescent stage, involving development in abstract thinking and reasoning and information processing skills (Paus, Keshavan, & Giedd, 2008).

In health care, adolescent patients are a specific age group. Answering to a special need of this group between childhood and adulthood, adolescent medicine and adolescent psychiatry are specific areas of expertise in Finland. In the Act on the Status and Rights of Patients, rapid entry to mental health treatment is required for adolescent patients, conceptualized as those between 13 and 23 years of age. Both inpatient and outpatient units for treating adolescent psychiatric patients are available, the emphasis of the care being on outpatient clinics and involving the young person’s social network in the treatment process.

Support of the school health care (e.g., school nurse and psychologist) promotes the mental health of students in the adolescents’ daily environment. Trouble at school and disconnection from social relationships are warning signs of mental health problems,

and staying in school is important for the well-being of the young person (Kaltiala-Heino, Ranta, & Frojd, 2010). Prompt intervention in school bullying also promotes mental health among all those in the school environment (Kaltiala-Heino et al., 2010).

The prevalence of psychiatric disorders in adolescence doubles when compared to childhood, being 15–25% across epidemiological studies (Marttunen & Kaltiala-Heino, 2014). Many mental disorders still affecting life in adulthood start in adolescence (Paus et al., 2008). These include anxiety and mood disorders, eating disorders, and substance-related problems. Specifically, depression and social phobia are common disorders among adolescents, and often occur in a comorbid fashion, as found for example in the prospective Adolescent Mental Health Cohort study in Finland among 15-year-olds from the population (Väänänen et al., 2011).

The incidence of psychotic disorders, particularly schizophrenia, also peaks in adolescence and early adulthood (Pedersen et al., 2014). Early recognition of symptoms and effective interventions may have the greatest impact on the long-term outcome in this age group. This is why psychosis risk symptoms are often studied among adolescents.

1.8 Motivation of the current study

Earlier results concerning psychotic-like symptoms cannot be generalized to all adolescents seeking help in a general psychiatric setting. In addition, the validity of the psychosis risk assessment methods translated into Finnish have not yet been studied. The Helsinki Prodromal Study was therefore designed to shed light on psychotic-like symptoms and clinical high-risk status in an unselected clinical adolescent population. Detecting subclinical positive symptoms, it is often possible to identify an individual as having a high risk of psychosis before the onset of the first episode of the disease. However, the predictiveness of these psychotic-like symptoms depends on the population, and many earlier high-risk studies have been conducted in preselected samples with subjects referred to the services because of a suspicion of psychosis risk.

In this study, a questionnaire was used to screen for psychosis risk symptoms, and the predictive validity of the screen was studied. Another goal was to identify adolescents with CHR from patients who sought help from adolescent psychiatric

clinics, and to investigate whether CHR status is as predictive of psychotic disorder in these services as it is in services specialized for the treatment of psychosis prodrome.

Performance on specific tests of neurocognition may prove to be early risk predictors for psychosis. The association between positive symptoms and a decline in cognitive performance can already be seen before the onset of psychosis among persons with an increased risk for psychosis. Including measures of cognitive functioning could therefore potentially improve the discriminability of the current psychosis risk detection criteria. At the moment, the psychosis risk concept does not include cognitive deterioration, although some efforts have been made to add cognition to prodromal criteria: the importance of negative symptoms and cognitive deficits in schizophrenia risk is stressed both in the CASIS approach (Cornblatt et al., 2003) and in the schizotaxia concept (Tsuang, Stone, & Faraone, 2000; Tsuang, Stone, Tarbox, & Faraone, 2002). In identifying cognitive markers of psychosis risk, the association between different psychosis risk symptoms and cognitive performance can be recognized and addressed.

Further, while psychotic disorders are linked to high rates of suicides and self-harm, it has also been noticed that there is an association between subclinical psychotic symptoms and suicidal behavior. This association has not been fully studied among adolescents referred to general psychiatric care, and it is addressed in this study.

2 **Aims of the study**

The main aim of this study project was to systematically map the psychotic-like symptoms of the young patients seeking psychiatric care for the first time. The study also wanted to find out how usable the internationally used psychosis risk criteria and methods were in general adolescent psychiatric care.

The specific aims of the study were:

I) To investigate the association of cognitive performance and clinical high-risk status and psychosis risk symptoms among adolescents in psychiatric care (Study I)

II) To find out whether it is possible to predict psychosis and hospitalizations for psychotic disorder and any mental disorder with the SIPS interview in general adolescent psychiatric care (Study II)

III) To explore the structural validity of the Prodromal Questionnaire and its ability to identify hospitalizations for psychotic disorder and any mental disorder in the following years (Study III)

IV) To investigate the association of suicidality and self-harm with psychotic-like symptoms and clinical high-risk status in a general adolescent psychiatric sample (Study IV)

3 Methods

3.1 Participants

The Helsinki Prodromal Study is a prospective study of psychosis risk conducted among adolescent psychiatric patients. The study cohort included all consecutive new patients aged 15–18 years who started their treatment in any public adolescent psychiatric outpatient and inpatient clinic or ward in Helsinki, Finland. Data were collected in two phases, 1.1.2003–15.3.2004 and 14.2.2007–31.12.2008, altogether constituting a three-year period. The only exclusion criterion for the study was previous psychiatric treatment within the preceding two years. At their first or second visit to the treating unit, the adolescents were asked to fill in the Finnish version of the Prodromal Questionnaire (PQ, Loewy et al., 2005), a self-report measure for screening psychosis risk symptoms.

Based on the amount of patients visiting the units who were suitable for the study, the return rate of completed questionnaires was estimated at 75%. In total, 819 questionnaires were returned. Some units also collected PQ data between the study periods but they were not used for screening. Excluding those with psychosis at the time the PQ was completed, or PQ dated between the two study periods, 683 adolescents were screened with the PQ; 90.0% were outpatients and 10.0% inpatients. 66.5% of the adolescents with PQ data were female and the average age was 16.5 years.

As suggested by Loewy (2012), 18 or more positive symptom items of the PQ were used as the cut-off score for an in-depth assessment. The screen-positive adolescents numbered 145 (21.2%), with 538 screen-negative. All screen-positives were invited to the assessment as they were at psychosis risk according to the screening, and 114 agreed to participate. In addition, a random sample of 87 screen-negatives was invited as a clinical control group, and 60 participated. Altogether, 174 participants went through the whole research protocol. Of the interviewed sample, 89.7% were outpatients and the mean age was 16.6 years (16.5 for the girls and 17.0 for the boys). 77.0% were girls. Of the girls, 93.3% were outpatients, and of the boys, 77.5%. See Figure 1 for the participant flow diagram of the study.

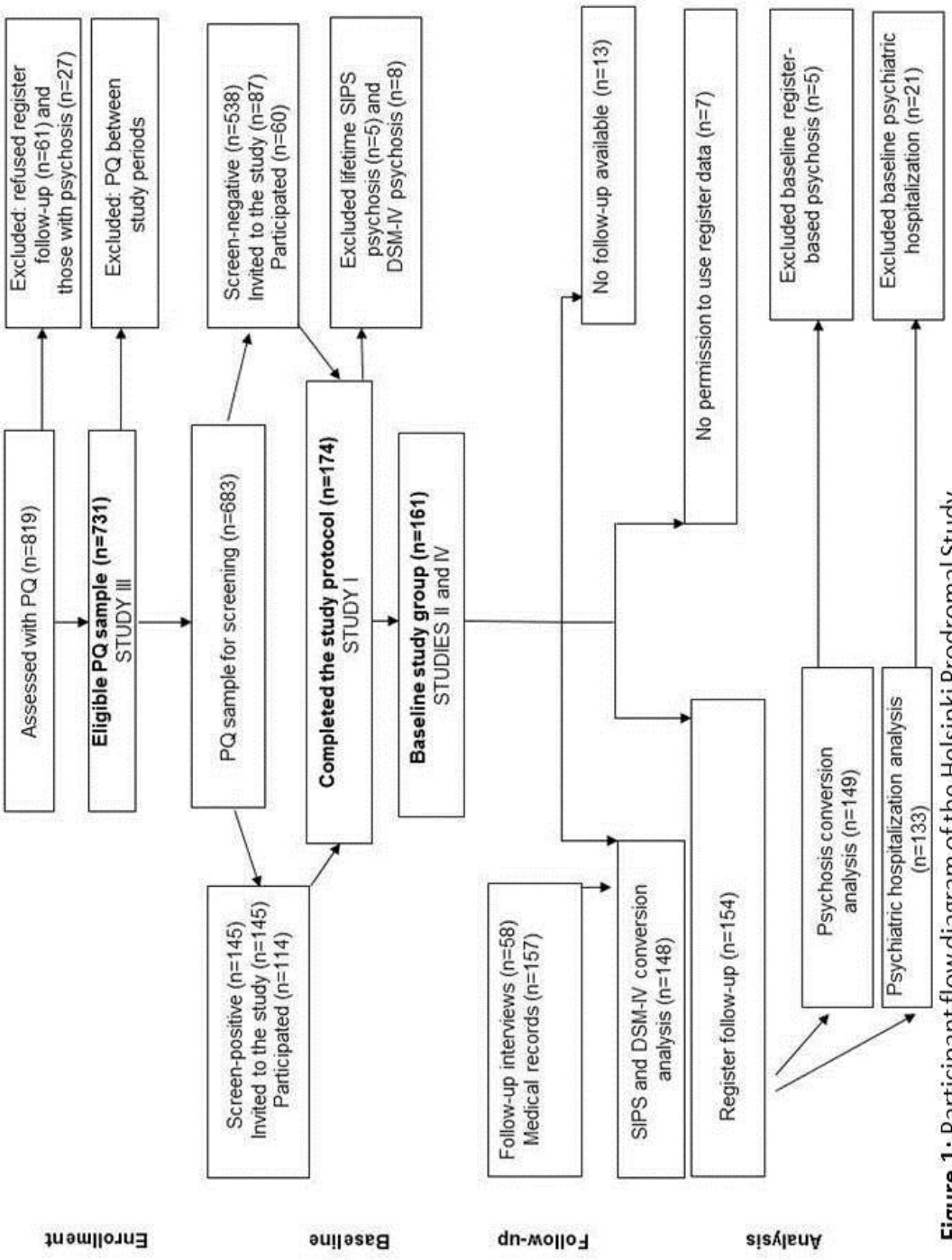

Figure 1: Participant flow diagram of the Helsinki Prodromal Study

In Study I, concerning psychotic-like symptoms and neurocognitive performance, the number of patient participants was 174, of whom 134 (77.0%) were female. In addition, 72 volunteers from a local school acted as a cognitive performance control group.

In Study II, with the topic of predicting psychosis with the SIPS, and Study IV, suicidality and psychotic-like symptoms, 13 participants were excluded from the interviewed sample because of lifetime SIPS or DSM-IV psychosis already at baseline (diagnoses not available at the time of Study I). The number of participants was thus 161 in these two studies. Of them, 127 (78.9%) were female.

In Study III, the sample size for the analyses was 731 adolescents with PQ data who had not refused use of register data or had not been diagnosed with psychosis during or before the same treatment episode as they completed the PQ. Of this study group, 496 (67.9%) were female.

3.2 Screening

The Prodromal Questionnaire (PQ, Loewy et al., 2005) was designed because of the specific training and time required for the administration of psychosis risk interviews. The PQ, one of the most widely used psychosis risk questionnaires, is a self-report measure for screening putative prodromal symptoms. It has 92 items in a Yes/No format, grouped into positive, negative, disorganized, and general symptoms. Some of the items have been adapted from the SIPS interview probe questions. The PQ only takes approximately 10–20 minutes to complete and it is easy to score. As a limitation, all items are keyed so that a Yes response indicates a symptom, possibly resulting in response bias among participants.

The PQ was translated into Finnish in 2001 and was available for this study. A cut-off point of 18 or more positive symptoms was used, representing the top 20% of the distribution in the pilot phase of the Helsinki Prodromal Study. This cut-off score has been recommended by Loewy and colleagues (2012) reporting the results of the Helsinki Prodromal Study, with the PQ predicting CHR status with a sensitivity of 82% and specificity of 49%. Another widely used cut-off score is 14 or more positive symptoms, with 71% sensitivity and 81% specificity (Loewy et al., 2005).

A shorter version of 16 items has also been developed, with a sensitivity of 87% and specificity of 87% regarding psychosis risk or clinical psychosis in a help-seeking population (Ising et al., 2012).

3.3 Cognitive testing

The evaluations were conducted during two meetings that took place at the psychiatric unit where the participant was treated. The patients were administered a large, standardized neurocognitive test battery, which was designed to measure functions relevant to the neuropsychology of psychosis (Cannon et al., 2000; Stone, Gabrieli, Stebbins, & Sullivan, 1998). It consisted of subtests from internationally used standardized test batteries, such as WAIS-R, WAIS-III, WMS-R, and WMS-III, and of individual tests such as CVLT, Verbal Fluency Test, Trail Making Test and Dual Task that are commonly used in psychosis research. These tests assessed verbal and non-verbal reasoning, verbal and visual memory, working memory, visuomotor speed, executive functioning, and attention. See Table 5 for description of the neuropsychological variables.

Table 5. Description of neuropsychological variables used in the Helsinki Prodromal Study

Ability	Test
Simple reaction time	Computerized task; response time in milliseconds to randomly timed visual stimulus, as described in Therman (2009)
Choice reaction time	Computerized task; response time in milliseconds to correctly chosen response matching one of two stimuli, as described in Therman (2009)
Verbal fluency	Number of words generated in 1 minute in response to two letters (s, k) and one category (animals). Verbal fluency subtest of the Multilingual Aphasia Examination (Benton & Hamsher, 1976)
Visuomotor speed	Connection of numbers in ascending sequence, seconds to completion; Trail Making Test subtest A (TMT-A) of Halstead-Reitan battery (Reitan & Wolfson, 1985) with correction of errors Connection of letters in ascending sequence, seconds to completion; novel task named Trail Making Test subtest C, analogous to TMT-A
Task switching	Alternating connection of letters and numbers in ascending sequence, seconds to completion; Trail Making Test subtest B of Halstead-Reitan battery (Reitan & Wolfson, 1985)
Processing speed	Digit Symbol subtest of Wechsler Adult Intelligence Scale – revised (WAIS-R, Wechsler, 1981)
Visuoconstructive ability	Block design subtest of WAIS-R

Table 5. Description of neuropsychological variables used in the Helsinki Prodromal Study, continued

Ability	Test
Verbal learning, immediate recall	Words correctly recalled on five initial trials of California Verbal Learning Test I (CVLT I, Delis, Kramer, Kaplan, & Ober, 1987)
Verbal learning, long delay	Words correctly recalled in Long delay recall condition of CVLT I
Verbal learning, recognition discriminability	Discriminability index *d'* in Recognition condition of CVLT I**,** calculated according to the corrected formula described in the CVLT II manual (Delis, Kramer, Kaplan, & Ober, 2000)
Verbal episodic memory	First story from Logical memory learning subtest of Wechsler Memory Scale – revised (WMS-R, Wechsler, 1987)
Visual episodic memory	Visual reproduction subtest of WMS-R
Digit span	Backward and forward scores on Digit span subtest of WMS-R
Visual span	Backward and forward scores on Visual span subtest of Wechsler Memory Scale – third edition (WMS-III, Wechsler, 1997b)
General verbal ability	Abbreviated version of the Vocabulary subtest of WAIS-R
Verbal abstraction ability	Similarities subtest of WAIS-R
Non-verbal reasoning	Matrix reasoning subtest of Wechsler Adult Intelligence Scale – third edition (WAIS-III, Wechsler, 1997a)
Counting backwards	Numbers correctly counted within 60 seconds minus errors, separate subtest condition of Bourdon-Wiersma dual task (Vilkki, Virtanen, Surma-Aho, & Servo, 1996)
Dot cancellation	Dots correctly cancelled within 60 seconds minus errors, separate subtest condition of Bourdon-Wiersma dual task (Vilkki et al., 1996)
Dual task numbers	Standardized residual of Counting backwards performance in dual task condition of Bourdon-Wiersma dual task, based on individual performance in Counting backwards and expected score distribution calculated from control group scores (Vilkki et al., 1996)
Dual task dots	Standardized residual of Dot cancellation performance in dual task condition of Bourdon-Wiersma dual task, based on individual performance in Dot cancellation and expected score distribution calculated from control group scores (Vilkki et al., 1996)
Fine motor control	Purdue pegboard subtasks: number of pins inserted with dominant hand in 30 seconds (dominant hand); number of pins inserted with nondominant hand in 30 seconds (nondominant hand); number of pin pairs inserted with both hands in 30 seconds (pairs); number of parts assembled in 60 seconds (assembly). Tasks administered as detailed in the test manual (Purdue pegboard model #32020 instructions and normative data, 1999)
Speeded motor control	Spatial tapping scores; novel motor test. Number of correct taps (minus errors) into large (easy) or small (difficult) circles in 10 seconds, keeping the best score of two trials

3.4 Interviews

The participants were administered the Structured Interview for Prodromal Syndromes (SIPS, Miller et al., 2003), version 3.0. The SIPS addresses positive (psychotic-like), negative, disorganization, and general symptoms, and they are rated on 19 SOPS scales (Scale of Prodromal Symptoms), see Table 6.

Based on the SIPS interview, the adolescents were divided into psychotic, clinical high-risk (CHR), and non-CHR groups. Three different kinds of risk states are rated with the method: Attenuated Positive Symptom (APS) syndrome, Brief Limited Intermittent Psychotic Symptoms (BLIPS), and Genetic Risk and Deterioration syndrome (GRD).

The most common risk state is the APS. The criteria for it include a rating of 3–5 on any of the positive symptoms, with a frequency of at least once per week in the past month, and with the symptom having begun or worsened during the last year. In Table 7, an example of symptom severity assessment can be seen, with symptoms rated as 3, 4, or 5 representing possible psychosis risk symptoms. For every symptom, anchors are provided to give guidelines for the rater as examples of the symptoms.

Table 6. SIPS symptom scales

Positive symptoms	Negative symptoms	Disorganization symptoms	General symptoms
P1 Unusual thought content and delusional ideas	N1 Social anhedonia or withdrawal	D1 Odd behavior or appearance	G1 Sleep disturbance
P2 Suspiciousness and persecutory ideas	N2 Avolition	D2 Bizarre thinking	G2 Dysphoric mood
P3 Grandiosity	N3 Decreased expression of emotions	D3 Trouble with focus and attention	G3 Motor disturbances
P4 Perceptual abnormalities and hallucinations	N4 Decreased experience of emotions and self	D4 Personal hygiene / social attentiveness	G4 Impaired tolerance to normal stress
P5 Disorganized communication	N5 Decreased ideational richness		
	N6 Deterioration in role functioning		

Table 7. Severity scale of SIPS P4 Perceptual abnormalities and hallucinations. From SIPS 3.1 (McGlashan, Woods, Rosen, Hoffman, & Davidson, 2001)

Score	Symptom description and anchors
0 Absent	
1 Questionably present	Minor, but noticeable changes in perceptual sensitivity (e.g. heightened, dulled, distorted)
2 Mild	Unexpected, unformed perceptual changes that are puzzling but are not considered to be significant
3 Moderate	Repeated, unformed images (shadows, trails, sounds, etc.), illusions, or persistent perceptual distortions that may be worrisome or experienced as unusual
4 Moderately severe	Recurrent illusions or momentary hallucinations that are recognized as not real yet can be frightening or captivating, and may affect behavior slightly. Not sure of source of experiences
5 Severe but not psychotic	Hallucinations that occasionally affect thinking or behavior, experienced as possibly external to self or real. Skepticism can be induced
6 Psychotic	Recurrent hallucinations perceived as real and distinct from the person's thoughts. Clearly influence thinking, feeling, and/or behavior. Skepticism cannot be induced

The adolescents were also interviewed with the Structured Clinical Interview for the DSM-IV, Clinician Version (SCID, First, Spitzer, Gibbon, & Williams, 1996). The diagnostic assessments were completed at the National Institute for Health and Welfare. The research staff was trained to high standards of reliability on the SCID by Professor Jaana Suvisaari, MD. In 2002, they completed a three-day SIPS training workshop with Rachel Loewy and excellent inter-rater agreement (kappa=.97 for CHR status) was achieved. Most of the SIPS ratings were assigned by team consensus using a videotaped interview, blind to the screening status of the participant.

3.5 Other clinical data

As a part of the study protocol, the participants also completed the Beck Depression Inventory II (BDI-II, Beck, Steer, & Brown, 1996), the Beck Anxiety Inventory (BAI, Beck, Epstein, Brown, & Steer, 1988), and the Beck Hopelessness Scale (BHS, Beck, Weissman, Lester, & Trexler, 1974).

Complete medical records were available for 170 of the 174 participants (97.7%). DSM-IV Axis I diagnoses were made (n=169) using all available data including medical records, and six diagnosis clusters were formed: 1) psychotic disorder, 2) non-psychotic mood disorder, 3) anxiety disorder, 4) eating disorder, 5) substance-related

disorder, and 6) disorder usually first diagnosed in infancy, childhood, or adolescence. The baseline diagnosis was made blind to follow-up information.

Global Functioning: Social and Global Functioning: Role (Cornblatt et al., 2007) were scored for the adolescents based on interview data and medical records. In addition, based on all available data, each participant was rated for having been bullied at school (Yes/No). Similarly, family background, i.e. if they had always lived at home with both parents without any child welfare intervention was scored as Yes/No. This variable was formed in this manner because of the difficulty of forming groups with the variety of different family situations of the adolescents. Age of onset of the first psychiatric symptom and age of treatment onset were scored. Aggression was assessed with two variables, “threatened with violence” and “has been physically violent towards others”, both scored using all available information and scored as Yes/No.

Suicidality at baseline was assessed in two ways: *Current suicidality* data was gathered from BDI-II item 9, and was available for 151 (93.8%) participants. Filling out the BDI, patients were asked to rate their agreement on a four-point scale according to how they have felt lately. The options were: 0) "I don’t have any thoughts of killing myself” (no ideation), 1) "I have thoughts of killing myself but I would not carry them out" (mild ideation), 2) "I would like to kill myself" (moderate ideation), and 3) "I would kill myself if I had the chance" (severe ideation). *Lifetime suicidality* was assessed based on all available data including patient files and interview data concerning the patient’s whole life before baseline, i.e. the day of the SIPS interview. Adolescents were classified on a scale of 0–3, the options being: 0) not suicidal, 1) thinking of death or having death wishes, 2) suicidal thoughts, 3) self-harm (intention to die not assessed).

3.6 Follow-up

Follow up information was gathered from three sources. Firstly, there was a one-year follow-up assessment including SCID and SIPS interviews for a proportion (n=61) of the participants. At the first phase of the study (2003–2004), only CHR patients were invited to follow-up if they had given permission to contact them (n=26). However, SIPS was not part of the procedure and was done with only three patients. At the second

phase of the study (2007–2008), all participants who had given permission to be contacted (n=88) were invited and SIPS data was gathered from 58. Secondly, follow-up information from the medical records of the participants was collected for the total duration of their psychiatric treatment.

DSM-IV Axis I diagnoses were made for follow-up (1 year or less if the treatment had ended before that, n=156) using all available data, medical records and follow-up assessment. Conversion to psychosis was assessed separately as defined by SIPS and by DSM-IV. As defined by SIPS, conversion to psychosis meant a positive symptom rated six with either a frequency of ≥1h/day four days/week during the past month or being a seriously disorganizing or dangerous symptom. A scoring of six is given for symptoms where there is delusional conviction with no doubt at least intermittently, or there are recurrent hallucinations perceived as real and distinct from own thoughts, affecting functioning.

Thirdly, register data was used from the Finnish Hospital Discharge Register HILMO (Care Register for Health Care) of the adolescents' treatments, medications, and diagnoses until the end of 2011, giving a register follow-up time of 1025–3249 days (2.8–8.9); mean 2058 days (5.6 years), standard deviation 823 days. The diagnostic system used in the register is the International Classification of Diseases, 10th edition (ICD-10). Outcome variables derived from the register were *psychotic disorders* (ICD-10 codes F20, F22–F29, F30.2, F31.2, F31.5, F32.3, or F33.3), *psychiatric hospital treatments* (a stay at a psychiatric hospital, or any hospital stay with a primary or secondary psychiatric diagnosis, ICD-10 codes F00–F99, X60–X85, or Y87.0), and *intentional self-harm* (ICD-10 codes X69–X84, Y87, Y87.0, Z91.5, or Z72.8). Permission to register follow-up was available for 154 participants. The register includes both public and private hospitals, and it has an excellent accuracy in detecting psychoses (Perälä et al., 2007). Data of completed suicides were also gathered from the Causes of death statistics (Statistics Finland).

3.7 Data analysis

In Study I, the data were analyzed using the IBM SPSS 15.0 statistical package. Adolescents were divided into those who fulfilled the clinical high-risk (CHR) criteria and those who did not (non-CHR) based on the SIPS interview. Missing neuropsychological test scores (3.5% of all scores) were replaced with expectation-maximization algorithm estimates based on all available scores. All test results were transformed so that higher scores on the subtest indicated better performance. Maximum likelihood factor analyses were conducted for the SIPS symptoms and the neurocognitive tests with Varimax rotation, and standardized factor scores were extracted. Mann-Whitney test and Cohen's *d* were used to examine associations between variables and to compare the cognitive performance between groups. Spearman correlations between symptom and cognitive factors were calculated for the groups separately.

In Study II, gender, participation rate, and screening outcome of the participants were taken into account using weights in all analyses. R 3.0.1 (R Core Team, 2013) and its packages *survival* (Therneau, 2013) and *survey* (Lumley, 2012) were therefore used. *Screening weight* for the screen-positives was 1, as they were all selected to the study. For the screen-negatives, screening weight was returned PQ's (538) / selected cases (86) = 6.256. *Attrition weights* were calculated for the screen-positives by dividing their total number (145) by the number interviewed (114) = 1.272; and in the same way for the screen-negatives: 538/60=8.967 (Pickles, Dunn, & Vázquez-Barquero, 1995). *Total weights* were calculated by screening weights X attrition weights. They were then scaled into *analysis weights* so that their sum was = N. All weights were calculated separately for males and females.

SIPS and DSM-IV psychosis conversion at the one-year follow-up was assessed for the 148 participants with adequate follow-up data. Sensitivity, specificity, positive predictive value, and negative predictive value of the CHR status were calculated. Additionally, an adjusted Wald test of association (Thomas & Rao, 1987) was used. Register follow-up analyses were conducted with Cox regression survival analysis. From the interviewed 174 adolescents, those with baseline SIPS (n=5) or DSM-IV psychosis (n=8) were excluded from these analyses, as were those without permission to register follow-up (n=7), leaving a group of 154 participants. The hazard ratios of

hospitalization for psychosis and any psychiatric disorder were calculated without those with such hospitalization at baseline, leading to groups of 149 (hospitalization for psychosis) and 133 participants (hospitalization for any psychiatric disorder). CHR status and symptom factors derived from the SIPS were used as predictors of hospital treatment. In all the regression analyses, gender was included as stratum.

In Study III, MPLUS version 7.11 (Muthén & Muthén, 2012) was used. Exploratory factor analysis of the 731 response sets was conducted with the WLSMV algorithm and default parameters. Symptom factor scores and PQ Total and Positive subscale sum scores were used as predictors in Cox proportional hazards models of any psychiatric hospitalization and hospitalization with a psychosis diagnosis. Predictors were first entered individually, and those significant at the p=.01 level were included in a forward-stepping Cox model. Before survival analyses, all factor scores and PQ sum scores were normalized. Survival analyses were conducted with gender as a stratum. One-year predictive values for psychosis of the previously (Loewy, Johnson, & Cannon, 2007) suggested cut-offs for the positive symptoms subscale (at least 14 symptoms) and total sum score (at least 36 symptoms) were also assessed.

In Study IV, the data were analyzed using the IBM SPSS Statistics 21. The group comparisons for categorical variables were calculated using the Pearson's $\chi 2$ and Fisher's Exact test. The Mann-Whitney *U* test was used for comparisons in ordinal or non-normally distributed continuous variables. Symptom factors derived from the SIPS were used in addition to SIPS subscale scores and CHR status. Because the BDI-II item 9 was used to assess current suicidality, the BDI total score was calculated without this item in Study IV. Spearman correlations were calculated to investigate associations between continuous or ordinal variables. Analyses of intentional self-harm during follow-up were calculated among females only, as all patients with intentional self-harm resulting in hospitalization were female. A Cox regression analysis was performed to predict hospital-treated self-harm during follow-up among the 121 girls with permission to use register data. The significant variables in bivariate analyses were entered into the model and forward selection model was used.

All statistical tests across the studies were two-tailed. P-values <.05 and hazard ratios (HR) with 95% confidence intervals (95% CI) were considered statistically significant.

3.8 Attrition analysis

Participants were enrolled to the study by the Prodromal Questionnaire which was instructed to be given to every new adolescent patient in the clinics and wards. Approximately 75% of the eligible patients filled in the questionnaire and 819 questionnaires were returned (Figure 1). Of those, participants with psychosis diagnosis at baseline were excluded, as were those refusing register follow-up. Those who had filled in the questionnaire between the study periods when screening for interview was not done were also excluded.

Of the group of 683 adolescents eligible for screening (of whom 66.3% were girls), all screen-positives were invited to the interview (124 girls and 21 boys). 78.6% participated (99 girls and 15 boys). Of the screen-negatives, 50 girls and 36 boys were invited and 69.0% of them participated in the study, of whom 35 were girls and 25 boys.

3.9 Ethical considerations

The adolescents gave written informed consent to participate in the study. As they were aged at least 15 years, consent from their parents was not needed but the parents received an information letter of the study. Inclusion in the study was voluntary and it did not affect the treatment the adolescents had in the psychiatric unit.

If the adolescent gave permission, the SIPS interview was videotaped to improve the accuracy and reliability of the scoring of the interview. The tapes were destroyed after the scoring or after 2 years at the latest.

The participants were asked if their medical records could be used in the study and if they provided register follow-up permission. They were also asked if they could be contacted for inquiry about follow-up study phases in 6 or 12 months. A small compensation was paid to the adolescents participating in the follow-up studies.

The study protocol was reviewed and approved by the institutional review boards of the National Public Health Institute (the National Institute for Health and Welfare since 2009) and the Ethics Committee for gynaecology and obstetrics, pediatrics and psychiatry of the Hospital District of Helsinki and Uusimaa. The study was carried out in accordance with the Declaration of Helsinki.

4 Results

4.1 Characteristics of the study group

731 adolescents completed the PQ and 174 were interviewed. At the baseline interview, 54 of the 161 non-psychotic adolescents (33.5%) met criteria for at least one of the SIPS prodromal syndromes (CHR group) and 107 (66.5%) were considered non-CHR. Of the girls, 34.6% fulfilled the CHR criteria, and of the boys, 29.4%. Almost all fulfilling the CHR criteria met criteria for Attenuated Positive Prodromal Syndrome (APS, 51 adolescents), one for Genetic Risk and Deterioration syndrome (GRD), and two for both risk syndromes. The characteristics of the CHR and non-CHR groups can be seen in Table 8. Of the PQ screen-positive, 40.2% met the psychosis risk criteria, whereas 20.4% of the PQ screen-negative met the risk criteria. See Table 9 for a cross-tabulation of screening results and interview assessed psychosis risk.

4.2 Cognitive performance and psychotic-like symptoms (Study I)

A three-factor model of the neurocognitive test scores was formed and the factors identified as processing speed, verbal performance, and visuospatial performance (Table 10). As the only gender difference, girls' performance was better in the processing speed factor compared to boys (Mann-Whitney U=2357, p=.013; and Cohen's d=0.5).

Symptom levels of CHR and non-CHR groups can be seen in Table 11. SIPS symptoms formed three factors that were interpreted as general, positive, and negative symptoms (Table 12). Compared to boys, girls had higher general symptoms scores (Mann-Whitney U=1764, p=.001; and Cohen's d=0.6). There were no other gender differences.

At the test level, there were tasks from all three cognitive factors—processing speed, verbal performance, and visuospatial performance—in which non-CHR adolescents performed better than the CHR group. CHR status was associated with impaired visuospatial task performance (Mann-Whitney U=2641, p=.009; and Cohen's d=0.5). However, both positive and negative symptoms were associated with lower levels of neurocognitive functioning among adolescents in psychiatric treatment, regardless of CHR status. Among patients in the CHR group, negative symptoms correlated

negatively with processing speed (r=−.31, p<.05) and verbal performance (r=−.37, p<.01). Among non-CHR patients, there were negative correlations between negative symptoms and verbal performance (r=−.19, p<.05), and positive symptoms and visuospatial performance (r=−.24, p<.05).

Table 8. Demographic and clinical data for the interviewed participants at baseline, those with psychosis excluded

	Total, n=161	CHR, n=54 (33.5%)	non-CHR, n=107 (66.5%)
Female	127 (78.9%)	44 (81.5%)	83 (77.6%)
Age (years); range, mean (sd)	15.2-18.3, 16.6 (.85)	15.2-18.1, 16.7 (.85)	15.2-18.3, 16.6 (.85)
Age of symptom onset (years); range, mean (sd)	7-18, 14.0 (2.3)	7-17, 13.8 (2.5)	7-18, 14.1 (2.3)
Age of treatment onset (years); range, mean (sd)	7-18, 15.2 (2.1)	7-18, 14.7 (2.5)	7-18, 15.4 (1.9)
Inpatient (at the time of the PQ)	11 (6.8%)	4 (7.4%)	7 (6.5%)
PQ screen-positive (18+ positive symptom items)	107 (66.5%)	43 (79.6%)	64 (59.8%)
PQ screen-negative, clinical control group	54 (33.5%)	11 (20.4%)	43 (40.2%)
Born in Finland and has Finnish parents	144 (89.4%)	48 (88.9%)	96 (89.7%)
Family structure: two-parent family without any child welfare intervention	66 (41.0%)	18 (33.3%)	48 (44.9%)
First-degree relative with psychosis or bipolar disorder	10 (6.2%)	7 (13.0%)	3 (2.8%)
Second-degree relative with psychosis or bipolar disorder	13 (8.1%)	6 (11.1%)	7 (6.5%)
Substance abuse of a first-degree relative	51 (31.7%)	22 (40.7%)	29 (27.1%)
Bullied at school	62 (38.5%)	22 (40.7%)	40 (37.4%)
Global Functioning: Social, range, mean (sd)	3-9, 7.0 (1.2)	3-9, 6.6 (1.3)	4-9, 7.2 (1.0)
Global Functioning: Role, range, mean (sd)	3-9, 6.5 (1.4)	4-8, 6.1 (1.3)	3-9, 6.7 (1.4)
BDI-II (item 9 excluded), range, mean (sd)	0-57, 22.5 (13.1)	6-57, 28.3 (13.2)	0-52, 19.7 (12.2)
BAI, range, mean (sd)	0-45, 16.3 (9.4)	2-41, 19.2 (9.5)	0-45, 15.0 (9.1)
BHS, range, mean (sd)	0-20, 9.7 (5.4)	1-20, 11.4 (5.6)	0-20, 8.9 (5.1)
No psychiatric medication	94 (58.4%)	23 (42.6%)	71 (66.4%)
Diagnosis clusters at baseline [a]			
Any non-psychotic mood disorder diagnosis	122 (75.8%)	47 (87.0%)	75 (70.1%)
Any anxiety disorder diagnosis	51 (31.7%)	20 (37.0%)	31 (29.0%)
Any eating disorder diagnosis	15 (9.3%)	1 (1.9%)	14 (13.1%)
Any substance-related diagnosis	23 (14.3%)	8 (14.8%)	15 (14.0%)
Any disorder usually first diagnosed in infancy, childhood, or adolescence	22 (13.7%)	6 (11.1%)	16 (15.0%)

[a] The same person can have diagnoses from multiple clusters so the numbers exceed 100%.

Table 9. PQ screening and CHR status among adolescents

		SIPS psychosis risk status				Total	
		CHR		non-CHR			
		n	%	n	%	n	%
PQ screening result	Screen-negative	11	20.4	43	40.2	54	33.5
	Screen-positive	43	79.6	64	59.8	107	66.5
Total		54		107		161	

Table 10. Three-dimensional structure of cognitive performance. Maximum Likelihood model with Varimax rotation

Factors	Test variables with factor loading >0.4
Processing speed	Purdue pegboard nondominant hand
	Digit symbol
	Trail Making A
	Purdue pegboard pairs
	Purdue pegboard dominant hand
	Spatial tapping (easy)
	Purdue pegboard assembly
	Spatial tapping (difficult)
	Dot cancellation
	Trail Making C
	Trail Making B
	Simple reaction time
	Choice reaction time
	Fluency K
	Counting backwards
Verbal performance	Logical memory, immediate recall
	Logical memory, delayed recall
	Verbal learning, immediate recall
	Vocabulary
	Verbal learning, long delay
	Similarities
	Verbal learning, recognition discriminability
Visuospatial performance	Block design
	Visual reproduction, delayed recall
	Matrix reasoning
	Visual reproduction, immediate recall
	Similarities

Table 11. SIPS baseline symptom scores of the 161 non-psychotic participants

	Total, n=161		Male, n=34		Female, n=127		CHR, n=54		non-CHR, n=107	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
P1 Unusual thought content and delusional ideas	1.9	1.5	1.4	1.4	2.0	1.5	3.1	1.2	1.3	1.2
P2 Suspiciousness and persecutory ideas	1.7	1.2	1.3	1.4	1.9	1.2	2.7	1.2	1.3	1.0
P3 Grandiosity	0.5	0.9	0.5	1.0	0.6	0.9	1.0	1.2	0.3	0.7
P4 Perceptual abnormalities and hallucinations	1.9	1.6	1.4	1.5	2.0	1.7	3.2	1.5	1.2	1.3
P5 Disorganized communication	0.7	0.8	0.8	1.2	0.7	0.7	1.0	1.0	0.5	0.7
N1 Social anhedonia or withdrawal	1.6	1.4	1.8	1.8	1.5	1.3	2.3	1.6	1.3	1.2
N2 Avolition	2.4	1.4	2.0	1.6	2.5	1.4	3.1	1.4	2.1	1.3
N3 Decreased expression of emotions	1.2	1.3	1.3	1.7	1.2	1.1	1.7	1.4	1.0	1.1
N4 Decreased experience of emotions and self	1.9	1.5	1.3	1.2	2.0	1.6	2.7	1.5	1.4	1.4
N5 Decreased ideational richness	0.6	0.9	0.9	1.0	0.6	0.9	1.0	1.1	0.5	0.8
N6 Deterioration in role functioning	2.8	1.5	2.6	1.7	2.8	1.5	3.5	1.5	2.4	1.4
D1 Odd behavior or appearance	1.3	1.2	1.5	1.3	1.3	1.1	1.7	1.1	1.2	1.1
D2 Bizarre thinking	0.8	1.0	0.6	0.9	0.8	1.1	1.3	1.1	0.5	0.9
D3 Trouble with focus and attention	1.9	1.0	1.6	0.9	2.0	1.0	2.5	0.8	1.7	1.0
D4 Personal hygiene / social attentiveness	0.5	0.9	0.7	1.0	0.5	0.9	0.7	1.1	0.4	0.8
G1 Sleep disturbance	2.4	1.4	2.1	1.3	2.5	1.4	2.9	1.5	2.1	1.3
G2 Dysphoric mood	3.7	1.5	3.0	1.7	3.8	1.3	4.4	1.0	3.3	1.5
G3 Motor disturbances	0.5	0.8	0.4	0.9	0.5	0.8	0.7	0.9	0.3	0.7
G4 Impaired tolerance to normal stress	2.4	1.7	1.9	1.7	2.6	1.6	3.1	1.6	2.1	1.6

Table 12. Three-dimensional structure of SIPS symptoms. Maximum Likelihood model with Varimax rotation

Factors	SIPS symptoms with factor loading >0.4
General symptoms	G2 Dysphoric mood
	N2 Avolition
	G1 Sleep disturbance
	G4 Impaired tolerance to normal stress
	N6 Deterioration in role functioning
	D3 Trouble with focus and attention
	N4 Decreased experience of emotions and self
	P2 Suspiciousness and persecutory ideas
Positive symptoms	P1 Unusual thought content and delusional ideas
	D2 Bizarre thinking
	P4 Perceptual abnormalities and hallucinations
	P2 Suspiciousness and persecutory ideas
	D1 Odd behavior or appearance
	N4 Decreased experience of emotions and self
	P3 Grandiosity
	P5 Disorganized communication
Negative symptoms	N1 Social anhedonia or withdrawal
	N3 Decreased expression of emotions
	D1 Odd behavior or appearance
	D4 Personal hygiene / social attentiveness
	N5 Decreased ideational richness
	G3 Motor disturbances

4.3 Predicting psychosis with the SIPS interview (Study II)

At baseline, the participants were mostly diagnosed with non-psychotic mood disorders (76%), anxiety disorders (32%), and substance-related disorders (14%). Mood disorders were more prevalent in the CHR group than in the non-CHR group (Fisher's exact test, p=.020), and eating disorders more prevalent in the non-CHR group compared to the CHR group (Fisher's exact test, p=.021).

Mood disorders were especially prevalent among girls (81% of girls, 56% of boys). Anxiety disorders were the second largest diagnosis group for both genders (32% of girls, 29% of boys). For girls, the next diagnosis clusters were substance-related disorders (13%) and eating disorders (11%), and for boys, disorders usually first diagnosed in infancy, childhood, or adolescence (such as conduct disorder, ADHD, Asperger's syndrome; 32%) and substance-related disorders (18%).

During the 12-month follow-up, three (2.0%) of the 148 subjects developed psychosis as defined by SIPS (Figure 2). Of 51 CHR individuals with follow-up data, two (3.9%) converted. One of the 97 non-CHR individuals (1.0%) transitioned as well. CHR status did not predict psychosis, [$F(1,147)=.004$, $p=.949$]. The weighted sensitivity of the CHR status was 23% and specificity 76%.

Using the DSM-IV criteria for psychosis instead, five adolescents (3.4%) developed a psychotic disorder over follow-up. Three of the converters belonged to the CHR group so conversion took place for 5.9% of the CHR group. CHR status did not predict transition to DSM-IV psychosis either [$F(1,147)=.05$, $p=.831$]. The sensitivity and specificity of the risk status were 28% and 76%, respectively.

During the maximum of 9 years of register follow-up, seven admissions for psychosis emerged (four female, three male). Four persons (8.5%) of the CHR group and three (2.9%) of the non-CHR group were hospitalized for psychosis. The sensitivity and specificity of the CHR status were 40% and 80%, respectively. CHR status did not predict psychotic disorders in a regression model [*HR*=2.2, $p=.284$, *95%CI*=.5–9.0]. The Kaplan-Meier survival curves by risk status are shown in Figure 3. In a separate Cox analysis, psychotic disorders were predicted by SIPS positive symptom factor [*HR*=2.2, $p=.016$, *95%CI*=1.2–4.2] and not by general and negative symptoms.

During the follow-up time, there were 26 psychiatric hospitalization events. In a Cox regression model, they were predicted by CHR status [*HR*=3.1, $p=.005$, *95%CI* =1.4–6.9], positive symptoms [*HR*=1.9, $p=.001$, *95%CI*=1.3–2.9], and general symptoms [*HR*=2.2, $p=.001$, *95%CI*=1.4–3.6].

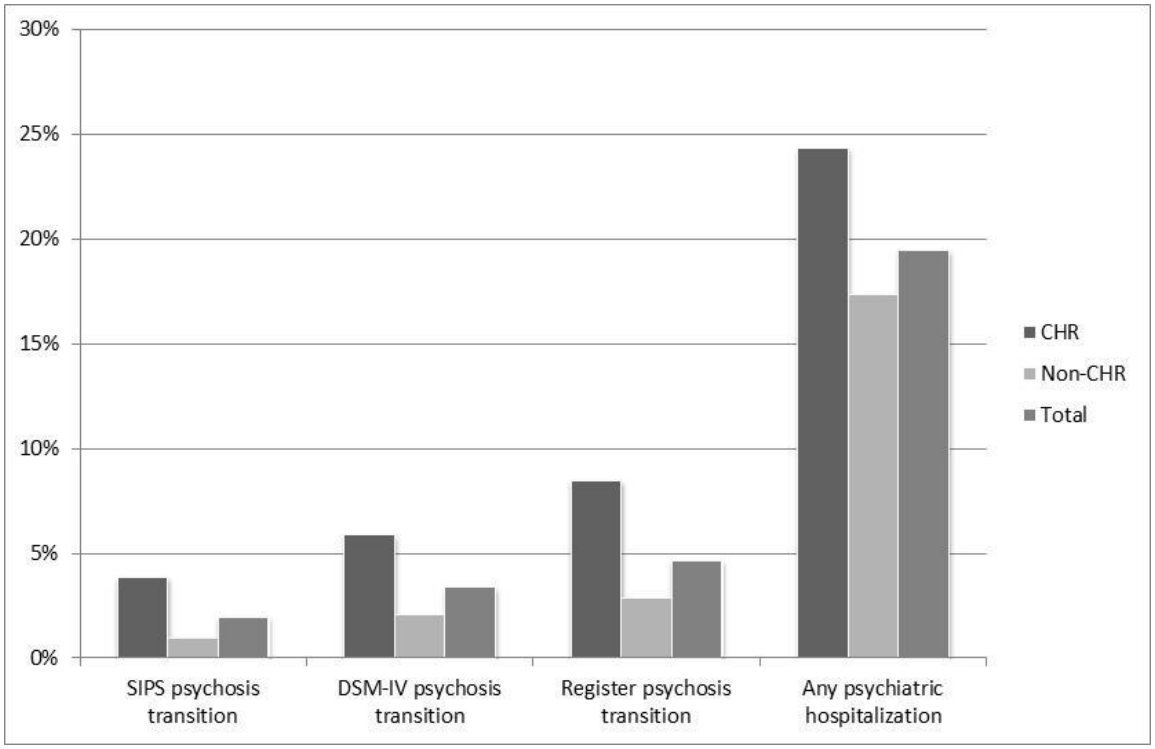

Figure 2. Follow-up data of participants by group

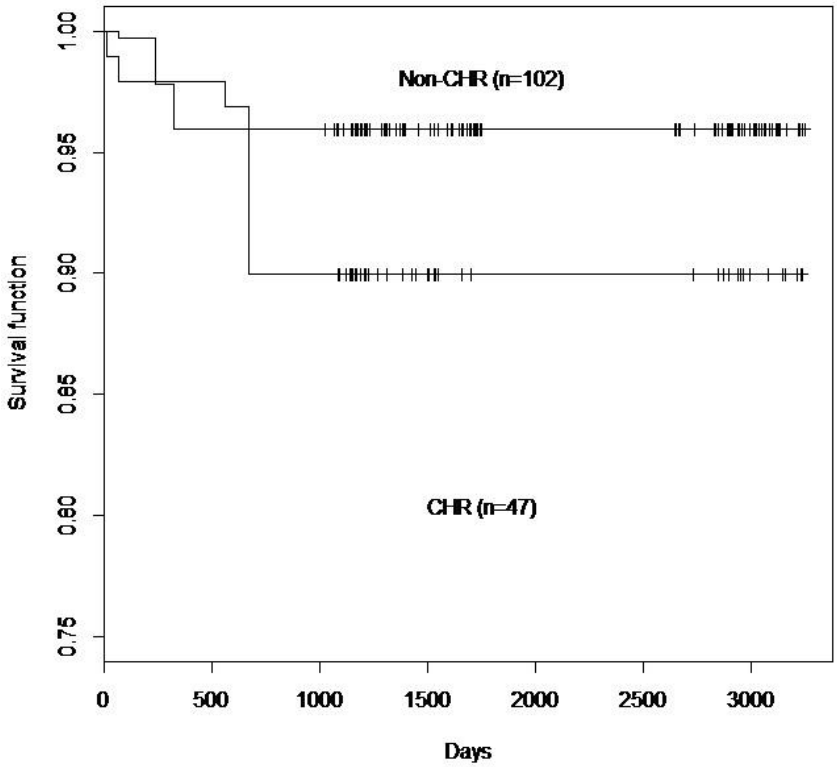

Figure 3. Cumulative survival distribution function modeling time to psychosis by CHR status

4.4 Predicting psychosis with the PQ questionnaire (Study III)

The Prodromal Questionnaire had high endorsement rates. The endorsement level of the individual items was lowest for items 84 and 79 ["*I have seen things that other people can't see or don't seem to*" and "*I have seen unusual things like flashes, flames, blinding light, or geometric figures*"] at 7.4% and 8.2%, and highest for items 28 and 8 ["*I have been feeling unhappy or depressed lately*" and "*I often seem to live through events exactly as they happened before (déjà vu)*"] at 67.9% and 67.1%.

A nine-factor latent structure was identified, the factors interpreted as role functioning, delusional ideation, hallucinations, oddness, social avoidance, magical thinking, dysphoria, depersonalization, and anhedonia (Table 13). Of the 731 adolescent psychiatric patients who completed the Prodromal Questionnaire at the clinic or ward at the beginning of their treatment, 120 were hospitalized during the register follow-up time, 41 with a psychosis diagnosis.

Of the factors, depersonalization predicted later hospitalization with a psychosis diagnosis (*HR*=1.6, *p*=.005, *95%CI*=1.2–2.2). Examples of the PQ items loading on the depersonalization factor are "*I have felt like I am at a distance from myself, as if I am outside my own body or that a part of my body did not belong to me*" and "*I have felt like I am looking at myself as in a movie, or that I am a spectator in my own life*".

Role functioning predicted psychiatric hospitalizations overall (*HR*=1.3, *p*=.002, *95%CI*=1.1–1.6). PQ items loading on the role functioning include "*I have had troubles at work or school recently*", "*I am less interested in school or work lately*", and "*I have difficulty concentrating, reading or listening*".

At 12 months, the criterion of 14 or more positive subscale symptoms provided a 48% sensitivity and 68% specificity for predicting psychosis. Using 18 positive symptoms as a cut-off instead, the sensitivity dropped to 28% and specificity raised to 81%. The total score criterion of 36 or more Yes responses had a 64% sensitivity and a 57% specificity.

Table 13. Nine-dimensional structure of Prodromal Questionnaire items

Factors	PQ items with factor loading >0.4	Item content
F1 Role functioning	PQ11	trouble at school
	PQ41	less interested in school
	PQ10	trouble concentrating
	PQ72	less able to do tasks
	PQ85	fatigue
	PQ01	distracted by noise
F2 Delusional ideation	PQ12	others read thoughts
	PQ32	thoughts broadcast
	PQ38	people are watching
	PQ76	people drop hints
F3 Hallucinations	PQ18	unusual sounds
	PQ13	hearing things
	PQ84	see things
	PQ19	illusions of people
	PQ79	see flashes
	PQ05	bugs on skin
	PQ26	strong sense of smell
	PQ50	suddenly distracted
	PQ57	reality confusion
	PQ52	invisible force around
F4 Oddness	PQ31	strange person
	PQ54	eccentric habits
	PQ45	odd person
	PQ62	strange ideas
	PQ40	mannerisms
	PQ15	collect unvalued things
	PQ69	unusual word use
	PQ22	odd appearance
	PQ76	people drop hints
	PQ61	bizarre beliefs
F5 Social avoidance	PQ43	social avoidance
	PQ21	quiet socially
	PQ78	not interested in new acquaintances
	PQ33	nothing to say
	PQ42	emotionally distant
	PQ58	aloof and distant
	PQ87	social anxiety
	PQ59	hiding feelings
	PQ80	anxious meeting strangers
	PQ06	don't get along

Table 13. Nine-dimensional structure of Prodromal Questionnaire items, continued

Factors	PQ items with factor loading >0.4	Item content
F6 Magical thinking	PQ24	belief in telepathy
	PQ35	superstitious
	PQ75	supernatural experiences
	PQ61	bizarre beliefs
	PQ30	special gifts
F7 Dysphoria	PQ83	cry often
	PQ47	unstable mood
	PQ28	unhappy
	PQ44	very guilty
	PQ70	often angry
	PQ55	something wrong with mind
	PQ29	brooding
	PQ88	hard to relax
	PQ63	feeling worthless
	PQ25	suspiciousness
F8 Depersonalization	PQ81	outside body experiences
	PQ71	spectator in life
	PQ65	thoughts almost audible
	PQ37	many thoughts compete
	PQ36	heard own thoughts
	PQ27	not in control of thoughts
	PQ67	arranged meanings in things
	PQ46	special meanings on TV
	PQ20	vision changes
	PQ02	altered passage of time
	PQ74	some force interferes
F9 Anhedonia	PQ48	unable to enjoy
	PQ89	uninterested
	PQ82	dulled feelings

4.5 Self-harm and psychotic-like symptoms (Study IV)

Only 30.5% of the adolescents interviewed reported no suicidal ideation in the BDI questionnaire (Table 14). The scores for current suicidality were higher among girls compared to boys and among the CHR group compared to the non-CHR group. Over a third of all the participants and 41% of all female patients were rated as having harmed themselves over their lifetime. This included, for instance, cutting and overdoses of medication.

Table 14. Current and lifetime suicidality among participants

	Total		Female		Male		CHR		non-CHR	
	n	%	n	%	n	%	n	%	n	%
Current suicidality										
0 No ideation	46/151	30.5	29/118	24.6	17/33	51.5	11/49	22.4	35/102	34.3
1 Mild ideation	81/151	53.6	68/118	57.6	13/33	39.4	26/49	53.1	55/102	53.9
2 Moderate ideation	18/151	11.9	16/118	13.6	2/33	6.1	8/49	16.3	10/102	9.8
3 Severe ideation	6/151	4.0	5/118	4.2	1/33	3.0	4/49	8.2	2/102	2.0
Lifetime suicidality										
0 Not suicidal	34/161	21.1	25/127	19.7	9/34	26.5	9/54	16.7	25/107	23.4
1 Thinking of death or death wishes	25/161	15.5	20/127	15.7	5/34	14.7	10/54	18.5	15/107	14.0
2 Suicidal thoughts	44/161	27.3	30/127	23.6	14/34	41.2	16/54	29.6	28/107	26.2
3 Self-harm	58/161	36.0	52/127	40.9	6/34	17.6	19/54	35.2	39/107	36.4

Compared to the non-CHR group, the CHR group scored higher in current suicidality (Mann-Whitney U=2016.5, n_1=49, n_2=102, p=.034) but not in lifetime suicidality. Current suicidality was positively correlated with SIPS general and negative symptom factors and several positive, negative, and general symptom scales. Lifetime suicidality was correlated with SIPS general symptom factor and some negative and general symptom ratings. Of the Beck scale scores, BAI was correlated with current suicidality, and BDI and BHS with both suicidality measures.

Girls reported more current suicidality compared to boys (Mann-Whitney U=1391.0, n_1=118, n_2=33, p=.006). The gender difference in lifetime suicidality was not statistically significant. Non-intact family structure (Mann-Whitney U=3400.5, n_1=66, n_2=85, p=.020) and substance abuse of a first-degree relative (U=3387.5, n_1=106, n_2=51, p=.007) were associated with higher scores in lifetime suicidality. There was a higher risk for suicidality among those with any non-psychotic mood disorder present at baseline compared to those without such a diagnosis, for both current (Mann-Whitney U=1436.0, n_1=115, n_2=36, p=.002) and lifetime suicidality (U=3345.0, n_1=122, n_2=39, p<.001). There was no significant difference in suicidality between those with and without other disorder cluster diagnoses.

There was one completed suicide in the sample and in addition, based on the hospital discharge register, four girls had intentionally harmed themselves during follow-up (ICD diagnosis code X69 Intentional self-poisoning in all cases). Altogether, there were five patients (3.2%) with intentional self-harm. Adolescents with a psychosis risk status

did not harm themselves more than the non-CHR adolescents (Fisher's exact test, p=.661).

Self-harm during follow-up was associated with current suicidality (Mann-Whitney U=129.5, n_1=5, n_2=108, p=.027) and familial risk of psychosis (U=195.5, n_1=5, n_2=113, p=.027). SIPS scale N3 "Decreased expression of emotions" was higher among the patients with intentional self-harm (Mann-Whitney U=130.5, n_1=5, n_2=116, p=.030). In a Cox regression analysis among the 121 girls, this SIPS scale remained a significant predictor of self-harm during follow-up (HR=2.8, p=.004, $95\%CI$=1.4–5.5).

Two of the five patients with intentional self-harm were admitted to hospital care for psychosis before the self-harm and the association between transition to psychosis and self-harm was significant (Fisher's exact test, p=.008); see Table 15.

Table 15. Transition to psychosis and intentional self-harm during follow-up among girls with register follow-up data

		Psychosis				Total	
		Yes		No			
		n	%	n	%	n	%
Intentional self-harm	No	2	50.0	114	97.4	116	95.9
	Yes	2	50.0	3	2.6	5	4.1
Total		4		117		121	

5 Discussion

5.1 Summary of the main findings

The main aim of this study was to investigate whether clinical high-risk state or certain symptoms predict psychosis or psychiatric hospitalization in the following years in a general adolescent psychiatric sample. Secondly, this study aimed at looking for possible associations between cognitive performance and suicidality with psychosis risk symptoms in the sample.

Using the Prodromal Questionnaire (PQ) screen with a cut-off of 18 or more positive symptoms, there were 107 screen-positive and 54 screen-negative participants. Furthermore, a third of the interviewed sample of adolescents in general psychiatric care fulfilled the SIPS criteria of psychosis risk; 40% of those who were screened positive in PQ and 20% of those who were screen-negative.

Psychosis risk status was associated with deficits in visuospatial performance. However, both positive psychotic-like symptoms and negative symptoms were associated with neurocognitive problems regardless of the risk status. As cognitive deficits may be associated with lowered daily functioning, it can be concluded that even mild positive and negative symptoms have clinical relevance among adolescent psychiatric patients.

During the 3–9 year register follow-up, 5.6% of all who had completed the Prodromal Questionnaire were hospitalized for psychosis. The prevalence of transition to psychotic disorder was also low among the SIPS interviewed sample, where seven psychoses emerged (4.7%), and the high-risk status did not predict psychosis at 12-month follow-up. Hospital admissions for psychotic disorder were predicted by SIPS positive symptom factor and PQ depersonalization factor, but not by CHR status. Any psychiatric hospitalizations were predicted by CHR status, SIPS positive and general symptom factors, and PQ role functioning factor.

Rates of suicidal ideation and suicidal thoughts were high among adolescents in psychiatric care. Current suicidality was higher in the CHR group compared to the non-CHR group. Further, decreased expression of emotions predicted self-harm during follow-up. This symptom may be indicative of a higher risk to suicide among girls seeking help in psychiatric clinics and wards.

To sum up, patients in a non-selected public health care sample reported a lot of psychotic-like symptoms, especially delusional ideas, perceptual abnormalities, and suspiciousness. Although only modestly predictive of psychosis, psychotic-like symptoms can indicate a more serious disorder, represented as cognitive deficits, suicidality, and psychiatric hospitalization in the following years. Depersonalization symptoms, anomalies of self-experience such as a feeling of being outside of own body or living in a dreamlike world, can be indicative of a higher risk to later psychosis.

5.2 Cognition and psychosis risk (Study I)

Adolescents in psychiatric care presented with high levels of psychotic-like symptoms. Unusual thought content, suspiciousness, and perceptual abnormalities were among the commonly reported psychotic-like experiences in the interviewed sample. The adolescents maybe felt that something odd was going on and that something was wrong, or felt like others could read their mind, or had superstitious, magical thinking. It was also common that the young person reported feeling suspicious and being watched by others. Of the hallucinations, the adolescents typically said in the interview that they had started hearing some kind of banging or someone calling their name, or even voices saying what they should do. Some reported seeing figures or shadows or even people that were not really there.

However, grandiosity, the feeling of having special gifts or having been chosen for a special role, was seldom scored among the participants, which is consistent with previous results (Hawkins, McGlashan et al., 2004; Lencz et al., 2004). Disorganized communication, difficulties getting their point across because of rambling or blanking out, was another positive symptom not scored as often as the other positive symptoms.

The factorial structure of the SIPS instrument was confirmed, as the finding of this study was similar to the factorial structure obtained by other study groups (Comparelli et al., 2011; Hawkins, McGlashan et al., 2004; Jung et al., 2010). Factor 1 consisted of non-specific distress symptoms. All symptoms classified as positive within the SIPS loaded principally on factor 2, along with “Bizarre thinking” which is classified as a disorganization symptom in the SIPS. Factor 3 reflected negative symptoms.

Those subscales thought to measure disorganization symptoms in the SIPS interview did not form a separate factor in the analyses of this study, but were scattered in the three factors: in addition to the above-mentioned D2 "Bizarre thinking" loading to positive symptom factor, subscale D3 "Trouble with focus and attention" loaded to general symptom factor, and D1 "Odd behavior or appearance" and D4 "Personal hygiene / social attentiveness" to negative symptom factor. This is consistent with earlier findings and indicates the somewhat vague nature of the disorganization symptoms that do not form a separable cluster. Disorganization symptoms may also emerge more seldom in adolescents in the early course of psychiatric illness compared to patients with more severe psychosis risk or established psychosis.

Psychosis risk status was associated with weaker visuospatial task performance among adolescent psychiatric patients. This result is consistent with earlier findings. Visuospatial performance has been shown to be impaired among clinical or familial high-risk subjects (Bora et al., 2014) and specifically among those who later develop psychosis (Brewer et al., 2005; Jones et al., 1994; Niendam et al., 2003; Tiihonen et al., 2005; Wood et al., 2003). However, some studies have not found visuospatial performance to be impaired in psychosis risk patients (Hawkins et al., 2004; Lencz et al., 2006; Niendam et al., 2006). The differences in the results can possibly be explained by the fact that the definition of the visuospatial domain varies and it is measured with different sets of neurocognitive tests across studies. In sum, however, it appears that the visuospatial domain of cognition may be a vulnerability marker for being at risk for psychosis, and possibly a marker for onset of psychosis.

Negative symptoms appear to be closely linked to cognitive performance, affecting everyday functioning. In the CHR group, deficits in cognitive functioning were associated with stronger negative symptoms. There was also a connection between negative symptoms and poorer verbal performance in the non-CHR group, suggesting that along the whole continuum of negative symptoms there is a connection with verbal performance deficits. Negative symptoms include lack of motivation, persistence, and energy, therefore possibly influencing the results of cognitive testing. Among patients with psychosis, negative symptoms have been found to be associated with deficits in cognitive performance (Ohmuro et al., 2015), especially in processing speed (Cameron et al., 2002; Cuesta & Peralta, 1995; O'Leary et al., 2000; Rhinewine et al., 2005) and

verbal performance (Dominguez et al., 2009; Liddle, 1987; O'Leary et al., 2000). Negative symptoms were also associated with slower information processing speed in a general population sample of female twins (Simons et al., 2007).

Negative symptoms and cognitive deficits may not only have a special role in predicting transition to psychosis, but they may also be related to the severity and outcome of psychiatric disorder regardless of the psychosis risk status, as cognitive deficits are associated with reduced functioning (Lin et al., 2011) and poor outcome among first-episode schizophrenia patients (Bilder et al., 2000). It is therefore essential to pay attention to negative symptoms among all help-seeking adolescents. Although manifested separately as negative symptoms and cognitive difficulties, the underlying processes may perhaps be converging. Negative symptoms may also mediate the relationship between cognitive performance and functional outcome (Meyer et al., 2014; Ventura et al., 2009), suggesting need for rehabilitation targeting both negative symptoms and cognitive deficits as a means of enhancing functioning. Cognitive remediation has been found to improve the cognitive performance of schizophrenia, and in recent years this approach has also started to yield interest in high-risk research (Zaytseva, Korsakova, Agius, & Gurovich, 2013).

It is also important to identify positive symptoms among adolescent patients because even mild positive symptoms can have associations with cognitive functioning, and thus inform about a more serious disorder. In this study, positive symptoms, and especially P4 “Perceptual abnormalities and hallucinations”, were associated with poorer visuospatial performance in the non-CHR group. Mood and anxiety disorders were common in this group, and cognitive impairment is common among these disorders (Castaneda, Tuulio-Henriksson, Marttunen, Suvisaari, & Lönnqvist, 2008), as are subpsychotic hallucinations (Gaudiano & Zimmerman, 2013; Rietdijk et al., 2014). One earlier study has found positive symptoms to be associated with slower reaction speed in a general population sample of female twins (Simons et al., 2007), and another with memory and attention impairment in schizophrenia patients (Talreja et al., 2013). Both cognitive deficits and psychotic-like symptoms cluster in families of schizophrenia patients, suggesting shared genetic factors behind them. In a systematic review, processing speed was the only domain with a significant correlation to positive symptoms (Dominguez et al., 2009). However, according to the majority of earlier

research, compared to other symptom domains, positive symptoms interfere less with cognitive functioning (Ventura et al., 2009).

5.3 Predictiveness of the SIPS interview (Study II)

Based on the SIPS interview, one third of the pre-screened adolescent psychiatric patients belonged to a group of heightened psychosis risk. However, the significance of the high-risk status was limited in predicting psychosis. Psychosis incidence was low among these adolescents who had mostly sought help for depression and anxiety rather than for positive symptoms.

The matter of differences in defining psychosis is important in the field of psychosis research. The definitions of psychosis and psychosis risk state differ between SIPS, CAARMS, ICD-10, and DSM-IV or DSM-5 (Fusar-Poli & van Os, 2013; Miller et al., 2003; Olsen & Rosenbaum, 2006a), and different definitions of psychosis lead to different transition risks (Fusar-Poli, Bonoldi et al., 2012; Schultze-Lutter et al., 2013). The same symptoms can be interpreted in different ways depending on the approach, as demonstrated with a case description by Fusar-Poli and van Os (2013).

For instance, DSM-IV and DSM-5 diagnostic criteria for brief psychotic disorder include the presence of psychotic symptoms, with a duration of at least a day but less than a month, but there are no requirements for lowered functioning. The definition of psychosis in the SIPS is stricter, and an absence of insight is required for the symptom to be rated as psychotic. If the person realizes that an experience is not true, the symptom is not rated as psychotic. The enhancement of insight has traditionally often been the goal of treatment as it is associated with quality of life and outcome. A part of insight is realizing that hallucinations or delusions are pathological. However, insight is continuous and fluctuating by nature (McGorry and McConville, 1999).

Both SIPS and DSM-IV definitions for psychosis were used in this study because of the difference in definitions. However, the results were quite similar using both approaches. Depending on the definition of psychosis, there were three or five new conversions to psychosis during the one-year follow-up time.

Compared to international studies conducted in specialized early intervention clinics with patients preselected based on suspicion of a psychosis risk (Cannon et al., 2008;

Ruhrmann et al., 2010), lower transition rates were observed in an unselected sample of adolescents with a first admission to psychiatric services, as expected by Fusar-Poli, Borgwardt and colleagues (2013). High transition rates in many high-risk studies have been suggested to reflect sampling strategies more than the specific high-risk criteria (Fusar-Poli, Yung et al., 2014). The more enriched the sample is, the more effective the CHR approach is to detect psychoses. In addition, in some recent high-risk research papers, it has been stressed that the low conversion rates in some studies can also be related to careful exclusion of psychotic persons at baseline (Fusar-Poli & van Os, 2013). If the positive symptoms of a person fluctuate, they can be at a subpsychotic level in one assessment and at a psychotic level in the next one, thus interpreted incorrectly as transition to psychosis in some studies.

Though the validity of the CHR status was limited in predicting psychoses at 12 months, the predictive value of the psychotic-like symptoms appeared on a longer high coverage hospitalization register follow-up. The intensity of the positive, psychotic-like symptoms predicted psychiatric hospitalizations due to psychosis. The result is consistent with several (Cannon et al., 2008; Haroun et al., 2006; Ruhrmann et al., 2010; Werbeloff et al., 2012) but not all (Simon & Umbricht, 2010; Ziermans et al., 2011) earlier studies.

The important difference between the intensity of positive symptoms and CHR status is that symptom worsening is required for CHR. Another reason why positive symptoms predicted psychosis but CHR did not may be that for CHR status, positive symptoms can range from moderate to severe, and the information of the severity of the symptoms gets lost in the CHR/non-CHR coding.

Another issue is that the positive symptom factor loaded with positive symptom items and, in addition, with “Bizarre thinking”, which is a disorganization symptom in the SIPS (Table 12). Bizarre thoughts were quite rare in this study sample, but when they occurred they had a significant role. The EPOS study, a large European multi-center field study, has also found the best predictors of conversion to psychosis to be “Bizarre thinking” in addition to positive symptom items (Ruhrmann et al., 2010). “Bizarre thinking” in the SIPS is conceptualized as absurd, illogical ideas, either reported by the interviewee or observed by others (and difficult for them to understand).

The person may have strange, unusual ideas that violate the boundaries of physics that do not fit their subculture, for example the religion of the person.

In addition, the CHR status as well as positive and general symptoms predicted all psychiatric hospitalizations. This finding is consistent with a connection found between attenuated psychotic symptoms and psychiatric hospitalizations later in life among young adults in the general population (Werbeloff et al., 2012). Psychotic-like symptoms may hence be general predictors of later severe psychiatric illness requiring hospitalization.

The prevalence of transition to psychosis among adolescent psychiatric patients was relatively low in this study. One possible explanation for this is the effectiveness of the treatment received at the psychiatric clinics and wards. Antidepressive medication (Cornblatt et al., 2007; Cornblatt, 2002) or antipsychotics (Addington & Heinssen, 2012; Correll et al., 2010) can lower the psychosis risk of adolescents with risk symptoms, and the same has been observed for cognitive psychotherapy (Okuzawa et al., 2014).

On the other hand, it is possible that the current treatment system does not reach all adolescents with psychosis risk symptoms. Adolescents tend to have little knowledge about mental health problems and experience, and find seeking help for them stigmatizing (Yap, Reavley, & Jorm, 2013). Parental knowledge of and attitudes towards mental health services affect the swiftness of getting help (Chen, Gearing, DeVylder, & Oh, 2014). Especially boys with externalizing symptoms, low functioning, negative symptoms, and odd behavior may not seek help inasmuch as girls with internalizing symptoms such as depression and anxiety.

Low threshold care in the adolescent's own network has proved to work well in reducing stress and supporting the functioning of symptomatic adolescents in Finland (Granö et al., 2009). Every young person should get the care they need without stigma, and young people's awareness of mental health should be enchanced (The International Declaration on Youth Mental Health, 2013).

5.4 Predictiveness of the PQ questionnaire (Study III)

Several specific questionnaires have been constructed for the screening of psychotic symptoms and selection of patients for targeted interviews. In this study, the Prodromal Questionnaire (PQ) was used. Endorsement rates were high for most symptoms of the PQ, consistent with other studies finding psychotic-like symptoms measured with questionnaires common among non-psychotic help-seekers (Brandizzi et al., 2014; Hanssen et al., 2003; Yung et al., 2006).

In a Dutch study, virtually all respondents in a non-psychotic help-seeking population reported at least one item on the positive symptom scale of the PQ (Rietdijk et al., 2014). In their study, four classes of psychotic-like experiences were found (normative, mild, moderate, and severe), replicating the finding of four class structures of the psychosis phenotype found earlier in the population (Rietdijk et al., 2014). In another study conducted among help-seeking adolescents in Italy, the psychotic-like experiences measured with the PQ formed four factors interpreted as "conceptual disorganization and suspiciousness", "perceptual abnormalities", "bizarre experiences", and "magical ideation", with only the first factor related to psychopathology, as measured with the negative, general, and disorganization scales of the PQ (Brandizzi et al., 2014).

In prospectively testing the predictiveness of the PQ in the adolescent sample of this study, it was found that many adolescents with low PQ scores were also hospitalized for psychosis during the follow-up (false negatives), leading to a low predictive value of the questionnaire. Although the PQ is sometimes used in clinical settings for strict screening of psychosis risk without any second-stage clinical interview, using PQ on its own cannot be recommended, as previously published cut-off scores were poor predictors of psychosis. Hence, the idea of a two-phase assessment procedure, with PQ as an initial screen for a more rigorous interview-based risk assessment, is supported.

However, the structural validity of the Finnish language PQ was supported through nine interpretable latent factors, of which role functioning predicted hospital treatments for any psychiatric disorder during follow-up. PQ items loading to role functioning reflect issues of everyday ability to function, such as problems at school and trouble concentrating or getting things done. It is not very surprising that this baseline

functioning factor predicts hospitalizations, an outcome indicating illness severity and deterioration in functioning during follow-up.

Further, the depersonalization factor predicted psychosis. Depersonalization symptoms, such as feeling less real or dreamlike or watching oneself act, though not specifically scored in the clinical high-risk approach, were common among the interviewed adolescents. The adolescents sometimes said in the interview that they felt like they had changed and everything felt unreal. A sense of distance from the world or from oneself was described by some participants; they felt disconnected from themselves or from their lives. These experiences were sometimes reported in the N4 "Decreased experience of emotions and self" part of the SIPS interview, sometimes spontaneously during the interview, as distracting experiences affecting everyday living.

Depersonalization occurs along a continuum, with short-lasting episodes being a part of normal experience, and long-lasting and disabling episodes as an extreme form of the phenomenon. The finding of depersonalization symptoms associating with psychosis is consistent with the theory of multisensory integration deficits in schizophrenia affecting self-experience (Postmes et al., 2014). Perceptual incoherence in psychosis can evoke depersonalization and other anomalous self-experiences (Postmes et al., 2014).

As a concept close to depersonalization, dissociation has been found to be linked to self-reported psychotic-like experiences (Moskowitz, Barker-Collo, & Ellson, 2005). Among healthy subjects, depersonalization predicted proneness to hallucinations, supporting the idea of hallucinations as a product of dissociative processes splitting positions of the self apart (Perona-Garcelán et al., 2013).

Psychosis risk symptoms have been found to be associated with a high prevalence of childhood trauma (Kraan, Velthorst, Smit, de Haan, & van der Gaag, 2015), which in turn is linked to depersonalization (Vermetten & Spiegel, 2014). Among psychosis risk patients, levels of self-disturbances have been found to predict psychosis onset (Nelson, Thompson, & Yung, 2012; Parnas et al., 2011). Incoherencies in self-experience are a common characteristic preceding psychosis onset, strengthened and thematized in the form of delusions and hallucinations in the transition to frank psychosis (Parnas & Handest, 2003; Raballo, 2012).

Depersonalization can thus be seen as an important psychosis vulnerability phenotype. Though not specifically included in the SIPS or CAARMS interviews,

depersonalization has been covered in the basic symptoms approach as one of the psychosis risk experiences (Klosterkötter et al., 2001).

It has been stated that assessing these kinds of symptoms with a self-disturbance measure would be a valuable asset to psychosis risk identification in addition to the CHR/UHR strategy (Nelson et al., 2012). In addition, early psychosis intervention could include diminished concentration on depersonalization experiences, thus affecting the hallucination proneness, as focusing on these experiences tends to strengthen them further (Perona-Garcelán et al., 2013).

5.5 Self-harm and psychosis risk (Study IV)

In the baseline assessment of this study, a continuous model of suicidality was used, reflecting the full continuum from suicidal ideation to self-harm. Information was collected on suicidal thoughts and behavior from interviews and medical records. As it was found to be incorrect to suggest that suicidal intention was related to hospitalization (for instance, absent in a case of cutting when it did not lead to hospitalization and present in an overdose with hospital admission), all self-harm was analyzed as a whole, regardless of intention, which was not formerly assessed in this study.

In contrast, the register outcome status used was dichotomous in a Yes/No format. The self-harm cases cannot be referred to as suicide attempts as there was no evidence of suicidal intent among the self-harm incidents. Hospital presentations for self-injurious behavior can be motivated by other factors than intention to die. The data of intentional self-harm leading to hospitalization was combined with data of completed suicide during follow-up. Altogether, five girls harmed themselves during follow-up.

Psychosis risk status was significantly associated with more severe baseline suicidality, consistent with previous results (DeVylder et al., 2012; Granö et al., 2013; Hutton et al., 2011). Depending on the suicidality measure used, 78–83% of the CHR group was at least mildly suicidal and 35% had harmed themselves before baseline.

Current suicidality was associated with delusions, suspiciousness, and hallucinations, paralleling the findings of a large population study by Saha and colleagues (2011), where a dose-response relationship between delusional-like experiences and suicidality was found. Furthermore, in their study, there was also an association between

delusional-like experiences and suicide attempts among those with a history of any mental disorder (Saha et al., 2011). Similarly, in a previous study conducted among adolescents with more severe suicidal behavior (plans or acts), the majority reported psychotic-like symptoms (Kelleher et al., 2012). Among adolescents with depressive disorders, those who also experienced psychotic-like symptoms had nearly 14-fold increased odds of more severe suicidal behavior, compared with adolescents who did not experience psychotic-like symptoms (Kelleher et al., 2012). Among adolescent students, psychotic-like symptoms were associated with a higher risk of suicidality and this was especially true if the symptoms were accompanied with distress and poor help-seeking behavior (Nishida et al., 2014).

In sum, psychotic-like experiences seem to be a risk marker of suicidality. Instead of a direct causal association, a third factor may be behind both psychotic-like experiences and suicidality, possibly some kind of general psychological distress or stressful or traumatic life experiences (Saha et al., 2011). Psychotic-like experiences can indicate a more serious non-psychotic disorder, often also manifesting as suicidal ideation and/or self-injury.

Girls reported more current suicidal ideation compared to boys, which is in line with previous results (Delfabbro et al., 2013; Hawton et al., 2012; Schrijvers et al., 2012). The associations between lifetime suicidality and substance misuse of a first-degree relative and troubled family background are consistent with previous research (Delfabbro et al., 2013; Hawton et al., 2012). The association can possibly be explained by traumatic childhood experiences. Dysfunctional parenting has been found to be somewhat associated with psychopathology non-specifically and the association seems at least partly causal (Kendler & Prescott, 2006). As another environmental risk factor, loss of a parent by death or divorce is associated with an increased risk for mood, anxiety, and substance use disorders (Kendler & Prescott, 2006). It has been found in other studies that adolescents with separated parents tend to be more suicidal than those with intact families (Delfabbro et al., 2013; Hawton et al., 2012).

Not surprisingly, there was a higher risk for suicidality among those with a mood disorder at baseline compared to those without a mood disorder. Depressive symptom severity, as measured with the BDI, was also positively correlated with baseline suicidality. According to a large WHO study, mood disorders are the strongest

predictors of suicide attempts in developed countries (Nock et al., 2009). Continuing mood disorder also predicted suicidal behavior among adolescent outpatients (Tuisku, Pelkonen, Kiviruusu, Karlsson, & Marttunen, 2012). In a review, depressive symptoms were among the best predictors of adolescent suicidality (Hawton et al., 2012). Further, severity of self-rated depressive symptoms differentiated suicidal children and adolescents from non-suicidal among depressive patients (Hetrick, Parker, Robinson, Hall, & Vance, 2012). Among depressed adolescent outpatients, those with deliberate self-harm had more severe depressive symptoms than those without self-harm (Tuisku et al., 2009). In addition, adolescents with suicidal ideation or suicide attempts had more depressive and anxiety symptoms than adolescents with self-harm without intention to die (Tuisku et al., 2009).

In this study, all the patients with intentional self-harm during follow-up were girls. The prevalence of self-harm (3.2%) was low and closer to the prevalence of suicide attempts found in the population (Nock et al., 2013; Riala et al., 2007) than in psychiatric samples. However, in this study, history of self-harm was not assessed in an interview as in previous studies, but all cases resulted in hospital care. The low prevalence of self-harm in this study can be explained by the fact that self-harm is suspected to be much more common in the community than presenting at clinical services, and only a small proportion of individuals who self-harm ever need hospital care (Hawton et al., 2012).

This study also explored the Causes of Death statistics (Statistics Finland) and was able to systematically follow 758 adolescents who completed the PQ at baseline. In the whole group, there were six deaths (0.8%) until 2012, three of which were suicides. Only one of these adolescents was included in the interviewed sample of 161 patients. Deaths were thus rare in this adolescent psychiatric sample, although a third fulfilled the criteria for clinical high-risk state. Low suicide risk during the follow-up suggests a high quality of care in these adolescent psychiatric services.

Decreased expression of emotions, which in the SIPS is regarded as a negative symptom, may indicate an elevated risk of severe suicidal behavior among adolescent psychiatric patients. This scale of the SIPS can be seen as related to alexithymia, characterized by an inability to identify and describe emotions leading to dysfunction in empathy, emotional responding, and social attachment (Sifneos, 1996). Alexithymic

individuals also suffer from affective dysregulation, part of which is emotional inexpressivity, and alexithymia may lessen the capacity to cope with emotional stressors. Alexithymic features have been found to be positively associated with depression (Honkalampi et al., 2009; Manninen et al., 2011) and suicidal ideation (De Berardis et al., 2013; Garisch & Wilson, 2010; Verrocchio, Conti, & Fulcheri, 2010).

Further, female college students with frequent deliberate self-harm have been found to report high levels of emotion dysregulation and emotional inexpressivity (Gratz, 2006; Gratz & Roemer, 2008). It has been discussed that self-harm may function as a maladaptive way to express distressing emotions that the person is unable to otherwise express, or to avoid difficult emotions (Gratz & Roemer, 2008).

5.6 The heterogeneity of psychotic-like symptoms

Psychosis risk patients are not a homogeneous group as only a small portion of them will develop psychosis. Though more research is needed into which symptoms best predict psychosis, it can be said with certainty that not all persons with psychotic-like experiences are at risk for psychosis. These experiences are common among adolescents and adults in psychiatric care (Hanssen et al., 2003; Rietdijk et al., 2014; Yung et al., 2006). Even in population samples, infrequent psychotic-like experiences have been reported by a large proportion of the respondents (van Os, Hanssen, Bijl, & Vollebergh, 2001; Yung et al., 2009). When infrequent and not distracting, psychotic-like symptoms are not associated with a psychosis risk. This reflects the heterogeneity of attenuated psychotic experiences. It also has to be kept in mind that all psychotic-like symptoms are not of the same value. Even though psychotic experiences form a continuum, psychosis risk assessment is categorical and based on a cut-off point. A positive symptom rated as five is much more severe than one rated as three in the SIPS, yet they both indicate psychosis risk status according to the clinical high-risk approach.

Alison Yung (2009) has suggested that positive symptoms can be divided into three classes which may be: 1) predictive of psychosis, or 2) “clinical noise” related to non-psychotic disorders, or, 3) if not distracting, just variation of the psychosis continuum presenting in a healthy population. In the sample of this study, it seemed that most of the positive symptoms reported belonged to the second group. The psychotic-like

symptoms of the adolescents seemed to be "clinical noise" as a part of their symptomatology associated with the depressive, anxiety, and other symptoms that the adolescents were suffering from.

Psychosis risk state is especially often comorbid with anxiety and depressive disorders (Fusar-Poli, Nelson et al., 2014). When treating the presenting symptoms, the positive symptoms also tend to relieve (Wigman et al., 2011; Yung, Nelson, Thompson et al., 2010b). Nevertheless, comorbidity of psychotic-like symptoms and depression can be a sign of a more severe illness with worse treatment prognosis (Wigman et al., 2012), and comorbidity also adds the risk of suicidality among psychosis risk patients (Fusar-Poli, Nelson et al., 2014). In one study, following up risk patients with comorbid disorders, non-psychotic bipolar disorders were associated with increased and anxiety disorders with reduced psychosis risk, while depressive disorders were not associated with transition (Salokangas et al., 2012).

Although psychotic-like symptoms in the Helsinki Prodromal Study did not specifically predict psychosis to the extent it was expected, they can be associated with other clinical outcomes, such as suicidality. They also predicted psychiatric hospitalizations unspecifically. In a delinquent adolescent population, the psychosis risk status did not predict psychosis either; however, the risk status was associated with other psychiatric problems, such as symptoms of anxiety and depression, and mood and substance-related diagnoses (Manninen et al., 2014). Transition from the risk state to various disorders, such as mood disorders, is considered significant in the current field of high-risk research (Fusar-Poli, Yung et al., 2014). In the *clinical staging model*, the focus is not on a specific diagnosis but on deterioration of functioning. Each patient is staged on the continuum of mental illness course, aiming at individualized treatment and reducing the risk of progression to the next stage (Cross et al., 2014).

5.7 Psychotic-like symptoms in the clinical setting

When treating adolescent psychiatric patients, monitoring psychotic-like symptoms is significant. Longer duration of psychosis risk symptoms without treatment is associated with a higher transition rate to psychosis, indicating the importance of detecting risk patients and prompt referral to psychiatric care (Nelson et al., 2013; von Reventlow et

al., 2014). In early detection of adolescent psychosis risk, the role of general medical practice is important, whereas the sustained psychosocial and pharmacological treatment of first-episode psychosis belongs to specialized care (Mäki & Veijola, 2012).

General guidelines can be given of when psychotic-like symptoms might be alarming. These situations include severe, distracting positive symptoms that worsen with time. Because of the commonness of the experiences, it is the distress associated with them that matters, or if the symptom starts affecting the behavior of the person. Psychotic-like symptoms that are associated with lowered functioning, negative symptoms, or genetic risk to psychosis should raise the clinician's concern. Frequent monitoring of the young person with risk symptoms is recommended, so that the worsening of the symptoms gets noticed. Adolescent-onset psychosis tends to start gradually with subtle changes in behavior and symptoms so that there may be delay in treatment (Joa et al., 2009).

However, identifying and treating psychotic-like symptoms is important not just for the sake of psychosis prediction. Regardless of the symptoms being predictive of psychosis or not, they deserve attention in their own right, as they cause distress and affect quality of life and level of functioning (Addington & van der Gaag, 2015). Psychotic-like symptoms are associated with persistent disability even among those who do not convert to psychosis (Addington et al., 2011; Haroun et al., 2006). Especially paranoia may be linked to e.g. low or unstable self-esteem (Thewissen et al., 2007), shame (Johnson et al., 2014), and traumatic memories (Pinto-Gouveia, Matos, Castilho, & Xavier, 2014).

Clinicians should try to understand what the symptoms are about and how they can help to understand the situation of the young person. Asking about psychotic-like symptoms directly from adolescent psychiatric patients is therefore essential. Psychotic-like symptoms are confusing, possibly frightening experiences that may not be visible to others and that the adolescents may not spontaneously reveal, and as a consequence, they can often be left unnoticed in clinical settings. A questionnaire like the PQ or a semi-structured interview like the SIPS offer good opportunities to go through the symptoms systematically. Asking about psychotic-like symptoms directly and verbalizing them tells the adolescent that similar symptoms are experienced by other people too. Just talking about the experiences for the first time can therefore be

relieving. In the treatment system, it may even be somewhat secondary to categorize patients according to diagnosis or psychosis risk status; instead, the symptoms presented by the person and how they affect his or her life should be the focus.

In the treatment of psychosis risk patients, symptoms could be relieved and the risk of transition to psychosis lowered with a combination of antipsychotics and therapy according to some studies (Addington & Heinssen, 2012; van der Gaag et al., 2013). However, with high false-positive rates and side-effects, antipsychotic medication is not recommended for people considered to be at increased psychosis risk (Addington & van der Gaag, 2015; National Institute for Health and Care Excellence, NICE, 2014), and psychosis risk research is problematically influenced by the large proportion of prepsychotic individuals in the USA who are medicated with them (McGorry, Yung, Bechdolf, & Amminger, 2008). In the NICE guidance, individual cognitive behavioral therapy (CBT) with or without family intervention is recommended to a person at increased risk of developing psychosis. In addition, mood, anxiety, and other disorders that the risk individuals often have are treated according to the clinical guidelines of these disorders (National Institute for Health and Care Excellence, 2014).

In a meta-analysis, transition to psychosis was found to be reduced with the use of CBT, omega-3 fatty acids, and integrated psychotherapy (Stafford, Jackson, Mayo-Wilson, Morrison, & Kendall, 2013). A recent study found that combined with CBT, antidepressants were more effective than antipsychotics in reducing transition to psychosis among psychosis risk patients (Fusar-Poli, Frascarelli et al., 2014). In another study, family-aided assertive community treatment yielded good results in reducing symptoms and improving functioning of high-risk and early psychosis participants during a two-year follow-up (McFarlane et al., 2015).

Psychosocial treatments and efforts to keep risk patients involved with social networks, "on track in a shared reality", are currently being recommended (Addington & van der Gaag, 2015). Specifically, CBT has been found to effectively reduce transition rates to psychosis in some studies, but the effect is not always long-lasting (Okuzawa et al., 2014).

The cognitive approach to treating psychotic(like) experiences includes normalization and adaptive interpretation of them. It aims to reduce stress, emphasizing that the patient's fear of "being mad" can be more distressing than the experience itself

(Morrison, Renton, Dunn, Williams, & Bentall, 2004; Morrison et al., 2012). Eliminating the symptoms is thus not the primary goal of cognitive therapy, but reducing the distress that is associated with the symptoms. Cognitive therapy recognizes the biases in perception and reasoning related to the symptoms, and how the experiences often are somehow functional for the individual (Morrison et al., 2004). The experiences, for instance hallucinations, are maintained by misinterpretations, and interpreting them in a more adaptive way reduces fear and depression, hence improving the prognosis (Krabbendam et al., 2005; Morrison et al., 2004). In therapy, a case formulation of what may have caused the problem and what is maintaining it is essential (Anttonen, 2004; Morrison et al., 2004; Määttä & Anttonen, 2013). Enhancing alternative explanations for the odd experiences may prevent transition to psychosis among CHR individuals (Addington & van der Gaag, 2015). Treating positive symptoms, other symptoms can also be reduced; for example, in a case where a disturbing voice interferes with sleeping or concentration.

5.8 Strengths and limitations

5.8.1 Strengths of the study

The topic of this study was rather new with an unselected sample of first-admission adolescent patients in general psychiatric care. Because many psychosis risk study samples have been derived from highly specialized clinics, it is difficult to estimate how representative they are of patients encountered in a non-selected clinical setting. Further, this study used help-seeking adolescents who did not meet the CHR criteria as a comparison group, which gave a better chance of group comparisons than using healthy controls. In addition, a healthy control group was enrolled for cognitive performance. The participants of this study were aged 15–18, representing the middle adolescence stage, the phase with an elevated risk for psychosis.

Although the interviewed subsample was smaller, the sample with questionnaire data was quite large with over 700 youths. The strengths of this study also include the long follow-up using the Finnish Hospital Discharge Register, with good accuracy in detecting psychoses (Perälä et al., 2007).

5.8.2 Limitations of the study

In the sample of this study, two-thirds were girls, reflecting the gender distribution among adolescent psychiatric patients. Boys with psychosis risk symptoms were unfortunately not fully represented in this sample. In order to reduce the statistical analyses, factors of symptoms and cognitive performance were used, which can be seen as a limitation.

Follow-up assessment including SIPS interview was only done with a small subset, and transition to psychosis was often established using high quality medical records including outpatient records. The definition of psychosis varies across approaches, and categorizing a variable of a continuous nature can lead to some obscurities (Fusar-Poli & van Os, 2013). In this study, using SIPS and DSM-IV criteria of psychosis resulted in slightly different rates of transition.

The approximated 25% rate of Prodromal Questionnaire drop-outs among patients selected for inclusion can be considered acceptable. It may be accounted for by a failure of the clinic personnel to present the questionnaire to the patient, or the patient not coming in for their second appointment, or possible refusal to fill in the form. The original Prodromal Questionnaire was used. It does not include distress and frequency of the symptoms that the revised version measures (Loewy et al., 2007).

The study concerning suicidality was of an explorative nature, and lifetime suicidality was not assessed formally. The results of self-harm during follow-up only represent the most severe forms of suicidal behavior, as the hospital discharge register data does not illustrate the whole spectrum of suicidality.

Assessing symptoms in the high-risk approach is not a simple field, and there is a thin line between psychotic and severe but subpsychotic symptoms. When close to psychosis, it may be difficult to estimate how convinced the person is of the experiences and whether the symptoms should be rated at a psychotic or a subpsychotic level. The spectrum of adolescent symptomatology is wide, and it can be challenging to separate, for instance, panic attacks with extreme symptoms, dissociative symptoms, or severe obsessive-compulsive symptoms from psychotic episodes.

The issue of symptomatic overlaps has not been left unnoticed by another study group of Simon and colleagues (2014), who describe patients encountered in early psychosis services to present with various symptoms not expressing true psychosis risk.

These symptoms include, for instance, depersonalization, obsessive-compulsive symptoms, and hallucinations. The authors state that instead of merely defining the psychosis risk status, the "gestalt" of the symptoms has to be assessed, in order to evaluate if the person really is at heightened psychosis risk (Simon et al., 2014).

5.9 Future research recommendations

After gathering data on cognitive performance at baseline and on predicting psychosis and psychiatric hospital care with the SIPS interview, the next research question is the association between cognitive performance and later transition to psychosis and psychiatric hospital care. Further, a prediction algorithm combining all available information in this study (screening questionnaire, interviews, functioning measures, and cognitive performance) could be created, similar to those reported by other high-risk research centers.

Depersonalization symptoms, feelings of unreality and strangeness, were qualitatively important in the symptomatology of many young psychiatric patients and statistically significantly predictive of psychosis, though they are not systematically assessed in clinical high-risk research. Therefore, it would be useful to investigate depersonalization symptoms further. Another specific area of further research is decreased expression of emotions, which predicted self-harm in this study.

Further, investigating how young people at true psychosis risk are being caught by the treatment system is an area worthy of future research. The paths to treatment in cases of established psychosis could be retrospectively analyzed. For example, males and females may have different kinds of paths to treatment and possible psychosis, with gender differences in seeking psychiatric care and later psychosis. This would help examine how the psychiatric service system could be improved to enable early intervention for adolescents with severe risk symptoms. Early detection of risk symptoms and early intervention is needed to prevent cognitive and psychosocial deficits developing in the prodromal phase of psychosis.

5.10 Clinical implications

Although most persons with a psychotic disorder experience a prodromal period before the onset of psychotic-level symptoms, it is less clear how many persons who report psychotic-like symptoms will later develop a psychotic illness. False identification of a youth as prodromal can cause unnecessary concern and emotional harm through stigmatization, not to mention needless treatments especially if antipsychotics are used (Simon et al., 2011; Yung, Nelson, Thompson et al., 2010b). It is important to find a balance between, on one hand, discussing the psychosis risk with the patient and monitoring the risk and, on the other hand, normalizing the symptoms and reducing the anxiety of the patient (Broome & Fusar-Poli, 2012).

Psychotic-like experiences occur in a wide range of disorders and they should not be mistaken to always indicate psychosis (Kelleher et al., 2014). As young people often react to stressors with psychotic-like symptoms, they may fall within the normal spectrum of experience of childhood and adolescence. In general psychiatric care, psychotic-like symptoms are less predictive of a specific psychosis outcome than in specialized prodromal clinics. In this study, a third of the adolescent psychiatric patients met criteria for a psychosis high-risk state. Of those screened positive in PQ, 40% were considered at risk, and of the screen-negative, 20%. After all, the majority of the risk cases were in fact false alarms: the person never converted to psychosis in spite of risk symptoms, at least during the follow-up time of this study project.

However, the PQ and SIPS methods can be used to bring other useful information to clinical work. The PQ is especially used widely in clinical practice because it is easy to fill in and score without special training, and useful information on the psychosis risk symptoms experienced by the young person is obtained using the questionnaire. Psychotic experiences need clinical attention not only because they may predict psychosis but they are, by themselves, current, presenting symptoms. Further, psychotic-like symptoms do predict unspecific psychiatric hospitalizations, indicating illness severity and poor functional outcome. This result of the current study is in line with earlier results associating psychotic experiences with other mental disorders and psychiatric hospitalizations (Rössler et al., 2011; Werbeloff et al., 2012).

CHR status is also associated with cognitive deficits and can indicate a more serious disorder limiting ability to function in everyday life. Even mild positive and negative

symptoms may have clinical relevance in psychiatric adolescent patients. Young people with both psychotic-like symptoms and neurocognitive deficits constitute a group in need of special attention. The association between suicidality and psychosis risk symptoms also emphasizes the importance of detecting psychotic-like symptoms among adolescents seeking psychiatric care.

6 **References**

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