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PhD Thesis

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Mental disorders, psychotic experiences, and cognitive bias in preadolescent children at familial high-risk of schizophrenia or bipolar disorder

A prospective, longitudinal cohort study - The Danish High Risk and Resilience Study, VIA 11

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Table of Contents

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Overview of papers included in the thesis

This thesis is based on the following papers:

1. **Mental disorders in preadolescent children at familial high-risk of schizophrenia or bipolar disorder - a four-year follow-up study: The Danish High Risk and Resilience Study, VIA 11**

   Gregersen M; Søndergaard A; Brandt JM; Ellersgaard D; Rohd SB; Hjorthøj C; Ohland J; Krantz MF; Wilms M; Andreassen AK; Knudsen CB; Veddum L; Greve A; Bliksted V; Mors O; Clemmensen L; Møllegaard Jepsen JR, Nordentoft M; Hemager N; Thorup AAE. *The Journal of Child Psychology and Psychiatry, 2021, Dec 16*, online ahead of print, doi: 10.1111/jcpp.13548

2. **Developmental pathways and clinical outcomes of early childhood psychotic experiences in preadolescent children at familial high-risk of schizophrenia or bipolar disorder. A prospective, longitudinal cohort study – The Danish High Risk and Resilience Study, VIA 11**

   Gregersen M; Møllegaard Jepsen JR; Rohd SB; Søndergaard A; Brandt JM; Ellersgaard D; Hjorthøj C; Ohland J; Krantz MF; Wilms M; Andreassen AK; Veddum L; Knudsen CB; Greve AN; Bliksted V; Mors O; Clemmensen L; Nordentoft M; Hemager N; Thorup AAE. *Under peer review.*

3. **Jumping to conclusions and its associations with psychotic experiences in preadolescent children at familial high-risk of schizophrenia or bipolar disorder - The Danish High Risk and Resilience Study, VIA 11**

   Gregersen M; Rohd SD; Møllegaard Jepsen JR; Brandt JM; Søndergaard A; Hjorthøj C; Knudsen CB; Andreassen AK; Veddum L; Ohland J; Wilms M; Krantz MF; Burton BK; Greve A; Bliksted V; Mors O; Clemmensen L; Nordentoft M; Thorup AAE; Hemager N. *Manuscript.*

Abbreviations

ADHD: Attention-deficit/Hyperactivity Disorder

ANCOVA: Analysis of covariance

ANOVA: Analysis of variance

CBCL: Child Behavior Checklist

CGAS: Children's Global Assessment Scale

CI: Confidence Interval

DSM: Diagnostic and Statistical Manual of Mental Disorders

FHR: Familial high-risk

FHR-BP: Familial high-risk of bipolar disorder

FHR-SZ: Familial high-risk of schizophrenia spectrum disorders

ICD: International Classification of Diseases

JTC: Jumping to Conclusions

K-SADS-PL: Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime version

OR: Odds ratio

PBC: Population-based controls

PE: Psychotic experiences

PSP: The Personal and Social Performance Scale

SMI: Severe mental illness

Summary

Background

Having a first degree relative with schizophrenia or bipolar disorder is the strongest known risk factor for developing these disorders. Therefore, familial high-risk studies, i.e. studies of relatives of individuals with schizophrenia and bipolar disorder, provide a unique opportunity to examine their precursors. The conjoint study of children born to parents with schizophrenia or bipolar disorder enables characterization of early shared and distinct vulnerability markers and potential antecedents.

There is evidence that individuals at familial high-risk of schizophrenia or bipolar disorder have a heightened prevalence of mental disorders in childhood and adolescence, however, conjoint studies of these two groups and studies of same-aged children enabling detailed characterization and comparison of their early psychopathological pathways are lacking. Psychotic disorders are rare, while psychotic experiences, including hallucinations and delusions in the absence of a diagnosable psychotic disorder, are common, particularly in childhood and adolescence. Knowledge on the prevalence and clinical significance of psychotic experiences in childhood, potential predictors of adverse outcomes, including psychotic disorders, is sparse within this population. Finally, the cognitive bias “jumping to conclusions” is associated with both clinical and subclinical delusions in adults, but little is known of its association with psychotic experiences in children and adolescents.

Objectives

The aim of the studies in the current PhD thesis is to examine the occurrence and development over time of mental disorders and psychotic experiences, as well as to examine potential associations between psychotic experiences, mental disorders, and the cognitive bias jumping to conclusions in 11-year-old children at familial high-risk of schizophrenia or bipolar disorder and population-based controls.

Methods

The studies in the current PhD thesis are part of the Danish High Risk and Resilience Study, a prospective, longitudinal, population-based cohort study of 522 children at familial high-risk of schizophrenia, i.e. children with at least one parent with schizophrenia (N= 202), at familial high-risk of bipolar disorder, i.e. children with at least one parent with bipolar disorder (N=120), and population-based controls with parents without these disorders (N=200). This cohort was retrieved through Danish nationwide registers. Children were first examined at age 7 and follow-up took place when they were 11 years old. Age 11 data were provided for 465 children corresponding to a retention rate of 89%. Mental disorders were ascertained with the Kiddie Schedule for Affective Disorders and Schizophrenia – Present and Lifetime Version (K-SADS-PL). Psychotic experiences were ascertained with the psychosis supplement from K-SADS-PL. Jumping to conclusions was examined with the Beads Task.

Results

Paper 1 showed that children at familial high-risk of schizophrenia and familial high-risk of bipolar disorder had an approximately three-fold increased risk of having met criteria for a mental disorder by age 11 compared with controls. Both high-risk groups had an increased risk of affective disorders, anxiety disorders, and stress and adjustment disorders. In addition, children at familial high-risk of schizophrenia had an increased risk of ADHD and disruptive behavior disorders. The cumulative incidence of disorders increased non-differentially across the three groups from age 7 to age 11. In **Paper 2** we found that psychotic experiences were more prevalent in children at familial high-risk of schizophrenia than in controls during middle childhood. Psychotic experiences in early childhood predicted mental disorders in middle childhood, most strongly when there were several types of early childhood psychotic experiences and when they persisted over time. Psychotic experiences were non-differentially associated with risk of mental disorders across the three groups, and predicted both internalizing, externalizing, and other mental disorders. **Paper 3** showed that children at familial high-risk of schizophrenia had a more hasty decision making style, reflected in more jumping to conclusions, than controls. Presence of psychotic experiences with delusions, but not hallucinations, was associated with jumping to conclusions. The association with psychotic experiences became non-significant when adjusting for intelligence. Higher intelligence predicted less jumping to conclusions.

Conclusions

Familial liability to schizophrenia and bipolar disorder is expressed in an elevated risk of mental disorders which manifests in early childhood and remains throughout childhood. Psychotic experiences are associated with increased risk of childhood mental disorders and should be included in mental health screenings from early childhood. Jumping to conclusions is associated with subclinical delusions at this early stage. Both childhood mental disorders, psychotic experiences, and jumping to conclusions are relevant targets for future studies on early interventions within this population. Further follow-up in the current cohort will increase knowledge on how these early developmental expressions of risk predict severe mental illness and other detrimental outcomes.

Dansk resumé

Baggrund

At have en førstegradsslægtning med skizofreni eller bipolar lidelse er den stærkeste kendte risikofaktor for at udvikle disse lidelser. Studier af familiær højrisiko, dvs. studier af slægtninge til individer med skizofreni og bipolar lidelse, udgør derfor en unik mulighed for at studere forløbere for disse lidelser. Studier, der inkluderer både børn af forældre med skizofreni og bipolar lidelse, muliggør undersøgelse af lidelsernes fælles og specifikke sårbarhedsmarkører.

Der er evidens for, at individer, der er familiært disponeret for skizofreni og bipolar lidelse, har en forøget forekomst af psykiske lidelser i barndommen og ungdommen, men der mangler studier, der inkluderer begge disse grupper af børn inden for samme alder, hvilket kan muliggøre en detaljeret beskrivelse af deres tidlige psykopatologiske profiler og udvikling. Psykotiske lidelser er sjældne, imens psykoseoplevelser, herunder subkliniske hallucinationer og vrangforestillinger uden en diagnosticerbar psykotisk lidelse, er hyppige, især i barndommen og ungdommen. Viden om forekomsten og den kliniske betydning af psykoseoplevelser i barndommen, der potentielt prædicerer mange negative følgevirkninger, herunder psykotiske lidelser, er sparsom i denne population. Endelig er den kognitive bias "jumping to conclusions" associeret med både kliniske og subkliniske vrangforestillinger hos voksne, men der mangler viden om, hvordan denne bias er relateret til psykoseoplevelser hos børn og unge.

Formål

Formålet med studierne i denne ph.d.-afhandling er at afdække forekomsten af psykiske lidelser og psykoseoplevelser, at undersøge deres udvikling over tid samt at undersøge potentielle associationer mellem psykoseoplevelser og psykiske lidelser og den kognitive bias jumping to conclusions hos 11-årige børn af forældre med skizofreni eller bipolar lidelse samt populationsbaserede kontroller.

Metoder

Studierne i denne ph.d.-afhandling er en del af the Danish High Risk and Resilience Study, et prospektivt, longitudinelt, populationsbaseret kohortestudie af 522 børn med familiær højrisiko for skizofreni, dvs. med mindst én forælder med skizofreni (N=202), med familiær højrisiko for bipolar lidelse, dvs. med mindst én forælder med bipolar lidelse (N=120), og populationsbaserede

kontroller, som har forældre uden disse lidelser (N=200). Kohorten blev udtrukket fra landsdækkende danske registre. Børnene blev undersøgt første gang, da de var 7 år. Opfølgningen fandt sted, da de var 11 år, hvor der blev indsamlet data for 465 børn, svarende til en fastholdelsesprocent på 89. Psykiske lidelser blev undersøgt med the Kiddie Schedule for Affective Disorders and Schizophrenia – Present and Lifetime Version (K-SADS-PL). Psykoseoplevelser blev undersøgt med psykosesupplementet fra K-SADS-PL. Jumping to conclusions blev undersøgt med Beads Task.

Resultater

Artikel 1 viste, at børn, der er familiært disponeret for skizofreni eller bipolar lidelse, har en cirka tre gange forøget risiko for at have opfyldt kriterierne for en psykisk lidelse i 11-årsalderen sammenlignet med kontrolbørn. Begge højrisikogrupper havde forøget risiko for affektive lidelser, angstlidelser samt stress- og tilpasningsforstyrrelser. Børn med familiær disposition for skizofreni havde desuden forøget risiko for ADHD og adfærdsforstyrrelser. Stigningen i den kumulative incidens af psykiske lidelser var non-differentiel i de tre grupper fra 7- til 11-årsalderen. I **Artikel 2** fandt vi, at psykoseoplevelser var mere hyppigt forekommende hos børn med familiær disposition for skizofreni sammenlignet med kontrolbørn midt i barndommen. Psykoseoplevelser i tidlig barndom prædicerede psykiske lidelser midt i barndommen, især ved tilstedeværelsen af mere end to typer af psykoseoplevelser samt af vedblivende psykoseoplevelser. Psykoseoplevelser var non-differerentielt associeret med psykiske lidelser på tværs af de tre grupper af børn og prædicerede både internaliserende, eksternaliserende og andre psykiske lidelser. **Artikel 3** viste, at børn med familiær disposition for skizofreni i højere grad udviser en hurtig beslutningstagning, dvs. jumping to conclusions, end kontroller. Tilstedeværelse af psykoseoplevelser med vrangforestillinger, men ikke med hallucinationer, var associeret med jumping to conclusions. Associationen med psykoseoplevelser var ikke længere signifikant, når der blev taget højde for intelligens. Højere intelligens prædicerede mindre tilbøjelighed til jumping to conclusions.

Konklusioner

Familiær disposition for skizofreni og bipolar lidelse viser sig ved en forøget risiko for psykiske lidelser, en risiko, der manifesterer sig tidligt i barndommen og vedbliver igennem barndommen. Psykoseoplevelser er associeret med forøget risiko for psykiske lidelser i barndommen og bør fra tidlig barndom inkluderes i screeninger af psykisk helbred. Jumping to conclusions er relateret til subkliniske vrangforestillinger på dette tidlige tidspunkt. Både psykiske lidelser, psykoseoplevelser

og jumping to conclusion er relevante mål for fremtidige studier af tidlig intervention i denne population. Yderligere opfølgning i kohorten vil øge viden om, hvordan disse tidlige risikomarkører prædicerer alvorlig psykisk sygdom og andre negative følgevirkninger.

Introduction

Contribution of familial high-risk studies

Schizophrenia spectrum disorders and bipolar disorder together with major depressive disorder are collectively referred to as severe mental illness (SMI). These disorders are impairing to the individual (Harvey 2011), are associated with shorter life expectancy (Walker et al. 2015; Plana-Ripoll et al. 2019a), and impose a substantial economic burden on society (MacEwan et al. 2016; Jin and Mosweu 2017). Thus, improving prediction and prevention of these disorders is crucial. Prospectively studying individuals before the onset of SMI, which usually onsets in late adolescence or early adulthood (Baldessarini et al. 2012; Solmi et al. 2021), provides an opportunity to expand knowledge on the etiology and early manifestations of risk for SMI and to inform early prevention and intervention strategies to potentially alleviate the burden of SMI.

Only a minority of individuals in the general population will develop these disorders. According to data from the Danish National Registers the lifetime risk of schizophrenia spectrum disorders is 3.78% in males and 3.67% in females, while the risk of bipolar disorder is 1.32% vs. 1.84% (Pedersen et al. 2014). By age 18 the cumulative incidence of schizophrenia spectrum disorders is 0.48% and 0.76% for boys and girls, respectively, and 0.06% vs. 0.10% for bipolar disorder (Dalsgaard et al. 2020). Having a first-degree relative with schizophrenia or bipolar disorder is the strongest known risk factor for developing these disorders. Danish register data show that the risk of being admitted with a diagnosis of a schizophrenia spectrum disorder is more than 8 times higher in offspring of one parent with schizophrenia than in controls, whereas in offspring of one parent with bipolar disorder the risk of being admitted with bipolar disorder is more than 9 times higher than in controls (Gottesman et al. 2010). Thus, familial high-risk (FHR) studies, i.e. studies of relatives of individuals with SMI, provide a unique opportunity to study the pathogenesis of these disorders and studying children at FHR is ideal to examine the earliest precursors before onset of SMI without the confounds of illness or antipsychotic use.

Schizophrenia and bipolar disorder share partly overlapping pathogenic pathways, which is, among other things, reflected in findings that children at FHR of these disorders have an elevated risk of not only the concordant disorder but also of other SMI. A meta-analysis of FHR-studies found that by adulthood 32% of offspring at FHR of SMI had a diagnosis of SMI which is a 2.5-fold increased risk compared with control offspring. Offspring of parents with schizophrenia had an increased risk of bipolar disorder and vice versa, i.e. familial transmission is only partly disorder

specific (Rasic et al. 2014). The conjoint study of children at FHR of schizophrenia and bipolar disorder therefore provides the potential for elucidating shared and distinct early vulnerability markers in the pathogenesis of these disorders. Some recent FHR-studies, including the current study, have taken a transdiagnostic approach and included both offspring at FHR of schizophrenia and bipolar disorder (Maziade et al. 2008; Thorup et al. 2018a; De la Serna et al. 2020) and major depressive disorder (Uher et al. 2014). However, to our knowledge no prior study has included both children at FHR of schizophrenia and bipolar disorder with a narrow age range enabling detailed characterization of their early developmental trajectories.

Both schizophrenia and bipolar disorder are preceded by developmental impairments in childhood and are both viewed as partly stemming from abnormal neurodevelopmental processes with the strongest evidence for schizophrenia (Cannon et al. 2002; Walker et al. 2002; Murray et al. 2004; Laurens et al. 2015; Kloiber et al. 2020). Previous FHR-studies have documented that children at FHR of schizophrenia and bipolar disorder have behavioral and cognitive impairments in childhood (Hameed and Lewis 2016; Sugranyes et al. 2017; Sandstrom et al. 2019; Sandstrom et al. 2020). In our baseline study, the VIA 7 Study, we found that, at age 7, children at FHR of schizophrenia but not bipolar disorder had impaired neurocognitive, social, and motor functioning compared with population-based controls (Burton et al. 2017; Hemager et al. 2018; Christiani et al. 2019), whereas both groups had more categorical and dimensional psychopathology than controls (Ellersgaard et al. 2018). Previous findings from our study and other studies regarding the developmental domains covered in the current thesis are described in detail below.

Early mental disorders as precursors of adult mental disorders

In most cases adult mental disorders are preceded by mental disorders in childhood and adolescence, as most individuals with an adult mental disorder have had a disorder with onset in childhood or adolescence (Kim-Cohen et al. 2003; Kessler et al. 2005; Caspi et al. 2020). Half of all cases of mental disorders start before age 14 (Kessler et al. 2005). Additionally, childhood mental disorders are associated with long-term adverse effects on functioning beyond mental disorders (Copeland et al. 2015). The risk of receiving a diagnosis of schizophrenia is significantly elevated in those with any earlier child and adolescent mental disorders (Maibing et al. 2015). Development of mental disorders over time is both homotypic, i.e. the same disorder predicting itself, and heterotypic, i.e. one disorder predicting other disorders (Kim-Cohen et al. 2003; Copeland et al. 2009; Caspi et al. 2020). As an example ADHD in childhood confers increased risk of schizophrenia

in adulthood (Dalsgaard et al. 2014) whereas affective disorders are often preceded by early anxiety (Copeland et al. 2009; Duffy et al. 2014).

Mental disorders in children and adolescents at familial high-risk of schizophrenia or bipolar disorder

Although child and adolescent mental disorders appear to be important risk factors for later mental disorders, studies of mental disorders in same-aged children at FHR of schizophrenia or bipolar providing opportunity for detailed characterization of their psychopathological pathways are lacking. Furthermore, most previous studies have only included one group of offspring precluding direct comparison of their profiles while some have not included a control group precluding comparison with the general population. A Danish register-based study found that, compared with controls, children at FHR of SMI had an elevated prevalence of mental disorders across the diagnostic spectrum warranting psychiatric treatment before age 18 (Thorup et al. 2018b).

Previous observational studies of children at FHR of bipolar disorder have found elevated rates of affective disorders, anxiety disorders, disruptive behavior disorders, and ADHD (Hillegers et al. 2005; Henin et al. 2005; Singh et al. 2007; Duffy et al. 2007; Birmaher et al. 2009; Vandeleur et al. 2012; Garcia-Amador et al. 2013; Goetz et al. 2017; Birmaher et al. 2021). There is variability across studies though, as some studies have found elevated rates of ADHD (Singh et al. 2007; Garcia-Amador et al. 2013), whereas other have not (Nurnberger et al. 2011; Vandeleur et al. 2012) or differences in rates of ADHD became non-significant after adjustment for confounders (Birmaher et al. 2009; Goetz et al. 2017). Similarly for disruptive behavior disorders some studies found elevated rates (Singh et al. 2007; Birmaher et al. 2009), whereas other studies did not (Nurnberger et al. 2011; Vandeleur et al. 2012). A meta-analysis including both children and adults up to age 30 found that ADHD was elevated in offspring of individuals with bipolar disorder compared with offspring of parents without psychiatric disorders (Lau et al. 2018). One study (Duffy et al. 2007) reported that ADHD was only elevated in offspring of parents with lithium non-responsive bipolar disorder. Relatively fewer studies have assessed mental disorders in children and adolescents at FHR of schizophrenia with structured diagnostic interviews. High rates of mental disorders have been found, with ADHD, disruptive behavior disorders, affective disorders, and anxiety disorders most consistently reported (Ross and Compagnon 2001; Hans et al. 2004; Keshavan et al. 2008; Shah et al. 2019).

Few studies have examined child and adolescent mental disorders in offspring at FHR of schizophrenia and bipolar disorder conjointly. One study (age range 7-22 years) with no control group did not find any differences in rates of mental disorders between these two FHR-groups (Maziade et al. 2008). Another study, including a control group, found that both FHR-groups had higher rates of any disorder than controls. Offspring at FHR of schizophrenia had higher rates of ADHD than offspring at FHR of bipolar disorder and controls and higher rates of anxiety disorders than controls. Offspring at FHR of bipolar disorder had higher rates of ADHD and affective disorders than controls (age range 6-17 years at baseline) (Sanchez-Gistau et al. 2015). This study reported a gradient of severity with children at FHR of schizophrenia having the highest prevalence and children at FHR of bipolar disorder intermediate relative to controls (Sanchez-Gistau et al. 2015; De la Serna et al. 2020). In our baseline study, the VIA 7 Study, both children at FHR of schizophrenia and FHR of bipolar disorder had a higher prevalence of any disorder, anxiety disorders, and stress and adjustment disorders compared with population-based controls. Children at FHR of schizophrenia had higher rates of ADHD and disruptive behavior disorders than controls. Children at FHR of bipolar disorder had more autism spectrum disorders than controls. There were too few children with affective disorders to calculate confidence intervals. There were no diagnoses of mania. Very few children (< 5) met criteria for a psychosis spectrum disorder at age 7, and they all pertained to the schizophrenia high-risk group.

Psychosis spectrum disorders and bipolar disorder before adolescence are rare and usually onset in late adolescence or early adulthood in these populations (Duffy et al. 2014; Shah et al. 2019). There appears to be some early specificity with parental disorder in young offspring below age 20 (Rasic et al. 2014). In the previously mentioned Danish register-based study, offspring at FHR of schizophrenia had higher rates of early onset psychosis than offspring at FHR of bipolar disorder before age 18 (Thorup et al. 2018b).

Mapping psychopathological profiles in children at FHR of schizophrenia and FHR of bipolar disorder may expand knowledge on shared and distinct early antecedents of these disorders with the potential to improve early prediction and prevention.

The psychosis continuum

Although psychotic disorders are rare (Pedersen et al. 2014; Dalsgaard et al. 2020) psychotic experiences (PE), i.e. psychotic symptoms without a diagnosable psychotic disorder, are relatively common (Linscott and van Os 2013), particularly in childhood and adolescence, however, their prevalence decreases with advancing age (Kelleher et al. 2012a). PE in childhood and adolescence may even be characterized as part of normative development (Kelleher et al. 2012a; Maijer et al. 2019). Meta-analytic evidence from mixed-age samples suggests that in around 80% of individuals PE remit over time, whereas for a small proportion, around 20%, PE persist (Linscott and van Os 2013). PE are thought to be part of an extended psychosis phenotype, i.e. to lie on a continuum with psychotic disorders, with PE as distributed and mostly transitory manifestations of psychosis proneness across the population and the diagnostic spectrum, and psychotic disorders as the rare outcomes of PE becoming increasingly persistent and impairing (Linscott and van Os 2013; van Os and Reininghaus 2016). One study including adolescents and young adults found that in one fifth of cases psychotic disorders were preceded by persistent PE with risk of transitioning increasing progressively with increased persistence of PE (Dominguez et al. 2011).

Associations between psychotic experiences in childhood and adolescence and mental health

Although few individuals with PE will develop psychotic disorders, PE in childhood and adolescence are associated with a range of adverse mental health outcomes. As documented in both cross-sectional and longitudinal studies in the general population, PE are associated with concurrent and subsequent mental disorders (Kelleher et al. 2012b; Calkins et al. 2014; Jeppesen et al. 2015a; Healy et al. 2019a; Rimvall et al. 2020b; Carey et al. 2021). Further, presence of PE can be seen as an expression of higher severity of non-psychotic psychopathology (Guloksuz et al. 2015), including increased occurrence of comorbidity (Kelleher et al. 2012b; Kelleher et al. 2014; Jeppesen et al. 2015a). PE appear to predict psychopathology across the diagnostic spectrum (Jeppesen et al. 2015a; Healy et al. 2019b; Rimvall et al. 2020b) although the strongest evidence is for psychotic disorders (Poulton et al. 2000; Healy et al. 2019a). Longitudinal studies suggest that persistent PE relative to transient PE are particularly strongly associated with other psychopathology (Dominguez et al. 2011; De Loore et al. 2011; Wigman et al. 2011a; Downs et al. 2013; Havers et al. 2019; Rammos et al. 2021; Karcher et al. 2021).

Additionally, PE are associated with other detrimental mental health outcomes such as suicidality, self-harm, and increased mental health service use (Honings et al. 2016; Yates et al. 2019; Rimvall

et al. 2020b; Rimvall et al. 2020a). A recent study found that childhood PE which were both persistent and distressing most strongly predicted mental health service use (Karcher et al. 2021). Furthermore, childhood PE predict poorer global functioning with lasting effects into early adulthood beyond the effects of mental disorders (Healy et al. 2018; Trotta et al. 2020). Studies of PE before middle childhood are rare, but there is some evidence that hallucinations in early childhood predict later psychopathology (Bartels-Velthuis et al. 2011; Bartels-Velthuis et al. 2016).

Psychotic experiences in children and adolescents at familial high-risk of schizophrenia or bipolar disorder

The continuum theory for psychosis is supported by findings from general population studies that PE and psychotic disorders share risk factors, including a family history of psychosis (Polanczyk et al. 2010; Kelleher and Cannon 2011; Jeppesen et al. 2015b). However, findings regarding family history of psychosis are not unequivocal and one study found that parental psychotic psychopathology only suggestively predicted presence of PE whereas it predicted persistence of PE (Wigman et al. 2012b). In a large general population study PE were not associated with a parental history of psychosis (Zammit et al. 2008) and this did not predict persistence (Rammos et al. 2021). In another study effects of parental psychosis on presence of PE diminished when including covariates (Karcher et al. 2020), yet, parental psychosis predicted persistence of PE (Karcher et al. 2021).

In spite of the continuum between psychotic disorders and PE relatively few FHR-studies have examined the prevalence and significance of PE in samples of children and adolescents at FHR of psychosis. One FHR-study found that adolescents and young adults with at least two first degree relatives with schizophrenia had more PE compared with those without a family history of schizophrenia (Johnstone et al. 2000). Another study including both children, adolescents, and young adults found that the prevalence of PE did not differ between those with a family history of schizophrenia, bipolar disorder, or major depressive disorder (MacKenzie et al. 2016). A study including child and adolescent offspring at FHR of schizophrenia or bipolar disorder found that those at FHR of schizophrenia scored higher on prodromal symptoms than controls with those at FHR of bipolar disorder intermediate, not significantly different from either of the other groups (De la Serna et al. 2020). Another study similarly found that offspring aged 6-18 at FHR of bipolar disorder did not differ from controls in prevalence of PE (Mendez et al. 2019).

Knowledge on the developmental pathways and clinical outcomes of PE in FHR-populations is sparse and most evidence on PE stems from general population studies. A longitudinal FHR-study found that PE predicted psychosis in young first and second degree relatives of individuals with schizophrenia (Tandon et al. 2012). Another study documented that PE belonged to clusters of factors predicting transition to SMI in a sample of youth born to parents with schizophrenia or bipolar disorder (Paccalet et al. 2016). In our baseline study, the VIA 7 Study, we found that PE were more prevalent in children at FHR of schizophrenia than in population-based controls and, to a lesser extent, more prevalent in children at FHR of bipolar disorder, and that PE were cross-sectionally associated with mental disorders at age 7. To our knowledge, no prior study has prospectively examined clinical outcomes of early childhood PE in children at FHR of schizophrenia or bipolar disorder. Examining PE within this population is important to understand their potential as early vulnerability markers.

Jumping to conclusions in the psychosis continuum

Cognitive models for the positive symptoms of psychosis propose that delusions may in part stem from biased cognitive processes leading individuals to the erroneous appraisal and interpretation of their experiences (Garety et al. 2001; Freeman 2007). This proposition is empirically supported by findings that adults with delusions show cognitive biases (McLean et al. 2017), the most widely replicated of which referred to as the "jumping to conclusions" (JTC) bias, i.e. making decisions based on inadequate evidence (Dudley et al. 2016).

The JTC bias has consistently been found more frequently in adults with psychosis than in individuals with non-psychotic mental disorders and without mental disorders (Falcone et al. 2015b; Dudley et al. 2016; So et al. 2016). There is also some evidence that the JTC bias could be a vulnerability marker associated with familial liability for psychosis as this bias is found more frequently in adult first degree relatives of individuals with psychosis than in controls (Van Dael et al. 2006; Henquet et al. 2020). To our knowledge no prior study has examined whether the JTC bias marks familial liability for psychosis in preadolescence.

The JTC bias appears to covary with the presence of delusions across the delusion continuum. Individuals with delusions show more JTC than individuals without delusions in both clinical populations of individuals with psychosis (Garety and Freeman 2013; Falcone et al. 2015b; Dudley et al. 2016; McLean et al. 2017), those at clinical high risk for psychosis (Broome et al. 2007), as

well as in individuals with other mental disorders (McLean et al. 2017). In nonclinical adult populations JTC is associated with subclinical delusional ideation (Van Dael et al. 2006; Zawadzki et al. 2012; Menon et al. 2013; Ross et al. 2015; Livet et al. 2020) suggesting that JTC could be present before the formation of clinical delusions and is associated with delusion liability. JTC appears to be exacerbated toward the severe end of the delusion continuum (Garety and Freeman 2013; McLean et al. 2017). One study found that JTC was only associated with PE with need-for-care and not with PE without need-for-care (Ward et al. 2018). There are few studies on JTC in bipolar disorder. One study did not find more JTC in adults with bipolar disorder than in controls (Can et al. 2019). However, another study examining affective disorders more broadly documented that JTC was more frequent in individuals where affective disorders and PE co-occurred than in individuals with neither of these and that JTC increased with increasing severity of PE reflected in higher number of PE and psychosis-related help-seeking behavior (Reininghaus et al. 2019).

There is accumulating evidence that neurocognitive deficits are associated with JTC. Findings from a sample of children and adolescents as well as adult samples suggest that IQ deficits are associated with the bias (Falcone et al. 2015b; Hassanali et al. 2015; Tripoli et al. 2021). Evidence suggests that JTC could be causal to delusion formation as it is associated with persistence and worsening of delusions in individuals with psychosis (Dudley et al. 2013; Falcone et al. 2015a). Yet, studies of whether JTC precedes delusions in non-clinical populations are lacking.

It is relatively unexplored whether JTC is related to PE in children and adolescents. One study documented that JTC was associated with presence of PE in a sample of children and adolescents aged 5-14 who had been referred to child and adolescent mental health services (Hassanali et al. 2015). Expanding the understanding of the cognitive processes associated with PE in childhood and adolescence may improve early identification of at-risk individuals and inform early prevention and intervention.

Objectives

The studies in the current thesis aimed to examine the occurrence and development over time of mental disorders and PE, as well as the associations between PE, mental disorders, and the cognitive bias JTC in preadolescent children at FHR of schizophrenia or bipolar disorder and population-based controls from the longitudinal, prospective, FHR cohort study the Danish High Risk and Resilience Study.

In **Paper 1** we aimed to examine the cumulative incidence of mental disorders and comorbidity by age 11 as well as their development from age 7 to age 11. We also examined global functioning and its development over time across the three groups. In **Paper 2** we aimed to examine the prevalence of PE in middle childhood across the three groups and to examine whether early childhood PE and developmental pathways of PE predicted mental disorders in middle childhood. In **Paper 3** we aimed to examine the presence of the cognitive bias JTC across the three groups and whether JTC was associated with concurrent PE with and without delusions.

The aims and hypotheses for the three studies are described in detail in the individual papers.

Methods

Participants and procedures

The Danish High Risk and Resilience Study is a prospective, longitudinal, nationwide cohort study in Denmark. The cohort consists of 522 children who have at least one biological parent diagnosed with a schizophrenia spectrum disorder (N=202, ICD-10 codes: F20, F22, F25 or ICD-8 codes: 295, 297, 298.29, 298.39, 298.89, 298.99) or bipolar disorder (N=120, ICD-10 codes: F30, F31 or ICD-8 codes: 296.19, 269.39) and population-based controls (hereafter controls) where neither parent has been diagnosed with these disorders (N=200). Nine children had two parents who were both diagnosed with either schizophrenia or bipolar disorder. If one parent had schizophrenia and the other had bipolar disorder the child pertained to the schizophrenia high-risk group as per the ICD-10 hierarchy (World Health Organization 1993). The cohort was retrieved from Danish national registers (the Danish Civil Registration System and the Danish Psychiatric Central Research Register) (Pedersen et al. 2006; Mors et al. 2011), permission for which was granted by the Danish Ministry of Health. The study adheres to the guidelines from the Danish Committee on Health Research Ethics, however, approval of the study was deemed unnecessary by this authority due to the observational nature of the study. The study was approved by the Danish Data Protection Agency.

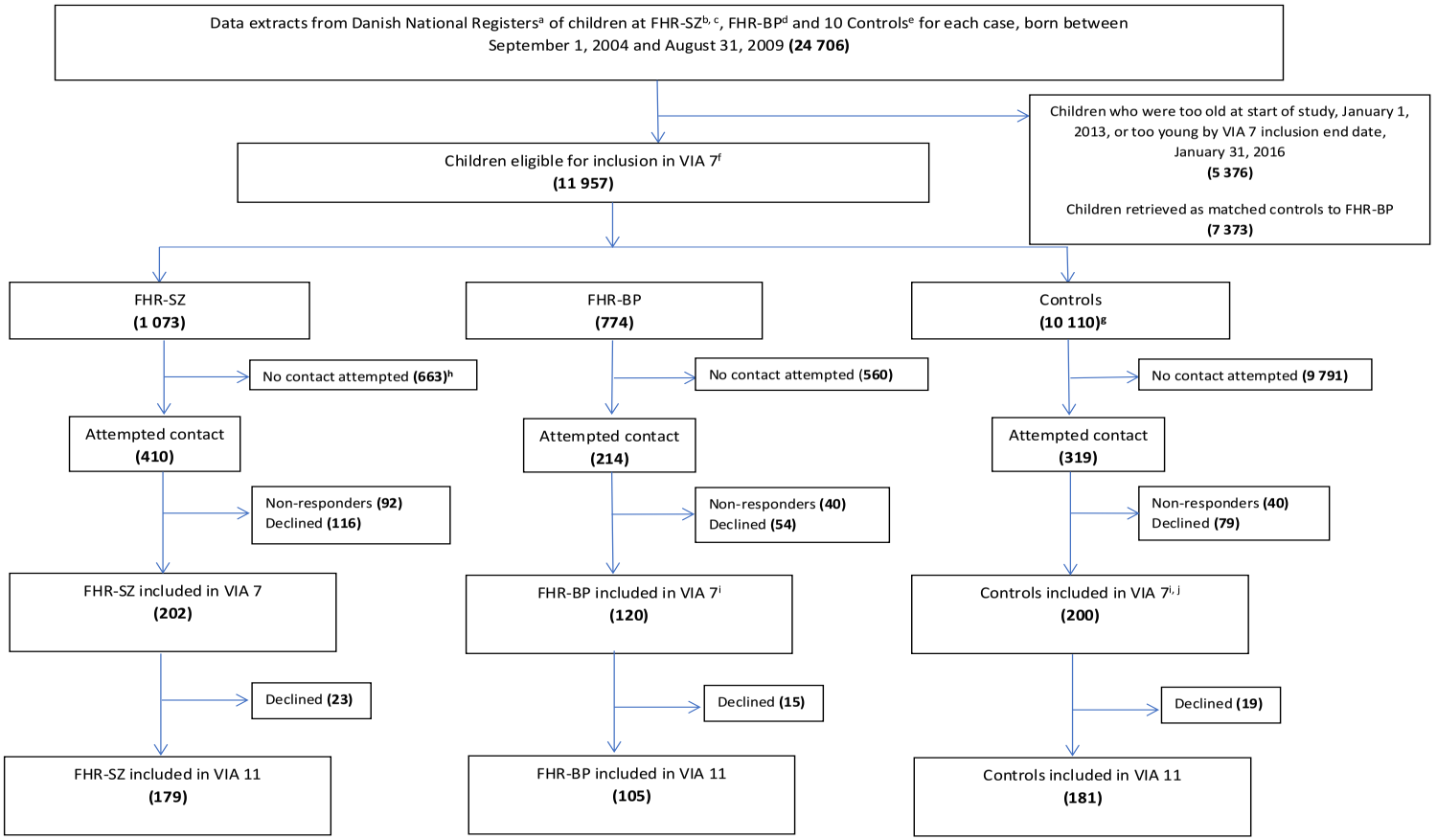
Controls were matched to the children at FHR of schizophrenia on sex, age, and municipality. Due to limitations on resources it was not possible to enroll as many children at FHR of bipolar disorder. Children at FHR of bipolar disorder were comparable to children in the other two groups on baseline inclusion age and sex. Children had to be born in Denmark to be eligible for inclusion in the study and all participating children had Danish as their first language. Retrieval of the cohort is presented in Figure 1. Background characteristics of the original cohort are presented in Table 1. Children at FHR of schizophrenia and FHR of bipolar disorder were less likely to live with both biological parents and more often lived in a single parent household than controls. Parents in the FHR of schizophrenia and FHR of bipolar disorder groups had lower levels of functioning than parents in the control group. Parents in the FHR of schizophrenia group had lower levels of education than parents in the FHR of bipolar disorder group and in the control group. For details, see Table 1. The included families were overall comparable to the non-included families, i.e. the cohort was representative of the background population (Krantz, MF et al.).

Children and their caregivers were first assessed at face-to-face assessments carried out from January 1, 2013 to January 31, 2016 when the children were 7 years old (the VIA 7 Study). The first face-to-face follow-up was conducted when the children were 11 years old (the VIA 11 Study) and took place from March 1, 2017 until June 30, 2020. All assessments were carried out at our two university hospital research facilities in Copenhagen and Aarhus and in the homes of the families by psychologists, medical doctors, and research nurses formally trained in all assessment instruments. Child assessors were blinded to the children's familial risk status and, at follow-up, to children's prior data. Written informed consent was obtained from the caregivers (parents or guardians) and assent was obtained from the children following explanation of the full study procedures.

In the VIA 11 Study data were provided for 465 children corresponding with a retention rate of 89%, see Figure 1. Children participating in the three studies included in this thesis did not differ on sex, age, or onset of puberty across the three groups, see **Papers 1-3**. Background characteristics and dropout analyses for the children providing data for the specific studies in this thesis have been described in each paper, see **Papers 1-3**. Children at FHR of schizophrenia had lower socioeconomic status reflected in lower levels of education of their primary caregivers than the other two groups, see **Paper 2**.

Children who dropped out did not differ from those who remained in the study regarding prevalence of any Axis I mental disorder or PE at age 7, see **Papers 1-2**. However, those who dropped out had significantly lower levels of global functioning than those who remained in the study, see **Papers 1 and 3**, and significantly higher levels of dimensional psychopathology, see **Paper 3**.

Figure 1. Data extraction and recruitment of the VIA 7 and VIA 11 cohort



[a] Danish National Registers: the Danish Civil Registration System and the Danish Psychiatric Central Research Register.
[b] FHR-SZ: Children at familial high-risk of schizophrenia spectrum disorders.
[c] Double diagnosed parents: Parents with diagnoses of schizophrenia and bipolar disorder were assigned to the schizophrenia high-risk group as per the ICD-10 hierarchy.
[d] FHR-BP: Children at familial high-risk of bipolar disorder.
[e] Controls: Population-based control children of parents with no diagnoses of schizophrenia spectrum disorders or bipolar disorder.
[f] Research protection: As of May 2011, legislation was enacted to protect individuals´ phone numbers from being called for participation in scientific research. Therefore, there were eligible children who were not contacted and enrolled in VIA 7.
[g] Controls selection: Up to 10 controls were retrieved for each child in the FHR-SZ group and the FHR-BP group. Controls were matched to cases on sex, municipality, and exact age. The original intent was to only select control cases that were matched to children at FHR-SZ. However, there are 38 FHR-BP controls among the 200 total controls.
[h] Definition of contact: First through letters sent to the child´s address. If the family did not respond, contact by telephone was attempted (calls and text messages), if a phone number could be found.
[i] Re-assigned control parent: One control parent was found to have a diagnosis of bipolar disorder made by a private doctor, therefore the diagnosis was not present/visible in the National Register extract, as private doctors do not report to the National Register. This family/parent was therefore reassigned to the FHR-BP group. Therefore the N=201 for controls is now N=200.
[j] Control children not in the extract: Two younger siblings were included in VIA 7 by request of the parents. They were not in the original extract.

Table 1. Background characteristics of 522 children participating in The Danish High Risk and Resilience Study and their biological parents

	FHR-SZ	FHR-BP	Controls	*P*	FHR-SZ vs. controls	FHR-BP vs. controls	FHR-SZ vs. FHR-BP
Children, N	202	120	200				
Female, N (%)	93 (46.0)	56 (46.7)	93 (46.5)	.99[b]	-	-	-
Age at inclusion, mean (SD)	7.84 (.22)	7.86 (.20)	7.81 (.20)	.10[a]	-	-	-
Two biological parents with SZ and/or BP, N (%)	8 (4.0)	1 (0.8)	-	-	-	-	-
CBCL score, N, mean (SD), (N=192/111/191)	27.2 (21.1)	23.4 (19.7)	17.0 (14.7)	<.001[a]	<.001[a]	.004[a]	.09[a]
CGAS, N, mean (SD), (N=199/118/197)	68.1 (15.4)	73.6 (14.9)	77.7 (13.5)	<.001[a]	<.001[a]	.02[a]	.001[a]
Child´s home environment							
Living with both biological parents, N (%)	82 (40.6)	63 (52.5)	169 (84.5)	<.001[b]	<.001[b]	<.001[b]	.04[b]
Living out of home, N (%)	11 (5.4)	0 (0.0)	1 (0.5)	.001[b]	.004[b]	.44[b]	.009[b]
Living with index parent, N (%)	124 (61.4)	84 (70.0)	189 (94.5)	<.001[b]	<.001[b]	<.001[b]	.12[b]
Living with a single parent, N (%), (N=202/120/199)	75 (37.1)	39 (32.5)	21 (10.6)	<.001[b]	<.001[b]	<.001[b]	.40[b]
PSP primary caregiver, mean (SD), (N=197/118/197)	73.1 (14.0)	74.5 (14.1)	84.4 (9.1)	<.001[a]	<.001[a]	<.001[a]	.35[a]
Index parents, N	200	116	204				
Female, N (%)	111 (55.5)	64 (55.2)	115 (56.4)	.97[b]	-	-	-
Age at child´s birth, mean (SD)	30.2 (6.1)	33.1 (7.0)	32.8 (4.8)	<.001[a]	<.001[a]	.67[a]	<.001[a]
PSP, mean (SD), (N=158/102/194)	66.1 (15.7)	68.9 (14.1)	84.3 (9.9)	<.001[a]	<.001[a]	<.001[a]	.10[a]
Employed or studying, N (%), (N=187/109/201)	93 (49.7)	61 (56.0)	185 (92.0)	<.001[b]	<.001[b]	<.001[b]	.30[b]
Education, N	178	109	197				
Primary/lower secondary, N (%)	54 (30.3)	10 (9.2)	8 (4.1)				
Upper secondary, vocational, short-cycle tertiary, N (%)	76 (42.7)	45 (41.3)	95 (48.2)	<.001[c]	<.001[c]	.99[c]	<.001[c]
Bachelor degree, equivalent or higher, N (%)	48 (27.0)	54 (49.5)	94 (47.7)				
Biological non-index parents, N	186	114	192				
Female, N (%)	82 (44.1)	51 (44.7)	83 (43.2)	.97[b]	-	-	-
Age at child´s birth, mean (SD)	30.9 (6.4)	33.1 (5.4)	33.0 (4.3)	<.001[a]	<.001[a]	.84[a]	.001[a]
PSP, mean (SD), (N=163/94/180)	76.4 (14.3)	81.8 (13.1)	85.5 (8.4)	<.001[a]	<.001[a]	.01[a]	.001[a]
Employed or studying, N (%), (N=177/109/188)	133 (75.1)	93 (85.3)	179 (95.2)	<.001[b]	<.001[b]	.003[b]	.04[b]
Education, N	176	106	187				
Primary/lower secondary, N (%)	31 (17.6)	5 (4.7)	10 (5.3)				
Upper secondary, vocational, short-cycle tertiary, N (%)	86 (48.9)	44 (41.5)	89 (47.6)	.002[c]	.002[c]	.28[c]	<.001[c]
Bachelor degree, equivalent or higher, N (%)	59 (33.5)	57 (53.8)	88 (47.1)				

Index parent refers to the biological parent with a diagnosis of schizophrenia or bipolar disorder. In the control group index parent refers to the matched biological parent without any of these disorders. Abbreviations: BP: Bipolar disorder. CBCL: The Child Behavior Checklist. CGAS: Children's Global Assessment Scale. FHR-BP: Children at familial high-risk of bipolar disorder. FHR-SZ: Children at familial high-risk of schizophrenia. PSP: The Personal and Social Performance Scale. SZ: Schizophrenia [a]One-way ANOVA test with posthoc Least Significant Difference. [b]Chi square test. [c]Linear by linear association p value is used when an ordinal variable has more than two categories

Measures

The face-to-face assessments of the children in the VIA 7 Study and the VIA 11 Study consisted of extensive, multi-day batteries of tests, interviews, and questionnaires including measures of psychopathology, neurocognition, social cognition, home environment, and physical measures. Caregivers were also assessed with a smaller assessment battery. The full procedures have been described in detail elsewhere (Thorup et al. 2015; Thorup et al. 2018a). The primary and secondary measures for the studies included in this thesis are described below.

Primary measures

Assessment of Axis I mental disorders

At age 7 and age 11 children's mental disorders were ascertained with the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children - Present and Lifetime Version (K-SADS-PL) which is a validated, semi-structured diagnostic interview for assessing Axis I mental disorders in children and youths aged 6 to 18 years (Kaufman et al. 1997). At age 7 children and the primary caregiver of each child were interviewed about mental disorders during the child's life. At age 11 they were interviewed about disorders during the four-year follow-up. As mentioned above, interviewers were blinded to the children's prior data and their familial risk status. In accordance with the K-SADS-PL manual all available information about the child could be taken into consideration for the summary ratings, e.g. anamnestic information, or information from questionnaires or cognitive tests, as well as the interviewer's clinical impression of the child. Summary ratings were based on the interviewer's best clinical judgment. All diagnoses were confirmed in consensus meetings with a child and adolescent psychiatrist (Anne Amalie Elgaard Thorup), blinded to the children's prior data and familial risk status. In the VIA 7 Study diagnoses were based on DSM-IV (American Psychiatric Association 1994) and in the VIA 11 Study they were based on both DSM-IV and DSM-5 (American Psychiatric Association 2013). For the analyses in the VIA 11 Study disorder categories from the VIA 7 Study were retained. Any Axis I disorder was defined as having any disorder from K-SADS-PL. Elimination disorders, specific phobias, as well as transient and unspecified tics were excluded due to their questionable clinical significance. For further details see **Paper 1**. Methods from the VIA 7 Study have been described in detail elsewhere (Ellersgaard et al. 2018). In the studies included in this thesis mental disorders during the child's life measured at age 7 are referred to as early childhood mental disorders, whereas disorders during the four-year follow-up measured at age 11 are referred to as middle childhood mental disorders. The cumulative incidence is defined as the proportion of children who have met

criteria for the specified mental disorder at any point during their lives until the specified time point.

For the analyses with PE and mental disorders we constructed three disorder categories: internalizing disorders (affective disorders and anxiety disorders), externalizing disorders (ADHD and disruptive behavior disorders), and other disorders (all remaining disorders), as detailed in the Online Supplement for **Paper 2.**

Assessment of psychotic experiences

PE were assessed in clinical interviews with the psychosis supplement from K-SADS-PL at both age 7 and age 11 by the same interviewer conducting the K-SADS-PL interview. All children and their primary caregivers were interviewed about all items from the psychosis supplement, i.e. 9 items for hallucinations and 13 for delusions, regardless of their initial answers to the two screening questions. If the child or caregiver endorsed a symptom, corresponding with a score of 2 "likely present" or 3 "definitely present" on K-SADS-PL, the child or caregiver was asked additional questions about the symptom (frequency, duration, degree of conviction, distress, and impact on functioning). The symptom was then re-evaluated on a 7-point scale ranging from 0 to 6 (0=absent, 1=possibly present, 2=mild, 3=moderate, 4=moderately severe, 5=severe but not psychotic, 6=severe and psychotic). At follow-up all ratings were confirmed in consensus meetings with a child and adolescent psychiatrist (Anne Amalie Elgaard Thorup). For the studies included in this thesis, the scores were dichotomized into a binary variable of presence or non-presence of PE, with presence of PE corresponding to a score of 2 or above on the 7-point scale, i.e. definite PE. For the analyses five types of auditory hallucinations were collapsed into one. At follow-up symptoms occurring only when the child was falling asleep or waking up and co-occurring with fever were excluded. The definition of PE was slightly broader at baseline as these symptoms were not systematically excluded. Methods from the VIA 7 Study have been described in detail elsewhere (Ellersgaard et al. 2021). Having any PE was defined as having any type of hallucination or delusion. To reflect severity a categorical variable with number of different types of PE was constructed as detailed in **Paper 2**. In the studies included in this thesis PE during the child's life measured at age 7 are referred to as early childhood PE, whereas PE during the four-year follow-up measured at age 11 are referred to as middle childhood PE. Current PE were defined as occurring within the past six months.

To reflect the development in PE over time, i.e. the developmental pathways of PE, we constructed four groups with the following definitions: Children with no early childhood nor any middle childhood PE were labelled the "Never psychotic experiences" group. Children with early childhood PE but no middle childhood PE were labelled the "Remittent psychotic experiences" group. Children with no early childhood PE but with middle childhood PE were labelled the "Incident psychotic experiences" group. Children with both early and middle childhood PE were labelled the "Persistent psychotic experiences" group.

Assessment of jumping to conclusions

JTC was measured with a modified version of the Beads Task (Huq et al. 1988; Garety et al. 1991) which is the most commonly used paradigm for this assessment (Dudley et al. 2016). In the Beads Task individuals are presented with a series of beads of two different colors and asked to guess which of two jars the beads are being drawn from. The two jars contain beads in equal but opposite color ratios (Huq et al. 1988; Garety et al. 1991). A previous study using a modified version of the task has demonstrated that it is suitable for measuring JTC in children (Hassanali et al. 2015). Instructions in Danish were devised by the PhD student along with a specialist in child neuropsychology (senior researcher Jens Richardt Møllegaard Jepsen).

In the current study children were first presented with a practice trial with two jars each containing 100 beads in ratios of 85:15 and 15:85. Afterwards children completed four trials with two jars containing beads in ratios of 60:40 and 40:60. Variations of the task have been employed in different studies (Dudley et al. 2016; So et al. 2016). However, we chose the harder 60:40/40:60 version as, in adults, this has shown better discrimination between individuals with an attenuated JTC bias, such as at risk groups, and controls than easier versions of the task (So et al. 2016). The child was instructed that beads would be drawn one at a time, consecutively from one of the jars in a random order, however, beads were in fact presented to the child in a prespecified order. The child was asked to guess which jar the beads were being drawn from when it felt certain. For the study included in this thesis the main outcome variable from the Beads Task indexing JTC was the average number of beads drawn across the four trials before the child made a guess. The number of beads drawn is usually referred to as "draws to decision", i.e. the lower the draws to decision, the more pronounced the JTC bias (Dudley et al. 2016). The continuous outcome variable draws to decision was dichotomized into a secondary outcome variable denoting an "extreme JTC" bias, defined as making a guess after seeing only a single bead on either of the four trials. We chose this

cutoff as it has been shown to better distinguish between groups with different levels of psychosis liability than using less stringent cutoffs (Van Dael et al. 2006). Further details regarding the method can be found in **Paper 3** of this thesis.

Secondary measures

Assessment of global functioning, IQ, dimensional psychopathology, puberty onset, and primary caregivers' level of education

The child's current global functioning was assessed with Children's Global Assessment Scale (CGAS) (Shaffer et al. 1983) as part of the K-SADS-PL interview. CGAS is an interviewer-based rating scale for global functioning ranging from 1-100, with higher scores denoting better functioning, taking into account all aspects of daily functioning, including the severity of psychiatric symptoms. At age 11 all CGAS scores were confirmed in consensus meetings with a child and adolescent psychiatrist (Anne Amalie Elgaard Thorup). Methods from the VIA 7 Study are described in detail elsewhere (Ellersgaard et al. 2018). IQ was measured with Reynolds Intellectual Screening Test (RIST). RIST is an abbreviated version of Reynolds Intellectual Assessment Scales (RIAS) (Reynolds, CR and Kamphaus, RW 2003; McNicholas and Floyd 2016) and consists of a verbal and nonverbal scale combined into an overall, age adjusted IQ estimate. Methods are described in detail elsewhere (Hemager et al. 2018; Knudsen, CB et al.). Dimensional psychopathology was measured with the Child Behavior Checklist (CBCL) (Achenbach, T.M. & Rescorla, L.A. 2001) completed by the child's primary caregiver. CBCL is a rating scale for assessing emotional and behavioral symptoms with higher scores indicating higher symptom severity. Puberty onset was measured with self-reported Tanner Stages (Marshall and Tanner 1969; Marshall and Tanner 1970) which is a commonly used and reliable measure of pubertal development (Coleman and Coleman 2002). Information on level of education of the primary caregiver of each child was obtained in anamnestic interviews.

Statistical analyses

Between-group differences in background characteristics were analyzed with chi-square tests and one-way analysis of variance with Least Significant Difference post hoc tests when appropriate. Analyses were not adjusted for covariates. Dropout analyses were performed with chi-square and t-tests.

Frequencies and percentages for the main outcomes were calculated through crosstabulations.

To ascertain between-group differences in the cumulative incidence of mental disorders and the prevalence of PE binomial logistic regression analyses adjusted for sex of the child were carried out. First controls were used as reference, then, for comparisons between children at FHR of schizophrenia and FHR of bipolar disorder, children at FHR of bipolar disorder were used as reference. Differences in global functioning were analyzed through analysis of covariance (ANCOVA) adjusted for sex of the child with post hoc Least Significant Difference.

To examine between-group differences in changes over time (i.e. from age 7 to age 11) in the cumulative incidence of mental disorders and in global functioning we performed repeated measures mixed-effects multivariable binomial logistic regressions and a linear mixed-model with repeated measures, respectively, with FHR-group, time, sex of the child, and interaction time x FHR-group as fixed factors.

To examine the stability of mental disorders from age 7 to age 11 we conducted a multivariable binomial logistic regression analysis on children with any early childhood Axis I disorder with any middle childhood Axis I disorder as dependent variable and FHR-group as predictor.

Prediction from early childhood PE to middle childhood PE and mental disorders, was examined with binomial logistic regression adjusted for sex of the child, first with presence or absence of PE as predictor, then with number of PE as predictor. Children with no PE were used as reference. For the analyses with middle childhood mental disorders as outcome analyses were successively adjusted for early childhood mental disorders, then FHR-group. Analyses with middle childhood mental disorders as outcome were repeated with developmental pathways of PE as predictor using the “Never psychotic experiences” group as reference. Cross-sectional analyses of associations between middle childhood PE and concurrent mental disorders were carried out in

the same way as the longitudinal analyses. To examine whether PE were differentially associated with outcomes across the three FHR-groups an interaction term with FHR-group x the specific PE variable was added to the first models in all analyses with PE as predictor. Finally longitudinal and cross-sectional analyses with PE as predictor were repeated with internalizing, externalizing, and other disorders as outcomes in separate models.

For JTC between-group differences in draws to decision were analyzed with ANCOVA adjusted for sex of the child with post hoc Least Significant Difference. IQ was then added as covariate. Associations between draws to decision and concurrent PE were analyzed with ANCOVA adjusted for sex of the child with a categorical predictor variable with three levels: no current PE, current PE with hallucinations only, and current PE with delusions. Analyses were successively adjusted for FHR-group, then IQ. To examine interaction effects an interaction term with FHR-group x the PE predictor variable was added to the first models. Yet, due to the low number of children within each PE group for this paper we also report analyses stratified by FHR-group. In exploratory analyses similar binomial logistic regressions were carried out using the dichotomous measure for extreme JTC as outcome.

All main analyses in the papers for this thesis were adjusted for sex of the child to control for effects of sex on the examined outcomes. Relation between sex, mental disorders, and PE is presented in the Online Supplement for **Paper 2.** The analyses were not adjusted for socioeconomic status due to the risk of overadjusting the data within this FHR design as socioeconomic status is intrinsically associated with familial risk status (Dickson et al. 2020).

Alpha was set to < .05. All data were analyzed using SPSS version 25.

Summary of results

The main findings from the three papers in this thesis are summarized below. Details of the findings can be found in the individual papers.

Paper 1

In **Paper 1** we found that children at FHR of schizophrenia and FHR of bipolar disorder had an approximately three-fold increased risk of having met criteria for a mental disorder by age 11 compared with controls. Both high-risk groups had an increased risk of affective disorders, anxiety disorders, and stress and adjustment disorders, whereas the risk of disruptive behavior disorders and ADHD was only elevated in children at FHR of schizophrenia, as illustrated in Table 2. There were few cases of psychotic disorders and only in children at FHR of schizophrenia. There were no cases of mania. The cumulative incidence of disorders increased equally across the three groups from age 7 to 11, as illustrated in Figure 2. Further, children at FHR of schizophrenia and FHR of bipolar disorder had lower levels of global functioning than controls with non-differential change over time across the three groups, as illustrated in Figure 3 and 4. There was some evidence that children at FHR of schizophrenia were less likely to remit from early childhood disorders than the other two groups, for details see **Paper 1**.

Table 2. Cumulative incidence of DSM-IV and DSM-5 Axis I mental disorders and comorbidity by age 11 years in 450 children at FHR-SZ, FHR-BP, and PBC in the Danish High Risk and Resilience Study, VIA 11 – from **Paper 1**

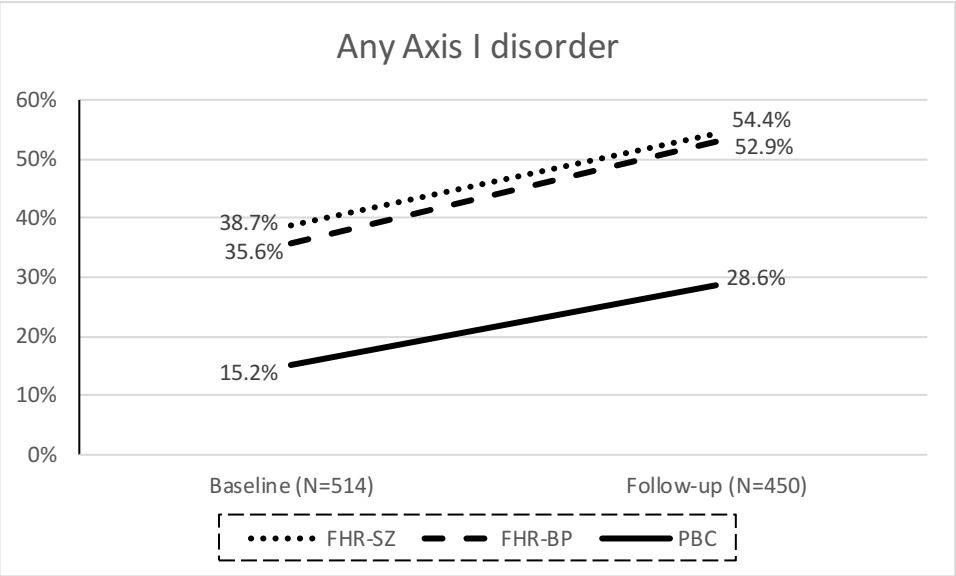
	N (%)			Pairwise comparisons					
				FHR-SZ vs. PBC		FHR-BP vs. PBC		FHR-SZ vs. FHR-BP	
	FHR-SZ (n = 171)	FHR-BP (n = 104)	PBC (n = 175)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)
Any Axis I disorder[a]	93 (54.4%)	55 (52.9%)	50 (28.6%)	**<.001**	3.0 (1.9-4.7)	**<.001**	2.8 (1.7-4.7)	.76	1.1 (0.7-1.8)
Affective disorders	16 (9.4%)	11 (10.6%)	4 (2.3%)	**.009**	4.4 (1.4-13.5)	**.007**	5.1 (1.6-16.4)	.73	0.9 (0.4-1.9)
Psychotic disorders[b]	6 (3.5%)	0 (0.0%)	0 (0.0%)	NA	NA	NA	NA	NA	NA
Anxiety disorders	30 (17.5%)	24 (23.1%)	16 (9.1%)	**.02**	2.1 (1.1-4.0)	**.002**	3.0 (1.5-6.1)	.24	0.7 (0.4-1.3)
Disruptive behavior disorders	15 (8.8%)	6 (5.8%)	6 (3.4%)	**.04**	2.8 (1.0-7.3)	.37	1.7 (0.5-5.4)	.33	1.6 (0.6-4.4)
ADHD[c]	44 (25.7%)	17 (16.3%)	19 (10.9%)	**<.001**	2.9 (1.6-5.3)	.20	1.6 (0.8-3.2)	.05	1.9 (1.0-3.5)
Pervasive developmental disorders	16 (9.4%)	13 (12.5%)	10 (5.7%)	.20	1.7 (0.8-3.9)	.06	2.3 (1.0-5.6)	.44	0.7 (0.3-1.6)
Post-traumatic stress disorder[b]	5 (2.9%)	6 (5.8%)	0 (0.0%)	NA	NA	NA	NA	NA	NA
Stress and adjustment disorders	23 (13.5%)	21 (20.2%)	8 (4.6%)	**.006**	3.3 (1.4-7.5)	**<.001**	5.3 (2.2-12.4)	.15	0.6 (0.3-1.2)
Tic disorders[d]	16 (9.4%)	6 (5.8%)	12 (6.9%)	.38	1.4 (0.6-3.1)	.70	0.8 (0.3-2.3)	.27	1.7 (0.7-4.6)
Comorbidity[e]	42 (24.6%)	30 (28.8%)	17 (9.7%)	**<.001**	3.0 (1.7-5.6)	**<.001**	3.8 (1.9-7.2)	.45	0.8 (0.5-1.4)

Significant *P* values (<.05) in bold

Abbreviations: FHR-BP: Children at familial high-risk of bipolar disorder; FHR-SZ: Children at familial high-risk of schizophrenia spectrum disorders; PBC: Population-based controls

[a]Any Axis I disorder excluding elimination disorders, transient and unspecified tics, and specific phobias, [b]Contained too few children to calculate confidence intervals, [c]In the logistic regression model with FHR-group and sex there was a significant effect of sex on ADHD, [d]Includes Tourette's disorder and chronic tic disorder, [e]Child has met criteria for disorders from at least two different disorder categories at some point during the study period, e.g. affective disorders and anxiety disorders

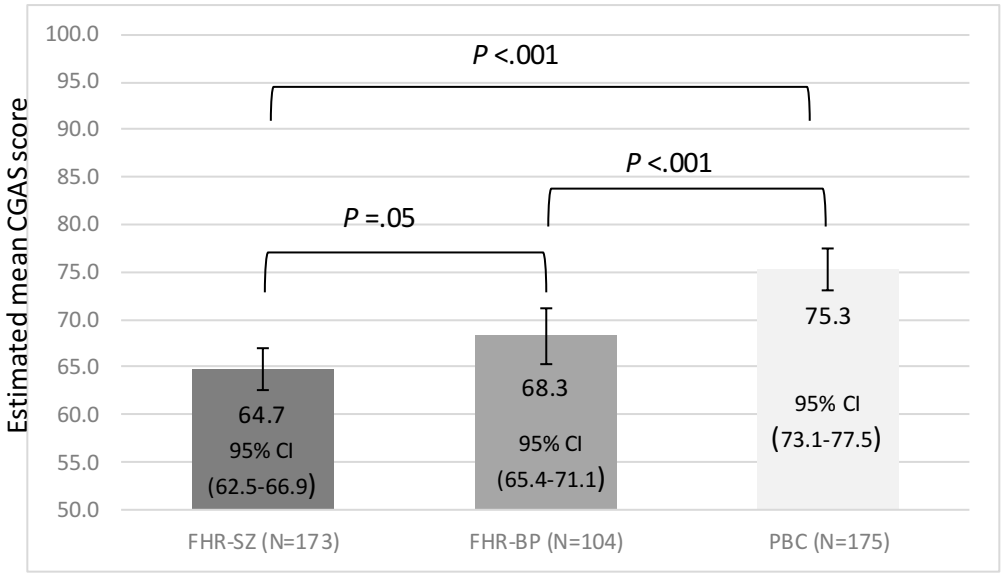
Figure 2. Cumulative incidence of DSM-IV and DSM-5 mental disorders at baseline (age 7 years) and follow-up (age 11 years) in The Danish High Risk and Resilience Study, VIA 11 – from **Paper 1**



Abbreviations: FHR-BP: Children at familial high-risk of bipolar disorder; FHR-SZ: Children at familial high-risk of schizophrenia spectrum disorders; PBC: Population-based controls

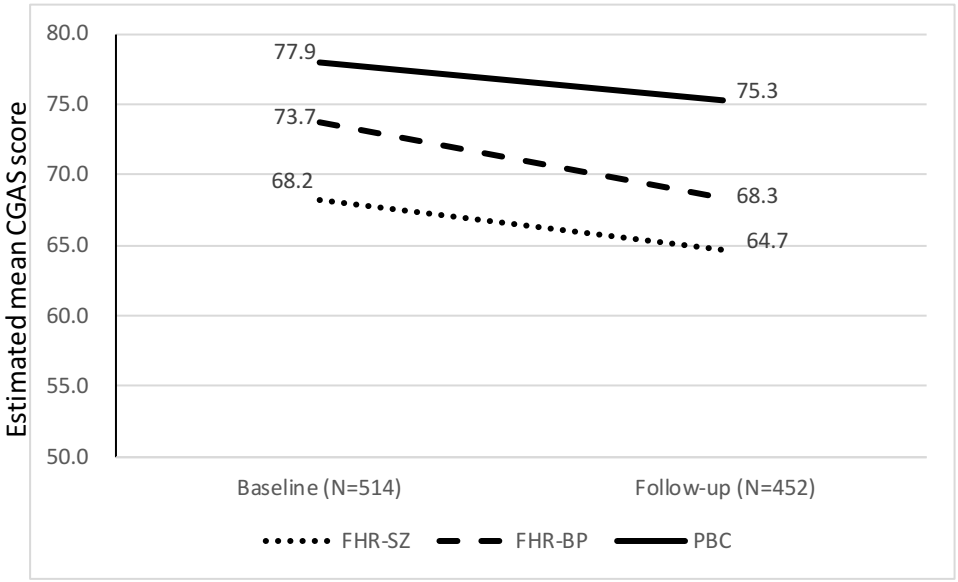
For development of specific disorder categories, see **Paper 1.**

Figure 3. Estimated mean CGAS score at age 11 years, adjusted for sex of the child – from **Paper 1**



Abbreviations: FHR-BP: Children at familial high-risk of bipolar disorder; FHR-SZ: Children at familial high-risk of schizophrenia spectrum disorders; PBC: Population-based controls
Error bars represent 95% CI
Observed means (SD) at age 11: FHR-SZ: 64.6 (15.6), FHR-BP: 68.1 (14.9), PBC: 75.2 (14.0)
In the ANCOVA with FHR-group and sex there was a significant effect of sex on CGAS score

Figure 4. Estimated mean CGAS score at age 7 and 11 years, adjusted for sex of the child – from **Paper 1**



Abbreviations: FHR-BP: Children at familial high-risk of bipolar disorder; FHR-SZ: Children at familial high-risk of schizophrenia spectrum disorders; PBC: Population-based controls
95% CI at age 7: FHR-SZ: 66.3-70.2, FHR-BP: 71.2-76.3, PBC: 75.9-79.9
95% CI at age 11: FHR-SZ: 62.5-66.9, FHR-BP: 65.4-71.1, PBC: 73.1-77.5

Paper 2

In **Paper 2** we found that PE were more prevalent in children at FHR of schizophrenia than controls during middle childhood, as illustrated in Table 3. Early childhood PE predicted persistence of PE into middle childhood in the presence of more than one type of early childhood PE. Early childhood PE predicted mental disorders in middle childhood, most strongly in children with three or more types of early childhood PE who had a 2.5 fold increased risk of middle childhood mental disorders after adjusting for early childhood mental disorders and familial risk, as illustrated in Table 4. Having persistent PE from early to middle childhood, compared with never having PE, was strongly associated with having a middle childhood mental disorder with a four-fold increased risk after accounting for the effects of these risk factors, as illustrated in Table 5. In cross-section middle childhood PE were associated with concurrent mental disorders, for details, see the Online Supplement for **Paper 2**. PE indexed risk of mental disorders non-differentially across the three groups of children. PE were associated with increased risk of both internalizing, externalizing, and other disorders, for details, see the Online Supplement for **Paper 2.**

Table 3. Psychotic experiences in middle childhood (age 11 years) in 447 children at FHR-SZ, FHR-BP, and controls in The Danish High Risk and Resilience Study, VIA 11 – from **Paper 2**

	N, %						Between-group comparisons								
	FHR-SZ (n = 170)		FHR-BP (n = 103)		Controls (n = 174)		FHR-SZ vs. controls			FHR-BP vs. controls			FHR-SZ vs. FHR-BP		
	N	%	N	%	N	%	Odds ratio	95% CI	p	Odds ratio	95% CI	p	Odds ratio	95% CI	p
Four-year prevalence, Any Psychotic Experiences															
Unadjusted	54	31.8	21	20.4	32	18.4	**2.1**	**1.3-3.4**	**.005**	1.1	0.6-2.1	.68	1.8	1.0-3.2	**.04**
Adjusted for sex							2.1	1.3-3.4	**.005**	1.1	0.6-2.1	.68	1.8	1.0-3.2	**.04**
Six-month prevalence, Any Psychotic Experiences															
Unadjusted	42	24.7	14	13.6	23	13.2	2.2	1.2-3.8	**.007**	1.0	0.5-2.1	.93	2.1	1.1-4.0	**.03**
Adjusted for sex							2.2	1.2-3.8	**.007**	1.0	0.5-2.1	.91	2.1	1.1-4.0	**.03**

Significant *P* values (<.05) in bold
Abbreviations: FHR-BP: Children at familial high-risk of bipolar disorder; FHR-SZ: Children at familial high-risk of schizophrenia spectrum disorders.

Table 4. Associations between early childhood psychotic experiences (age 7 years) and middle childhood psychotic experiences and mental disorders (age 11 years) in 447 children at FHR-SZ, FHR-BP, and controls in The Danish High Risk and Resilience Study, VIA 11 – from **Paper 2**

	Early childhood psychotic experiences											
	Any psychotic experiences (n = 189)			1 type of psychotic experiences (n = 104)			2 types of psychotic experiences (n = 48)			3 or more types of psychotic experiences (n = 37)		
	Odds ratio	**95% CI**	**p**	**Odds ratio**	**95% CI**	**p**	**Odds ratio**	**95% CI**	**p**	**Odds ratio**	**95% CI**	**p**
Any middle childhood psychotic experiences												
Unadjusted	1.9	1.2-2.9	**.004**	1.6	0.9-2.7	.10	2.1	1.1-4.2	**.03**	2.6	1.2-5.4	**.01**
Adjusted for sex	1.9	1.2-2.9	**.005**	1.6	0.9-2.7	.10	2.1	1.1-4.2	**.03**	2.6	1.2-5.4	**.01**
Any middle childhood Axis I disorder												
Unadjusted	2.2	1.5-3.3	**<.001**	1.6	1.0-2.6	.06	2.8	1.5-5.2	**.002**	4.2	2.0-8.5	**<.001**
Adjusted for sex	2.3	1.5-3.4	**<.001**	1.7	1.0-2.7	**.04**	2.8	1.5-5.3	**.001**	4.3	2.1-8.8	**<.001**
Adjusted for sex and any early childhood Axis I disorder	2.1	1.3-3.2	**.002**	1.7	1.0-3.0	**.05**	2.3	1.1-4.7	**.03**	3.1	1.4-7.0	**.007**
Adjusted for sex, any early childhood Axis I disorder, and familial risk	2.0	1.2-3.1	**.004**	1.8	1.0-3.1	**.04**	2.0	1.0-4.2	.06	2.5	1.1-5.7	**.04**

Note: Children with no early childhood psychotic experiences (n = 258) were used as reference.
Significant *P* values (<.05) in bold
Abbreviations: FHR-BP: Children at familial high-risk of bipolar disorder; FHR-SZ: Children at familial high-risk of schizophrenia spectrum disorders

Table 5. Associations between developmental pathways of psychotic experiences from early to middle childhood and middle childhood mental disorders in 447 children at FHR-SZ, FHR-BP, and controls in The Danish High Risk and Resilience Study, VIA 11 – from **Paper 2**

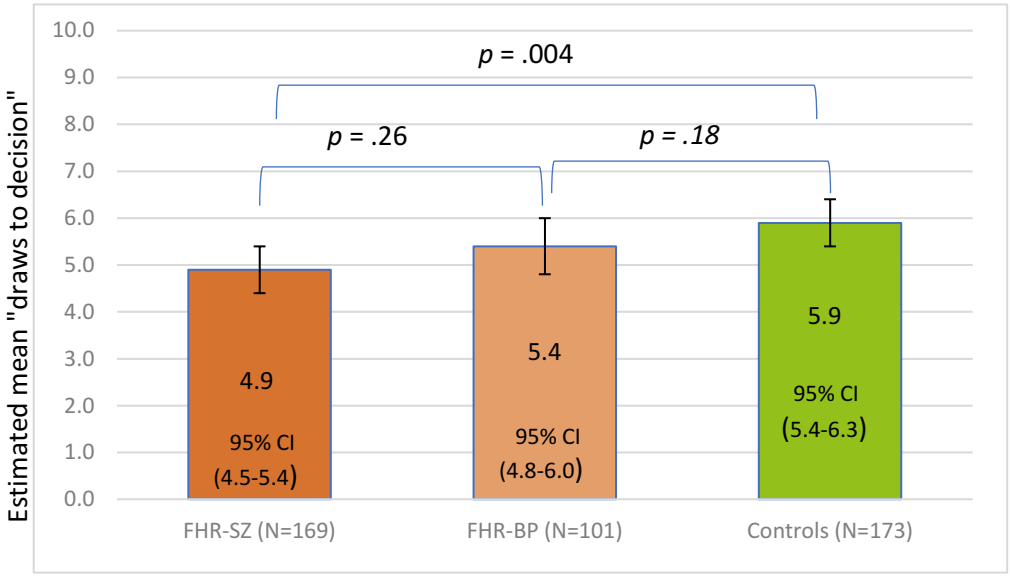
	Developmental pathways of psychotic experiences								
	Remittent psychotic experiences (n = 131)			**Incident psychotic experiences** (n = 49)			**Persistent psychotic experiences** (n = 58)		
	Odds ratio	**95% CI**	**p**	**Odds ratio**	**95% CI**	**p**	**Odds ratio**	**95% CI**	**p**
Any middle childhood Axis I disorder									
Unadjusted	2.0	1.2-3.2	**.004**	2.3	1.2-4.3	**.01**	4.9	2.7-9.1	**<.001**
Adjusted for sex	2.1	1.3-3.4	**.002**	2.3	1.2-4.5	**.01**	5.2	2.8-9.8	**<.001**
Adjusted for sex and any early childhood Axis I disorder	1.8	1.1-3.1	**.03**	2.1	1.0-4.3	.05	4.5	2.3-9.0	**<.001**
Adjusted for sex, any early childhood Axis I disorder, and familial risk	1.7	1.0-2.9	.06	1.8	0.9-3.9	.10	4.1	2.1-8.4	**<.001**

Note: The "Never psychotic experiences" group (n = 209) was used as reference
Significant *P* values (<.05) in bold
Abbreviations: FHR-BP: Children at familial high-risk of bipolar disorder; FHR-SZ: Children at familial high-risk of schizophrenia spectrum disorders

Paper 3

In **Paper 3** we found that children at FHR of schizophrenia showed more JTC than controls reflected in fewer draws to decision on the Beads Task, as illustrated in Figure 5 and Table 6. This was not the case for children at FHR of bipolar disorder. Between-group differences were attenuated when adjusting for intelligence. Due to low numbers in each group for interaction analyses we report analyses stratified by FHR-group for associations between JTC and PE. Presence of PE with delusions, relative to no PE, was associated with more JTC in children at FHR of schizophrenia and controls. Presence of hallucinations only was not associated with more JTC. Associations between delusions and JTC became non-significant when adjusting for intelligence, as illustrated in Table 7. Higher intelligence predicted less JTC across models. Presence of the categorical JTC bias, extreme JTC, did not differentiate between FHR-groups or between groups with or without subclinical delusions, for details see **Paper 3.**

Figure 5. Draws to decision on the Beads Task in 443 children at FHR-SZ, FHR-BP, and controls in The Danish High Risk and Resilience Study, VIA 11 – **from Paper 3**



Error bars represent 95% CI.
Abbreviations: FHR-BP, Children at familial high-risk of bipolar disorder; FHR-SZ, Children at familial high-risk of schizophrenia spectrum disorders.

Table 6. Draws to decision on the Beads Task in 443 children at FHR-SZ, FHR-BP, and controls in The Danish High Risk and Resilience Study, VIA 11 – from **Paper 3**

	Pairwise comparisons					
	FHR-SZ vs. controls		**FHR-BP vs. controls**		**FHR-SZ vs. FHR-BP**	
Mean draws to decision	***P* value**	**Cohen's D**	***P* value**	**Cohen's D**	***P* value**	**Cohen's D**
Adjusted for sex[a]	**.004**	0.31	.18	0.16	.26	0.15
Adjusted for sex and IQ[ab]	**.02**	0.24	.20	0.15	.49	0.09

Abbreviations: FHR-BP, children at familial high-risk of bipolar disorder; FHR-SZ, children at familial high-risk of schizophrenia spectrum disorders;
[a]A significant effect of sex was found on draws to decision in this model. Being female was associated with a higher number of draws to decision.
[b]A significant effect of IQ was found on draws to deicision in this model. Having higher IQ was associated with a higher number of draws to decision.

Table 7. Draws to decision on the Beads Task in children with psychotic experiences in The Danish High Risk and Resilience Study, VIA 11 – stratified by familial high-risk group – from **Paper 3**

Mean draws to decision	**FHR-SZ** (*n* = 169)				**FHR-BP** (*n* = 100)				**Controls** (*n* = 170)			
	Psychotic experiences without delusions (*n* = 18)		**Psychotic experiences with delusions** (*n* = 26)		**Psychotic experiences without delusions** (*n* = 4)		**Psychotic experiences with delusions** (*n* = 9)		**Psychotic experiences without delusions** (*n* = 12)		**Psychotic experiences with delusions** (*n* = 12)	
	***P* value**	**Cohen's D**	***P* value**	**Cohen's D**	***P* value**	**Cohen's D**	***P* value**	**Cohen's D**	***P* value**	**Cohen's D**	***P* value**	**Cohen's D**
Adjusted for sex[a]	.68	0.14	**.04**	0.46	.75	0.17	.64	0.17	.12	0.47	**.05**	0.60
Adjusted for sex and IQ[a,b]	.66	0.10	.14	0.32	.68	0.20	.52	0.23	.15	0.41	.17	0.42

Children with no psychotic experiences during the past six months in each group (FHR-SZ, *n* = 125, FHR-BP, *n* = 87, controls, *n* = 146) were used as reference
Significant *p* values (<.05) in bold.
Abbreviations: FHR-BP, children at familial high-risk of bipolar disorder; FHR-SZ, children at familial high-risk of schizophrenia spectrum disorders.
[a]A significant effect of sex was found on draws to decision in children at FHR-SZ in this model. Being female was associated with a higher number of draws to decision.
[b]A significant effect of IQ was found on draws to decision in children at FHR-SZ and controls in this model. Having higher IQ was associated with a higher number of draws to decision.

Discussion

Main findings and contributions

Paper 1 supports the existing knowledge that offspring at FHR of schizophrenia and bipolar disorder are at increased risk of a range of mental disorders, mostly non-diagnostically specific to parental disorders, in childhood and adolescence. The study adds to the sparse knowledge from conjoint studies of these high-risk groups by showing that in same-aged preadolescent children familial liabilities to schizophrenia and bipolar disorder are expressed in both shared and distinct disorders. Longitudinal follow-up and the early age of first assessment enabled us to show that vulnerability to mental disorders in these children manifests in early childhood and remains stable throughout childhood.

Paper 2 adds to the existing evidence that PE in childhood and adolescence are vulnerability markers of familial risk of psychosis. The study also supports previous evidence that PE in childhood mark increased risk of mental disorders while extending these findings to include early childhood PE in children at FHR of schizophrenia and bipolar disorder. The study shows that PE are associated with increased risk of mental disorders with non-differential associations across groups, both longitudinally and cross-sectionally. Further, it shows that higher severity of PE, reflected in higher number of PE and persistence, confers a particularly increased risk of clinical outcomes.

Paper 3 is to our knowledge the first study to evidence that JTC is a potential early vulnerability marker of familial risk of psychosis in preadolescence. This association is not reducible to general intelligence. Additionally, the study extends the sparse knowledge on JTC in relation to PE in children and adolescents by showing that JTC covaries with presence of subclinical delusions, but not with hallucinations, while general intelligence is a potential underlying trait accounting for this association.

Interpretation

Our findings in **Paper 1** that children at FHR of schizophrenia and FHR of bipolar disorder had an elevated risk of a range of mental disorders are in keeping with previous reports (Ross and Compagnon 2001; Wals et al. 2001; Hans et al. 2004; Henin et al. 2005; Singh et al. 2007; Duffy et al. 2007; Keshavan et al. 2008; Birmaher et al. 2009; Vandeleur et al. 2012; Garcia-Amador et al. 2013; Goetz et al. 2017; Shah et al. 2019; Birmaher et al. 2021). We extend these findings and the previous sparse evidence from conjoint studies of these two groups in childhood (Maziade et al. 2008; Sanchez-Gistau et al. 2015; De la Serna et al. 2020) by showing that by preadolescence in same-aged children familial risk of schizophrenia and bipolar disorder is expressed through both common and distinct disorders.

As previously outlined conflicting results regarding the prevalence of ADHD in children at FHR of bipolar disorder have been reported. While our findings that children at FHR of bipolar disorder did not have an elevated rate of ADHD are in keeping with some previous studies (Nurnberger et al. 2011; Vandeleur et al. 2012; Goetz et al. 2017) they contrast with others (Singh et al. 2007; Garcia-Amador et al. 2013). Differences in findings may be partly attributable to methodological differences, e.g. recruitment procedures and characteristics of the parents (Duffy et al. 2011; Duffy 2012). Parents in the current cohort were drawn from registers and may be better functioning than individuals drawn from in- or outpatient samples. Further, as mentioned, ADHD in offspring may be more specific to lithium nonresponsive bipolar disorder (Duffy et al. 2007). Also, differences may be attributable to variations in analytic strategies, as some studies have found that differences in rates of ADHD were rendered non-significant when taking confounders into account suggesting that it may reflect general psychopathology in the family or low socioeconomic status rather than risk of bipolar disorder per se (Birmaher et al. 2009; Goetz et al. 2017).

Our findings of early onset psychosis within the group of children at FHR of schizophrenia but not in the group of children at FHR of bipolar disorder suggest some early specificity with parental disorders in keeping with the previously mentioned review (Rasic et al. 2014). These children should warrant attention as longer duration of untreated early onset psychosis predicts poorer outcome (Díaz-Caneja et al. 2015).

Apart from mapping development in children at FHR an overarching aim of the Danish High Risk and Resilience Study is to identify early antecedents of SMI to inform early prevention and intervention. The identified psychopathological profiles in the current cohort combined with findings from other studies may provide some insights into potential early antecedents.

The elevated rates of anxiety and affective disorders in both children at FHR of schizophrenia and bipolar disorder in the current cohort are of note as these disorders may represent early transdiagnostic antecedents of schizophrenia and bipolar disorder in these groups. In children at FHR of bipolar disorder childhood anxiety disorders are predictive of affective disorders in adolescence (Duffy et al. 2014), whereas childhood and adolescent-onset unipolar depression is associated with increased risk of later bipolar disorder in children and adolescents at FHR of affective disorders (Geller et al. 2001; Mesman et al. 2013; Duffy et al. 2014). Childhood anxiety may thus for some mark an early stage of a progressive course toward bipolar disorder (Duffy et al. 2014). In young individuals at FHR of schizophrenia examined prospectively, those who developed schizophrenia had higher premorbid, dimensional affective and anxiety symptoms than those who did not (Johnstone et al. 2005). In another study of offspring at FHR of schizophrenia, anxiety and mood disorders with childhood onset were often comorbid with schizophrenia spectrum disorders in adolescence (Hans et al. 2004).

Children with ADHD may constitute a subgroup with increased liability to schizophrenia. ADHD appears to predict schizophrenia in young offspring at FHR of schizophrenia as shown in findings that young offspring with externalizing disorders had more symptoms of schizotypy (Keshavan et al. 2008) and findings that ADHD and psychosis proneness were associated in young first-degree relatives of individuals with schizophrenia (Keshavan et al. 2003). As previously mentioned, childhood ADHD predicted schizophrenia in the overall population in a Danish register-based study (Dalsgaard et al. 2014). Whether ADHD is reliably associated with subsequent risk of bipolar disorder in offspring at FHR of bipolar disorder is less clear (Duffy 2012). A recent study found that preschool ADHD in this group increased risk of subsequent bipolar disorder (Birmaher et al. 2021). There is some evidence to suggest that ADHD may be associated with developing the specific subtype of bipolar disorder which does not stabilize with lithium (Duffy 2012). In a Danish register study of the general population both ADHD and anxiety prospectively predicted a subsequent diagnosis of bipolar disorder in individuals followed from age 16 (Meier et al. 2018).

In summary, presence of childhood mental disorders likely characterizes a group at particularly high risk of SMI within the FHR-population. This is also supported by a study documenting that in both FHR-groups childhood Axis I disorders belong to clusters of risk factors predicting transition to later SMI (Paccalet et al. 2016). This aligns with the previously mentioned findings from the Danish general population that all childhood mental disorders are associated with increased risk of schizophrenia (Maibing et al. 2015).

In **Paper 2** the higher prevalence of PE among children at FHR of schizophrenia than controls in middle childhood agrees with previous findings of associations between familial risk of psychosis and higher occurrence of PE from both general population studies and FHR-studies (Johnstone et al. 2000; Kelleher and Cannon 2011; De la Serna et al. 2020). These findings suggest that PE are vulnerability markers of familial risk of psychosis and are thus in support of the continuum theory of psychosis (van Os and Reininghaus 2016). PE in middle childhood did not index familial risk of bipolar disorder in the current study which is in keeping with some previous reports (Mendez et al. 2019; De la Serna et al. 2020). However, a large general population study, which included bipolar disorder with psychotic disorder, found that a family history of psychotic disorders predicted PE, whereas a family history of nonpsychotic mental disorders did not. Prediction from individual disorders was not reported (Jeppesen et al. 2015b).

In the current cohort PE marked increased risk of concurrent and subsequent mental disorders which aligns with the previously described findings from general population studies in childhood and adolescence (Kelleher et al. 2012b; Jeppesen et al. 2015a; Healy et al. 2019a; Rimvall et al. 2020b). Similarly, we corroborated the limited evidence of PE measured as early as age 7-8 predicting later psychopathology in the general population (Bartels-Velthuis et al. 2011; Bartels-Velthuis et al. 2016). Even after accounting for known risk factors for mental disorders in middle childhood, i.e. mental disorders in early childhood and familial risk, early childhood PE stood out as a significant predictor of mental disorders in middle childhood. A smaller study in an adolescent general population sample similarly found that childhood PE predicted psychopathology in adolescence after taking other risk factors, including childhood mental disorders, into account (Healy et al. 2019b). PE were associated with increased risk across the diagnostic spectrum in the current cohort aligning with previous evidence (Healy et al. 2019b; Healy et al. 2019a; Rimvall et al. 2020b).

Having several PE and persistent PE were most strongly associated with clinical outcomes in the current cohort corroborating previous findings. A recent general population study of preadolescent children found that more severe PE were more closely associated with concurrent psychopathology (Laurens et al. 2020) while, as mentioned, others have documented that persistent PE relative to transient PE or no PE are associated with greater risk of other psychopathology (Dominguez et al. 2011; De Loore et al. 2011; Wigman et al. 2011a; Downs et al. 2013; Rammos et al. 2021). Similarly, the study on hallucinations measured at age 7-8 found a higher risk of clinical psychopathology five years later in those with persistent hallucinations than in those with no hallucinations (Bartels-Velthuis et al. 2011).

Identifying predictors of persistence of PE is of interest as persistent PE are the most clinically relevant. Different predictors of persistence have been examined across studies, and some have found that higher levels of other psychopathology (Havers et al. 2019; Steenkamp et al. 2021) and lower levels of global functioning (Calkins et al. 2017) at baseline predict persistence of PE. Yet, according to a recent scoping review predictors of persistence have not been sufficiently replicated (Kalman et al. 2019). However, our findings that having several PE at baseline predicted persistence are in keeping with findings from other studies that higher severity of PE increases persistence (Bartels-Velthuis et al. 2011; Calkins et al. 2017; Rimvall et al. 2020a; Steenkamp et al. 2021).

We found that PE and developmental pathways of PE were non-differentially associated with clinical outcomes across the three groups, whereas a large general population study found that PE in conjunction with parental mental illness more broadly defined conferred higher risk of subsequent mental disorders than PE without parental mental illness (Rimvall et al. 2020b). In the current cohort we expect that cumulative effects with parental mental illness may emerge later in light of the evidence from general population samples that PE become more strongly associated with psychopathology with advancing age (Kelleher et al. 2012b).

It should be noted that the PE field is somewhat diverse as numerous definitions and instruments for measuring psychotic symptoms are being employed (Lee et al. 2016; Seiler et al. 2020). This may partly account for the widely varying estimates of the prevalence of PE in children and adolescents (Kelleher et al. 2012a). While self-report measures tend to yield higher estimates than interviewer-based measures (Linscott and van Os 2010; Downs et al. 2013; Linscott and van Os

2013; Karcher et al. 2020), self-reported PE are nonetheless clinically relevant (Rimvall et al. 2019). However, there is some evidence that clinician confirmed PE are more strongly associated with other psychopathology (Moriyama et al. 2019). Disparities in definitions and measures may account for some of the inconsistencies in findings regarding PE (Linscott and van Os 2010). In keeping with this, there is no universal definition of severity of PE, and while we used number of PE to reflect severity other indicators of increased severity such as associated distress also appear to increase risk of persistence and clinical outcomes (Havers et al. 2019; Sullivan et al. 2020). Despite the lack of common definitions, evidence is accumulating to show that PE in children and adolescents are important.

With the current study we attempted to expand knowledge on the associations between PE and other psychopathology. We added to the previous knowledge that PE index risk of other psychopathology across the diagnostic spectrum while extending these findings to include early childhood PE in children at FHR. We showed that persistent PE and several PE may characterize a vulnerable subgroup from this early age. As we found that early childhood PE predicted mental disorders in middle childhood and as mental disorders in childhood index increased risk of transitioning to SMI in children at FHR (Nurnberger et al. 2011; Duffy et al. 2014; Paccalet et al. 2016), early childhood PE should be considered when identifying early vulnerability and potential targets for intervention within this population.

Paper 3 is to our knowledge the first study to examine JTC in children at FHR of schizophrenia or bipolar disorder. Extending previous findings from older populations (Van Dael et al. 2006; Henquet et al. 2020) we found that JTC is a vulnerability marker of familial liability to psychosis in preadolescence. As expected given the previous, albeit sparse, evidence that JTC is not found in adults with bipolar disorder (Can et al. 2019), JTC did not mark familial liability to bipolar disorder within the current cohort. Considering the previously outlined evidence that JTC may be associated with psychotic features in affective disorders rather than affective disorders per se (Reininghaus et al. 2019), it would be of interest to examine whether JTC is an early marker of familial risk of psychosis in bipolar disorder, e.g. by examining whether JTC in children at FHR of bipolar disorder relates to psychotic illness features in parental bipolar disorder. Duffy and colleagues documented that offspring of parents with lithium nonresponsive bipolar disorder, but not lithium responsive bipolar disorder, developed psychotic disorders by adulthood suggesting that this type of bipolar disorder is more closely related to psychotic disorders (Duffy et al. 2014).

Supporting the previous sparse evidence that JTC and PE in preadolescence are associated (Ames et al. 2014; Hassanali et al. 2015) we found that JTC covaried with presence of delusions but not hallucinations in children at FHR of schizophrenia and controls. This suggests that JTC marks delusion proneness both with and without familial risk of psychosis in preadolescence extending findings from older populations (Van Dael et al. 2006; Freeman et al. 2008; Ross et al. 2015; Henquet et al. 2020). The findings that JTC is associated with both clinical and subclinical delusions support the proposition that PE and psychotic disorders form a continuum (Linscott and van Os 2013).

Differences in JTC between the FHR-groups were attenuated when accounting for general intelligence, yet remained significant suggesting that they were not solely attributable to between-group differences in intelligence. Attenuation of the effects of clinical status when accounting for intelligence has also been found in other studies (Van Dael et al. 2006; Falcone et al. 2015b; Tripoli et al. 2021). In our study as well as in other studies higher IQ was linked with less JTC (Van Dael et al. 2006; Falcone et al. 2015b; Hassanali et al. 2015; Tripoli et al. 2021). Thus our findings support the notion that JTC may be viewed as part of a general cognitive impairment. Associations between delusions and JTC were rendered non-significant when accounting for general intelligence in the current cohort. In previous studies some found that association with delusions remained (Falcone et al. 2015b), while others found that they were reduced or rendered non-significant when accounting for general intelligence (Van Dael et al. 2006; Lincoln et al. 2010). Considering evidence that low IQ confers higher risk of PE in preadolescence (Horwood et al. 2008), our findings may suggest that in children with subclinical delusions JTC expresses underlying impairments in general intelligence which are also associated with increased risk of schizophrenia (Zammit et al. 2004).

It should be noted that the results in the current cohort were only significant on the continuous draws to decision measure from the Beads task while the dichotomous, extreme JTC bias did not differentiate between FHR-groups or PE at this developmental stage. This may suggest that the continuous measure is more sensitive for detecting early, attenuated biases. In the previously mentioned sample of children and adolescents where the binary measure of JTC was associated with PE, only PE causing distress and impairment were considered and a less stringent cutoff for JTC was employed (Hassanali et al. 2015).

Strengths and limitations

The above findings should be viewed in light of the strengths and limitations of the studies. An important strength of the Danish High Risk and Resilience study is the inclusion of a large, nationwide cohort of same-aged children identified through Danish National Registers. Further, the included cohort was overall representative of the background population. The prospective, longitudinal nature of the study allowed for examination of the development of mental disorders over time and prediction from early childhood PE to middle childhood mental disorders. Having two measurements in childhood enabled identification of early developmental pathways before the age of peak incidence of SMI. Inclusion of both children at FHR of schizophrenia and bipolar disorder enabled characterization of shared and distinct early profiles regarding the examined outcomes. Including a population-based control group enabled comparison with the general population regarding the prevalence of the examined outcomes and, through interaction analyses, the associations between these outcomes. The use of K-SADS-PL interviews with both parents and children to assess mental disorders and PE at both age 7 and 11 is another strength, as is the blinding of interviewers to the children's risk status and prior data allowing for an unbiased assessment. All diagnoses were confirmed in consensus meetings and at age 11 all PE were consensus rated with a senior research child and adolescent psychiatrist. The use of a clinician-based rating of PE at both baseline and follow-up is a strength as they, as previously mentioned, appear to index risk of psychopathology more strongly than self-reported PE (Moriyama et al. 2019).

Some limitations should be taken into consideration. In the current cohort the group of children at FHR of bipolar disorder is smaller than the other two groups which weakens estimates of differences for this group. Further, we cannot distinguish between children born to parents with bipolar disorder with or without psychotic illness features, or with lithium nonresponsive vs. lithium responsive bipolar disorder, a potentially relevant distinction to identify subgroups with varying occurrences of the examined outcomes. We made a small amendment to the inclusion criteria for PE from age 7 to age 11, as described in **Paper 2,** as symptoms only pertaining to sleep and fever were systematically excluded at follow-up but not at baseline. This may account for a minor proportion of the symptoms appearing to have remitted over time. Due to the potential challenges in reliably subclassifying subclinical symptoms described in our baseline study (Ellersgaard et al. 2021) we refrained from supplementing the use of the dichotomous presence or absence of PE with our continuous scale for measuring severity of PE in the analyses at follow-up.

Instead, for the analyses, we only used the dichotomous cutoff and additionally employed number of PE to reflect severity for a larger extent of methodological continuation with other studies. Additionally, as described, other markers of severity of PE such as associated distress, also appear to increase risk of clinical outcomes and persistence of PE. Therefore, examining other aspects of severity could be of relevance to future studies within the current cohort. The long follow-up does not fully capture the potential heterogeneous pathways of PE and several shorter follow-ups would have been ideal, e.g. to discern whether symptoms classified as persistent were present during the entire interim, were time-limited continuations of early symptoms, or were intermittent. As we examined cross-sectional associations in **Paper 3** no causal inferences can be made regarding JTC and delusion formation and the groups appeared to be too small for interaction analyses with PE.

Residual confounding from other factors not examined in the included studies cannot be ruled out, e.g. exposure to trauma may impact on the prevalence of mental disorders (McLaughlin et al. 2012), and PE (Kelleher et al. 2013b; McGrath et al. 2017), as well as on their associations (Guloksuz et al. 2015). Parental mental disorders beyond schizophrenia and bipolar disorder, e.g. major depressive disorder, could also affect child outcomes as could severity of parental disorders (van Santvoort et al. 2014; van Santvoort et al. 2015; Sandstrom et al. 2020) and future studies should examine these effects. Regarding dropout, as presented in **Paper 1 and paper 3**, those who remained in the study had significantly higher levels of global functioning than those who dropped out, and in **Paper 3**, those who remained had lower levels of dimensional psychopathology, introducing a potential bias toward less heterogeneity in the remaining sample.

Conclusions and future perspectives

Conclusions

Familial liability to schizophrenia and bipolar disorder is expressed in elevated rates of a range of mental disorders in preadolescence, mostly non-diagnostically specific to parental disorders. Vulnerability manifests in early childhood and remains throughout childhood. Presence of PE reflects familial liability to schizophrenia and is associated with childhood mental disorders supporting the continuum theory for psychosis. Early childhood PE predict mental disorders in middle childhood across the diagnostic spectrum within this population, most strongly when there are several types of PE and when they persist over time. JTC marks familial liability to schizophrenia and covaries with subclinical delusions further supporting the continuum theory for psychosis.

In preadolescence children at FHR of schizophrenia and FHR of bipolar disorder have both shared and distinct characteristics potentially reflecting common and distinct pathogenic pathways toward schizophrenia and bipolar disorder. Further follow-up in the current cohort will increase knowledge on how early developmental expressions of risk predict SMI and other detrimental outcomes. Early identification of vulnerable individuals and preemptive intervention and prevention is warranted.

Future perspectives

In terms of predicting outcomes such as SMI based on early risk, the findings of the studies included in the current thesis should be viewed from within the framework of developmental psychopathology, i.e. the understanding that risk factors are probabilistically related to developmental outcomes and that numerous factors interact and transact over time to create outcomes (Sroufe 1997; Rutter and Sroufe 2000). This fits with the consensus that both schizophrenia and bipolar disorder arise from a broad array of interacting genetic and environmental factors and that no single factor is sufficient to lead to their onset (Uher and Zwicker 2017; Zwicker et al. 2018). Also the concepts of equifinality, i.e. different pathways and factors leading to the same outcome, and multifinality, i.e. the same pathways and factors leading to different outcomes, apply (Cicchetti and Rogosch 1996; Sroufe 1997).

Some factors show a propensity toward certain outcomes, e.g. PE and subsequent psychotic disorders, and we would expect some specificity with psychotic disorder outcomes in the current

cohort given the higher prevalence of PE in children at FHR of schizophrenia. However, PE can arise both with and without a parental history of psychosis, not all individuals with PE will develop psychotic disorders (Poulton et al. 2000), and the outcome of PE may depend on other exposures over time, e.g. adverse life events increasing risk of persistence of PE (Wigman et al. 2011a; Trotta et al. 2015). Similarly, parental schizophrenia and bipolar disorder show a propensity toward the concordant disorder in offspring, yet are not necessary nor sufficient to cause them, and parental mental illness can lead to more than the concordant disorder, and not all children at FHR will become ill (Rasic et al. 2014; van Santvoort et al. 2015). Early risk is pluripotent and in the current cohort, where re-assessments at age 15 are currently ongoing, future follow-ups beyond the age of peak incidence of SMI will allow for delineating how childhood mental disorders and PE and their developmental trajectories predict SMI. Using data-driven approaches (such as cluster analysis and growth mixture modeling) to characterize trajectories of psychopathological development over time and clusters of vulnerability markers within and across developmental domains, e.g. including psychopathology and cognition, may serve to identify vulnerable subgroups and will allow for the relevant study of heterogeneous pathways which are not captured in the current thesis.

In the current thesis, mental disorders were measured as dichotomous categories; however, psychopathology is also dimensional and cuts across diagnostic boundaries. The substantial overlap between different mental disorders, e.g. reflected in the many overlapping risk factors increasing risk of several disorders (Uher and Zwicker 2017) and the relative lack of specificity for parental disorders in predicting offspring disorders (Rasic et al. 2014; van Santvoort et al. 2015), has led to the suggestion that studying broader categories across existing diagnoses may be more fruitful to advancing the understanding of the etiology of SMI (Rasic et al. 2014; Uher and Zwicker 2017). Additionally, viewing psychosis as a continuous and transdiagnostic phenotype and considering the evidence that it extends across schizophrenia and bipolar disorder (Reininghaus et al. 2016), the introduction of a broad psychosis spectrum disorder encompassing existing disorder categories has been suggested (Guloksuz and van Os 2018). In the current cohort a disorder specific approach could be supplemented by examinations of children's developmental trajectories across parental disorders. Further, it could be examined how psychosis across parental disorders relates to children's developmental trajectories. It would be of interest to learn whether these approaches could identify groups at varying risk across the existing groups.

Extending from the dimensional approach, it has been suggested that the structure of psychopathology may be viewed in one unifying dimension, the "p factor" (Caspi et al. 2014). This dimension cuts across diagnostic categories, and includes internalizing symptoms, externalizing symptoms, and PE, which change over time, and vary in severity with psychotic disorders as the extreme elevation of the p factor (Caspi et al. 2014; Caspi and Moffitt 2018). This assertion is supported by findings of high rates of sequential comorbidity and heterotypic continuity, i.e. many disorders across diagnostic domains are comorbid over time, and findings that every disorder is associated with increased risk of every other disorder (Copeland et al. 2009; Copeland et al. 2013; Caspi and Moffitt 2018; Plana-Ripoll et al. 2019b; Caspi et al. 2020). In keeping with the overlapping causation and expression of mental illness transdiagnostic approaches to prevention and treatment suggest viewing the individual on a continuum of illness and treating symptoms across traditional disorder categories with the potential for preventing multiple types of psychopathology (van Os et al. 2019; Shah et al. 2020). Using the current cohort to study the structure of psychopathology over time in these children to identify a p factor and examine its correlates and potential to predict outcomes would be feasible and very intriguing and has, to our knowledge, not been done in a child and adolescent FHR-sample.

Our findings that PE are more prevalent in the context of FHR of schizophrenia and that PE are associated with childhood mental disorders and JTC add to the evidence of a continuum with PE and psychotic disorders and demonstrate the relevance of studying PE to learn about the etiology of psychosis (Kelleher and Cannon 2011; van Os and Reininghaus 2016). PE in adolescence share risk factors with psychosis such as exposure to trauma (Wigman et al. 2012b; Kelleher et al. 2013c) and cognitive impairments (Kelleher et al. 2013a). Other evidence for a continuum with PE in adolescence comes from findings that cognitive factors usually associated with psychosis in adults, including JTC, account for a large proportion of the variance in PE in adolescence (Gin et al. 2021) and findings from a twin study of the same genetic and environmental risk factors influencing PE across the severity continuum in adolescence (Zavos et al. 2014). Examining PE in conjunction with other putative risk factors for psychotic disorders in the current cohort and other FHR-cohorts may expand the understanding of PE and the psychosis continuum in children at FHR. Follow-up in the current cohort should establish causality and timing between JTC and the formation of delusions, e.g. by examining whether JTC contributes to secondary delusion formation in children with hallucinations.

Additionally, as some studies have shown that specific dimensions of PE in adolescence are more predictive of psychopathology (Yung et al. 2009; Wigman et al. 2011b), it would also be of interest to explore the underlying structure of PE and its associations with psychopathology in this population to potentially improve prediction. Our findings suggest that having several PE and persistent PE confers a particularly increased risk of clinical outcomes in middle childhood. While meta-analytic evidence suggests that higher severity of PE, including higher number of PE and persistence, confers higher risk of conversion to clinical psychosis in adolescents and adults from the general population (Kaymaz et al. 2012), future planned follow-ups will elucidate whether the severity of childhood PE has similar predictive value for later clinical outcomes in the current cohort. Detailed characterization of factors predicting persistence of PE could allow for further identification of subgroups at higher risk for psychosis and other adverse outcomes than the more heterogeneous FHR-groups. A recent study in the general population found that the same risk factors, including trauma exposure, associated with incidence of PE also predicted persistence of PE suggesting that severity rather than type of exposure may determine persistence (Rammos et al. 2021).

Our findings point to a need for clinicians' awareness toward this group of vulnerable children from a young age. When encountering adults with SMI clinicians should take an interest in the mental health of their children and, in turn, clinicians encountering children with mental health problems should inquire about parental mental health. The findings highlight the importance of early identification of vulnerability enabling targeted early preemptive intervention and prevention. The increased risk of SMI in children with childhood mental disorders demonstrates the importance of efforts to prevent and treat childhood mental disorders both to ameliorate current symptoms and improve well-being, but also to potentially mitigate illness progression and improve long-term outcome.

Integrating child and adolescent with adult mental health services would be relevant to provide access to prevention and intervention focusing on both parent and child. Previous findings from parent-focused interventions with young children of mothers with depression (Goodman and Garber 2017) and parents with bipolar disorder (Jones et al. 2017) show promise for ameliorating symptoms in children. A recent meta-analysis found that preventive interventions, including targeting parental psychopathology and parenting, substantially reduced incidence of mental disorders as well as severity of dimensional symptoms in children at FHR of broadly defined

mental illness (Lannes et al. 2021). In light of our findings that vulnerability to mental disorders manifests early and remains throughout childhood, the efficacy of interventions from early childhood in children at FHR of SMI should be elucidated. Preemptive interventions could start at knowledge about familial risk and target both parental disorders and early nonspecific symptoms in the children before potentially reaching clinical levels. There are at least two ongoing studies of interventions including children at FHR of SMI from early childhood involving the parents, one targeting early antecedents, including PE (Uher et al. 2014), and one providing tailored support for the entire family (Müller et al. 2019). In the general population a transdiagnostic intervention with cognitive-behavioral therapy for children from 6 years of age with common anxiety, depressive, and behavioral symptoms is ongoing in several municipalities in Denmark. This intervention substantially reduces children's symptoms and parental stress (Jeppesen et al. 2021). Examining how such an early, low-risk intervention may benefit children at FHR would be of interest.

We found PE clinically relevant and predictive of mental disorders in children at FHR similarly to what has been found in the general population (Healy et al. 2019a). Most previous studies have examined PE from middle childhood and onward. However, our findings suggest that including a measure of early childhood PE would be beneficial in future studies to further illuminate their role as vulnerability markers both inside and outside the context of familial risk. More studies on longitudinal, clinical correlates of early childhood PE in both the general population and FHR-populations as well as more studies on PE across childhood in FHR-populations are warranted. In keeping with what others have proposed (Healy et al. 2019b; Rimvall et al. 2020b), our findings suggest that inquiring about PE should be part of any mental health screening of children and adolescents. Our findings show that this could meaningfully be extended to early childhood PE and should encompass children at FHR. Presence of PE, especially when there are several types of PE and they persist over time, could indicate a need for early support. However, presence of PE is not necessarily cause for concern, so to discern needs for support PE should be considered in the context of other indicators of risk and resilience in the individual child. Although not examined as an outcome in the studies in this thesis, we noticed that children were far more likely to report PE themselves than their caregivers indicating that parents were not always aware of the presence of these symptoms. This agrees with findings from other samples (Bartels-Velthuis et al. 2011; Calkins et al. 2014) and underlines the importance of inquiring about PE with children themselves.

The findings from the current study and other studies that PE are associated with mental disorders across the diagnostic spectrum and with various later adverse outcomes show that PE could be important transdiagnostic targets of intervention. In addition, presence of PE in non-psychotic mental disorders is associated with both poorer clinical and functional outcomes. In adults with depression presence of PE predicts poorer treatment response to psychotherapy (Wigman et al. 2014b) and in adolescents and young adults with anxiety and depression presence of PE is associated with a more severe illness course (Wigman et al. 2012a). In adolescents with mental disorders those with PE have poorer functioning than those without PE (Wigman et al. 2014a; Kelleher et al. 2015). These findings underline the relevance of evaluating efforts to treat PE to improve outcomes (van Os and Murray 2013). There are some ongoing studies targeting PE in children and adolescents from the general population (Jolley et al. 2018; Maijer et al. 2020) and, as mentioned, a study targeting PE along with other putative antecedents in children at FHR of SMI (Uher et al. 2014). Examining whether interventions in individuals with PE improve outcomes in the FHR-population is pertinent. Further, examining PE as a moderator of treatment effects and studying whether treatment needs and outcomes in children and adolescents at FHR with PE differ from the general population is relevant to tailor interventions and to gain knowledge on the clinical significance of PE within this population. Examining potential reduction of PE as an effect of interventions toward non-psychotic psychopathology within this population would also be of interest. Of note, a general population study found that parent-child conflicts partly mediated the relationship between psychopathology and PE (Healy et al. 2020) while another study showed that parental support and supervision partly mediated the relationship between adverse life events and PE in adolescents (McMahon et al. 2021) suggesting that improving parent-child interactions could be an intervention target in children with PE. This appears very relevant to explore in the context of family-based interventions for children at FHR.

Interventions targeting the JTC bias such as metacognitive training are effective in reducing delusions in adults with psychosis (Moritz et al. 2013; Andreou et al. 2015; Garety et al. 2015; Eichner and Berna 2016; Ochoa et al. 2017). There is limited evidence on the efficacy of psychological interventions for symptom reduction in psychosis in children and adolescents (Anagnostopoulou et al. 2019) and to our knowledge no intervention has targeted JTC. Considering the associations found in the current cohort, future studies should examine the JTC bias as an intervention target in children with PE.

Regarding communication of our findings to mental health professionals, to families affected by SMI, as well as to the broader public, it is undoubtedly important to convey that these children can be vulnerable and are sometimes in need of early attention and that familial risk and early symptoms may contain important information. Meanwhile, it is equally important to communicate that early symptoms such as PE are not necessarily concerning, that there is substantial heterogeneity in developmental outcomes, resilience despite familial risk, and opportunities for change at many stages of development. Striking a balance between encouraging that attention is paid to early signs of vulnerability and avoiding inducing unnecessary fear of prognosis or stigma requires attention to the complex task of conveying the probabilistic rather than deterministic nature of psychological development.

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Paper 1

Mental disorders in preadolescent children at familial high-risk of schizophrenia or bipolar disorder - a four-year follow-up study: The Danish High Risk and Resilience Study, VIA 11

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Mental disorders in preadolescent children at familial high-risk of schizophrenia or bipolar disorder – a four-year follow-up study

The Danish High Risk and Resilience Study, VIA 11

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Background: Children at familial high-risk of schizophrenia and bipolar disorder have an elevated prevalence of mental disorders but studies of children within a narrow age range are lacking and there are few conjoint studies of these two groups. Knowledge on their mental health is important for prevention and early intervention. **Methods:** The authors examined mental disorders and global functioning in children at familial high-risk of schizophrenia (FHR-SZ) and bipolar disorder (FHR-BP) compared with population-based controls. In a longitudinal cohort study, 450 children (FHR-SZ, n = 171; FHR-BP, n = 104; controls, n = 175), were assessed for Axis I disorders at baseline and four-year follow-up (mean age 11.9, *SD* 0.2) with the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children and for global functioning with Children's Global Assessment Scale. **Results:** Cumulative incidence of Any Axis I disorder was elevated by age 11 in children at FHR-SZ (54.4%, OR 3.0, 95% CI 1.9–4.7, p < .001) and children at FHR-BP (52.9%, OR 2.8, 95% CI 1.7–4.7, p < .001) compared with controls (28.6%). Children at FHR-SZ and FHR-BP had higher rates of affective disorders (OR 4.4, 95% CI 1.4–13.5, p = .009; OR 5.1, 95% CI 1.6–16.4, p = .007), anxiety disorders (OR 2.1, 95% CI 1.1–4.0, p = .02; OR 3.0, 95% CI 1.5–6.1, p = .002), and stress and adjustment disorders (OR 3.3, 95% CI 1.4–7.5, p = .006; OR 5.3, 95% CI 2.2–12.4, p < .001). Disruptive behavior disorders (OR 2.8, 95% CI 1.0–7.3, p = .04) and ADHD (OR 2.9, 95% CI 1.6–5.3, p < .001) were elevated in children at FHR-SZ. Both FHR groups had lower global functioning than controls. Cumulative incidence of disorders increased equally across the three groups from early childhood to preadolescence and level of functioning did not change differentially. **Conclusions:** Children at FHR-SZ and FHR-BP have an elevated prevalence of mental disorders and poorer functioning than controls. Vulnerability in children at FHR manifests early and remains stable throughout childhood. Early attention toward their mental health and identification of those in need of intervention is warranted.
Keywords: Child and adolescent psychiatry; familial high-risk; psychopathology; schizophrenia; bipolar disorder.

Introduction

Having a first-degree relative with schizophrenia or bipolar disorder is the strongest known risk factor for developing these disorders (Gottesman, Laursen, Bertelsen, & Mortensen, 2010). There is converging evidence from observational studies (Rasic, Hajek, Alda, & Uher, 2014), population registry studies (Dean et al., 2010; Gottesman et al., 2010), family and twin studies (Cardno et al., 2012; Lichtenstein et al., 2009), and molecular genetic analyses (International Schizophrenia Consortium et al., 2009) that schizophrenia and bipolar disorder share partly overlapping pathogenic pathways. Additionally, they share prodromal characteristics (Correll et al., 2007) and phenotypic traits (Hill, Harris, Herbener, Pavuluri, & Sweeney, 2008). Both disorders are preceded by social, emotional, cognitive, and behavioral impairments in childhood, however, there is stronger evidence for early impairments in schizophrenia than bipolar disorder (Bora, 2016; Cannon et al., 2002; Hameed & Lewis, 2016; Laurens et al., 2015). Furthermore, there is evidence of more severe impairments in, for example, cognitive functioning in

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schizophrenia than bipolar disorder after illness onset (Bora, 2016) and schizophrenia is usually characterized by a more chronic course of illness (Duffy, Malhi, & Grof, 2017). Familial transmission is only partly diagnosis-specific, thus children born to parents with schizophrenia and bipolar disorder have an increased risk of developing the parental disorder and other severe mental illness (Rasic et al., 2014). Studying children at familial high-risk (FHR) of these disorders provides an opportunity to understand their premorbid course and identify the emergence of the earliest signs of illness vulnerability. The conjoint study of offspring at FHR of schizophrenia and bipolar disorder carries potential for elucidating shared and distinct pathways toward these disorders and for informing illness-specific and shared preventive interventions, however, few studies have examined the early vulnerability markers of these disorders simultaneously (Ellersgaard et al., 2018; Erlenmeyer-Kimling & Cornblatt, 1987; Maziade et al., 2008; Sanchez-Gistau et al., 2015; Uher et al., 2014).

Knowledge on mental disorders in children born to parents with schizophrenia and bipolar disorder is sparse, and studies of children within a narrow age range, enabling detailed mapping of psychopathological development, are lacking. The few studies using semistructured interviews to ascertain diagnoses in offspring at FHR of schizophrenia evidence an elevated prevalence of a range of Axis I disorders with ADHD, disruptive behavior disorders, affective disorders, and anxiety disorders most commonly observed (de la Serna et al., 2011; Hans, Auerbach, Styr, & Marcus, 2004; Keshavan et al., 2008; Ross & Compagnon, 2001; Shah et al., 2019). Elevated rates of these disorders are most consistently reported for offspring at FHR of bipolar disorder as well (Birmaher et al., 2009; Duffy, Alda, Crawford, Milin, & Grof, 2007; Garcia-Amador et al., 2013; Goetz et al., 2017; Henin et al., 2005; Singh et al., 2007; Vandeleur et al., 2012; Wals et al., 2001). Global functional impairments in childhood and adolescence are found in both groups (Hans et al., 2004; Henin et al., 2005; Singh et al., 2007). Only two previous studies apart from our baseline study have examined childhood mental disorders in these two groups simultaneously, albeit in smaller samples of mixed age (Maziade et al., 2008; Sanchez-Gistau et al., 2015). One of these studies (age range 7–22), which had no control group, found no differences between offspring at FHR of schizophrenia and bipolar disorder regarding rates of disorders or global functioning (Maziade et al., 2008). The other study found that at baseline (age range 6–17), both groups had higher rates of Any Axis I disorder compared with controls. Offspring at FHR of schizophrenia had higher rates of ADHD than offspring at FHR of bipolar disorder and controls and higher rates of anxiety disorders than controls. Offspring at FHR of bipolar disorder had higher rates of ADHD and affective disorders than controls (Sanchez-Gistau et al., 2015). Similar results were reported at two-year follow-up (De la Serna et al., 2020). In our baseline study, we observed elevated rates of Any Axis I disorder, anxiety disorders, and stress and adjustment disorders in both groups compared with controls as well as an increased risk of ADHD and disruptive behavior disorders among children at FHR of schizophrenia and of pervasive developmental disorders among children at FHR of bipolar disorder. Both groups had lower global functioning than controls, most pronounced for children at FHR of schizophrenia (Ellersgaard et al., 2018).

The aim of this study was to examine the cumulative incidence of mental disorders and level of global functioning in preadolescence as well as to assess between-group differences in development of cumulative incidence and functioning throughout childhood in these children.

Methods

Participants

The VIA 11 Study is the first follow-up of The Danish High Risk and Resilience Study, a prospective, longitudinal, nationwide cohort study in Denmark. The original cohort consisted of 522 children with at least one biological parent with a schizophrenia spectrum disorder (n = 202, ICD-10 codes: F20, F22, F25, or ICD-8 codes: 295, 297, 298.29, 298.39, 298.89, 298.99), or bipolar disorder (n = 120, ICD-10 codes: F30, F31, or ICD-8 codes: 296.19, 269.39), and population-based controls (PBC) with neither parent diagnosed with any of these disorders (n = 200). Nine children had two ill parents, that is, both parents were diagnosed with either schizophrenia or bipolar disorder. If one parent had schizophrenia and the other had bipolar disorder, the child pertained to the schizophrenia high-risk group as per the ICD-10 hierarchy. PBC were matched to the children at FHR of schizophrenia (FHR-SZ) on age, sex, and municipality. Due to capacity constraints, it was not possible to enroll as many children at FHR of bipolar disorder (FHR-BP) and they were unmatched, yet comparable to the other groups on baseline inclusion age and sex. Permission to retrieve the cohort from the Danish national registers (the Danish Civil Registration System and the Danish Psychiatric Central Research Register) was granted by the Danish Ministry of Health. The study was approved by the Danish Data Protection Agency. The Danish Committee on Health Research Ethics deemed ethical approval unnecessary due to the observational nature of the study. We obtained written informed consent from the parent or guardian and assent from the children upon explanation of all procedures. The cohort and study design are described in detail elsewhere (Thorup et al., 2018). Retention at follow-up was 89%. Data collection went from March 1, 2017 until June 30, 2020 at two university hospital research facilities in Copenhagen and Aarhus and in the homes of the families.

Measures

Mental disorders were ascertained with the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children —Present and Lifetime Version (K-SADS-PL) (Kaufman et al., 1997). Children and their primary caregivers were interviewed about the child's current and past disorders at age 7 (Ellersgaard et al., 2018) and reinterviewed at age 11 about symptoms during the four-year interim. Interviewers were mental health professionals with formal training in K-SADS-PL blinded to the participants' prior clinical data and parental

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illness. As per the K-SADS-PL manual, all available information about the child was taken into consideration, for example, anamnestic information could also be included, when determining the final scores. At age 7, diagnoses were based on DSM-IV. At age 11, they were based on DSM-IV and DSM-5. The disorder categories from baseline were retained (Ellersgaard et al., 2018). During follow-up there were no discrepancies between children's DSM-IV and DSM-5 diagnoses regarding the disorder categories described in this paper, that is, there were no cases with a DSM-IV disorder without a corresponding DSM-5 disorder within the same disorder category or vice versa. Since the DSM-5 version of K-SADS-PL was not available in Danish at the start of the VIA 11 Study, the revised interview questions (https://www.pediatricbipolar.pitt.edu/resources/instruments) were translated by the first and second authors (MG and AS). Current global functioning was assessed with Children's Global Assessment Scale (CGAS) (Shaffer et al., 1983) as part of the K-SADS-PL interview. Diagnoses and CGAS scores were confirmed in consensus meetings by a senior research child and adolescent psychiatrist (the last author, AAET) blinded to children's prior data and parental illness. IQ was measured with Reynolds Intellectual Screening Test (Reynolds & Kamphaus, 2003). Pubertal stage was assessed with self-reported Tanner Stages (Coleman & Coleman, 2002).

Statistical analyses

Between-group differences in background characteristics were analyzed with chi-square tests and one-way ANOVA. Dropout analyses were performed with chi-square and t-tests.

Frequencies and percentages for the main outcomes were calculated through crosstabulations. Between-group differences in cumulative incidence of mental disorders and comorbidity were analyzed through multivariable binomial logistic regressions adjusted for sex of the child. To ascertain between-group differences in changes in cumulative incidence of disorders from baseline to follow-up repeated measures mixed-effects multivariable binomial logistic regressions with FHR-group, time, sex of the child, and interaction time x group as fixed factors were performed.

To ascertain the effects of familial high-risk on the stability of disorders from early to middle childhood a multivariable binomial logistic regression analysis adjusted for sex of the child was conducted on children who had met criteria for Any Axis I disorder at baseline with Any Axis I disorder between baseline and follow-up as dependent variable and FHR-group as predictor.

Differences in global functioning were analyzed through ANCOVA adjusted for sex of the child. To ascertain between-group differences in changes in functioning from baseline to follow-up, a linear mixed-model with repeated measures with FHR-group, time, sex of the child, and interaction time x group as fixed factors was performed.

Due to their questionable clinical significance, elimination disorders, transient and unspecified tics, and specific phobias were excluded from the analyses. Due to the risk of overadjusting the data, we did not adjust for IQ which is intrinsically related to group status.

Alpha was set to <.05 and all p values were two-tailed. Data were analyzed using SPSS version 25.

Results

Demographic and clinical characteristics

This nationwide, population-based cohort study of 450 11-year-old (mean age 11.9, *SD* 0.2, range 10.9–12.7) children included 171 children at FHR-SZ, 104 children at FHR-BP, and 175 PBC. No between-group differences were found regarding age, sex, baseline IQ, or onset of puberty (Table 1).

Participants

Data on K-SADS-PL were provided for 514 children at age 7, 452 children at age 11 (FHR-SZ, $n = 173$, FHR-BP, $n = 104$, PBC, $n = 175$) and 450 children at both assessments (87.5% retention). No significant differences were found between children who participated in K-SADS-PL at follow-up and children who dropped out regarding cumulative incidence of Any Axis I mental disorder at baseline ($X^2(1) = 1.715$, $p = .19$), sex ($X^2(1) = 0.885$, $p = .35$), or distribution in FHR-groups ($X^2(2) = 0.814$, $p = .67$). Those who dropped out had significantly lower global functioning (CGAS 69.1, *SD* 15.4) at baseline than those who remained in the study (CGAS 73.6, *SD* 15.1, $t(512) = -2.198$, Cohen's $d = 0.30$, $p = .03$).

Cumulative incidence of mental disorders

At follow-up, 54.4% of children at FHR-SZ, 52.9% of children at FHR-BP, and 28.6% of PBC had met criteria for a mental disorder at some point during their lives. Both children at FHR-SZ (OR 3.0, $p < .001$) and FHR-BP (OR 2.8, $p < .001$) had a significantly higher cumulative incidence of Any Axis I disorder at age 11 than PBC (Table 2).

Children at FHR-SZ had a more than four-fold higher risk (OR 4.4, $p = .009$) and children at FHR-BP had a more than five-fold higher risk (OR 5.1, $p = .007$) of having met criteria for an affective disorder by age 11 than PBC. There were no diagnoses of mania. Children at FHR-SZ and FHR-BP had significantly higher rates of anxiety disorders (FHR-SZ, OR 2.1, $p = .02$; FHR-BP, OR 3.0, $p = .002$) and stress and adjustment disorders (FHR-SZ, OR 3.3, $p = .006$; FHR-BP, OR 5.3, $p < .001$). Children at FHR-SZ were more likely than PBC to have met criteria for disruptive behavior disorders (OR 2.8, $p = .04$) and ADHD (OR 2.9, $p < .001$, Table 2). Psychotic disorders were only found among children at FHR-SZ (3.5%).

There were no significant differences in cumulative incidence between the two FHR-groups in any of the disorders (Table 2).

The cumulative incidence of main disorder categories at baseline and follow-up is depicted in Figure 1A–H. There were no significant time x group interactions for Any Axis I disorder ($F(2, 957) = 0.113$, $p = .89$) or for any specific disorder categories (data not shown).

Comorbidity

Both children at FHR-SZ (OR 3.0) and FHR-BP (OR 3.8) had a significantly elevated risk of having met criteria for disorders from at least two different disorder categories during their lives compared with PBC ($p < .001$, Table 2).

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Table 1 Background characteristics of 450 children with K-SADS-PL data at age 7 and 11 in The Danish High Risk and Resilience Study, VIA 11

	Study group			
	FHR-SZ (n = 171[f])	FHR-BP (n = 104)	PBC (n = 175)	p Value
Female, No. (%)	83 (48.5%)	46 (44.2%)	82 (46.9%)	.79[a]
Age at inclusion in VIA 11, years, mean (*SD*)	11.96 (0.27)	11.94 (0.22)	11.93 (0.22)	.57[b]
Baseline IQ[c], VIA 7, mean (*SD*)	102.9 (11.3)	105.2 (8.8)	105.3 (9.8)	.06[b]
Onset of puberty[d], VIA 11, No. (%)[e]	137 (87.3%)	87 (90.6%)	152 (94.4%)	.09[a]

FHR-BP, Children at familial high-risk of bipolar disorder; FHR-SZ, Children at familial high-risk of schizophrenia spectrum disorders; K-SADS-PL, Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime Version; PBC, Population-based controls.
[a]Chi square test.
[b]One-way ANOVA test.
[c]Measured with Reynolds Intellectual Screening Test (RIST).
[d]Measured with self-reported Tanner Stages. Onset of puberty defined as Tanner Stage 2-4 (vs. Stage 1).
[e]Includes 157 children at FHR-SZ, 96 children at FHR-BP, and 161 PBC.
[f]At follow-up data on K-SADS-PL were provided for two children at FHR-SZ (FHR-SZ n = 173) who did not have data on K-SADS-PL at baseline. Since the main analyses are on children with data at both baseline and follow-up (n = 450), those two children are not included in Table 1.

Table 2 Cumulative incidence of DSM-IV and DSM-5 Axis I mental disorders and comorbidity by age 11 in 450 children at FHR-SZ, FHR-BP, and PBC in the Danish High Risk and Resilience Study, VIA 11

	No. (%)			Pairwise comparisons					
				FHR-SZ vs. PBC		FHR-BP vs. PBC		FHR-SZ vs. FHR-BP	
	FHR-SZ (n = 171)	FHR-BP (n = 104)	PBC (n = 175)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)
Any Axis I disorder[a]	93 (54.4%)	55 (52.9%)	50 (28.6%)	**<.001**	3.0 (1.9–4.7)	**<.001**	2.8 (1.7–4.7)	.76	1.1 (0.7–1.8)
Affective disorders	16 (9.4%)	11 (10.6%)	4 (2.3%)	**.009**	4.4 (1.4–13.5)	**.007**	5.1 (1.6–16.4)	.73	0.9 (0.4–1.9)
Psychotic disorders[b]	6 (3.5%)	0 (0.0%)	0 (0.0%)	NA	NA	NA	NA	NA	NA
Anxiety disorders	30 (17.5%)	24 (23.1%)	16 (9.1%)	**.02**	2.1 (1.1–4.0)	**.002**	3.0 (1.5–6.1)	.24	0.7 (0.4–1.3)
Disruptive behavior disorders	15 (8.8%)	6 (5.8%)	6 (3.4%)	**.04**	2.8 (1.0–7.3)	.37	1.7 (0.5–5.4)	.33	1.6 (0.6–4.4)
ADHD[c]	44 (25.7%)	17 (16.3%)	19 (10.9%)	**<.001**	2.9 (1.6–5.3)	.20	1.6 (0.8–3.2)	.05	1.9 (1.0–3.5)
Pervasive developmental disorders	16 (9.4%)	13 (12.5%)	10 (5.7%)	.20	1.7 (0.8–3.9)	.06	2.3 (1.0–5.6)	.44	0.7 (0.3–1.6)
Post-traumatic stress disorder[b]	5 (2.9%)	6 (5.8%)	0 (0.0%)	NA	NA	NA	NA	NA	NA
Stress and adjustment disorders	23 (13.5%)	21 (20.2%)	8 (4.6%)	**.006**	3.3 (1.4–7.5)	**<.001**	5.3 (2.2–12.4)	.15	0.6 (0.3–1.2)
Tic disorders[d]	16 (9.4%)	6 (5.8%)	12 (6.9%)	.38	1.4 (0.6–3.1)	.70	0.8 (0.3–2.3)	.27	1.7 (0.7–4.6)
Comorbidity[e]	42 (24.6%)	30 (28.8%)	17 (9.7%)	**<.001**	3.0 (1.7–5.6)	**<.001**	3.8 (1.9–7.2)	.45	0.8 (0.5–1.4)

Significant p values (<.05) in bold. FHR-BP, Children at familial high-risk of bipolar disorder; FHR-SZ, Children at familial high-risk of schizophrenia spectrum disorders; PBC, Population-based controls.
[a]Any Axis I disorder excluding elimination disorders, transient and unspecified tics, and specific phobias.
[b]Contained too few children to calculate confidence intervals.
[c]In the logistic regression model with FHR-group and sex there was a significant effect of sex on ADHD.
[d]Includes Tourette's disorder and chronic tic disorder.
[e]Child has met criteria for disorders from at least two different disorder categories at some point during the study period, for example, affective disorders and anxiety disorders.

Stability of mental disorders from early to middle childhood

Children at FHR-SZ who had met criteria for one or more Axis I disorders at baseline were significantly more likely to also meet criteria for any disorder during the four-year follow-up (83.9%) than PBC (60.7%; OR 3.3, 95% CI 1.2–9.1, p = .02,) and children at FHR-BP (61.1%; OR 3.4, 95% CI 1.3–8.9, p = .01, Figure 2A). There was no significant difference between children at FHR-BP and PBC (OR 1.0, 95% CI 0.35–2.7, p = .94). Prevalence of

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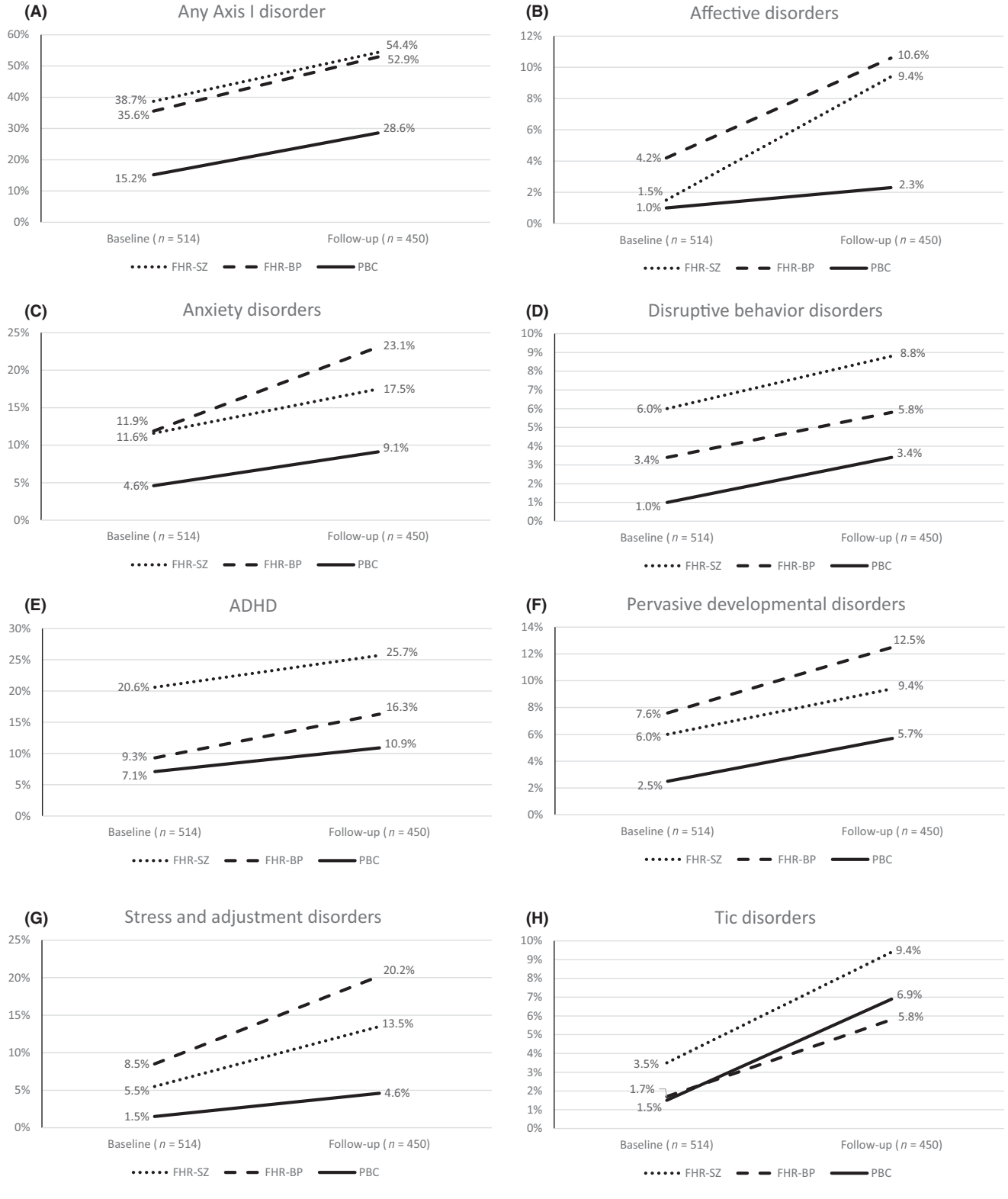

Figure 1 (A–H) Cumulative incidence of DSM-IV and DSM-5 mental disorders at baseline (age 7) and follow-up (age 11) in The Danish High Risk and Resilience Study, VIA 11. FHR-BP, Children at familial high-risk of bipolar disorder; FHR-SZ, Children at familial high-risk of schizophrenia spectrum disorders; PBC, Population-based controls. (H) Includes Tourette's disorder and chronic tic disorder

disorders during the four-year follow-up is shown in Table S1.

For percentages of children with persistent, incident, remittent, and no mental disorders see Figure 2B.

Current mental disorders

For prevalence of disorders during the preceding two months see Table S2. Children at FHR-SZ and FHR-BP had higher rates of Any Axis I disorder than PBC,

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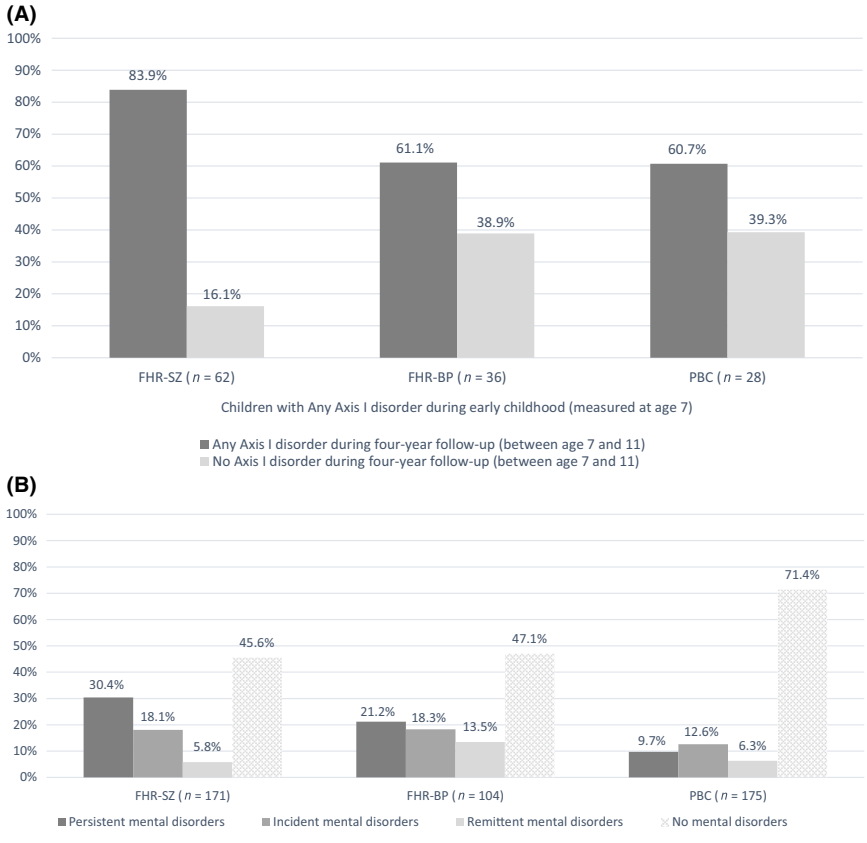

Figure 2 (A, B) Stability of mental disorders from early to middle childhood in The Danish High Risk and Resilience Study, VIA 11. (A) Stability of mental health in children with early childhood mental disorders. (B) Percentage of children with persistent, incident, remittent, and no mental disorders at age 11. FHR-BP, Children at familial high-risk of bipolar disorder; FHR-SZ, Children at familial high-risk of schizophrenia spectrum disorders; PBC, Population-based controls. Persistent mental disorders: Any Axis I disorder during early childhood (measured at age 7) and Any Axis I disorder during four-year follow-up (age 7–11). Incident mental disorders: No Axis I disorder during early childhood (measured at age 7) but Any Axis I disorder during four-year follow-up (age 7–11). Remittent mental disorders: Any Axis I disorder during early childhood (measured at age 7) but no Axis I disorder during four-year follow-up (age 7–11). No mental disorders: No Axis I disorder during early childhood (measured at age 7) and no Axis I disorder during four-year follow-up (age 7–11)

and children at FHR-SZ had higher rates of ADHD than PBC and children at FHR-BP.

Global functioning

Children at FHR-SZ (estimated mean 64.7, 95% CI 62.5–66.9) and FHR-BP (estimated mean 68.3, 95% CI 65.4–71.1) had significantly lower levels of current global functioning at age 11 than PBC (estimated mean 75.3, 95% CI 73.1–77.5, $p < .001$). Global functioning in children at FHR-SZ did not differ significantly from children at FHR-BP (Figure 3A).

There was no significant time x group interaction for global functioning, ($F(2, 959) = 0.615$, $p = .54$, Figure 3B).

Of children without current mental disorders those at FHR-SZ (estimated mean 74.0, 95% CI 72.0–76.0) and FHR-BP (estimated mean 74.6, 95% CI 72.2–77.0) had lower global functioning than PBC (estimated mean 79.7, 95% CI 78.0–81.4, $p < .001$ and $p = .001$, respectively). There was no difference between children at FHR-SZ and FHR-BP ($p = .70$). Of children with current disorders those at FHR-SZ (estimated mean 50.9, 95% CI 48.1–53.7) had lower global functioning than PBC (estimated mean 56.8, 95% CI 52.7–60.8, $p = .02$), whereas children at FHR-BP did not (estimated mean 53.8, 95% CI 49.6–57.9, $p = .31$). There was no difference between children at FHR-SZ and FHR-BP ($p = .26$).

Discussion

To our knowledge, this is the largest longitudinal study to date to concurrently examine mental disorders in children at FHR of schizophrenia and bipolar disorder compared with controls, and the first with a narrow age range. By preadolescence, both children at FHR-SZ and FHR-BP had an approximately threefold increased risk of having met criteria for Any Axis I disorder as well as an increased risk of affective disorders, anxiety disorders, stress and adjustment disorders, and comorbidity compared with PBC. Additionally, children at FHR had lower levels of global functioning than PBC. Moreover, children at FHR-SZ had a higher risk of disruptive behavior disorders and ADHD than PBC, and psychosis was only found among children at FHR-SZ. Cumulative

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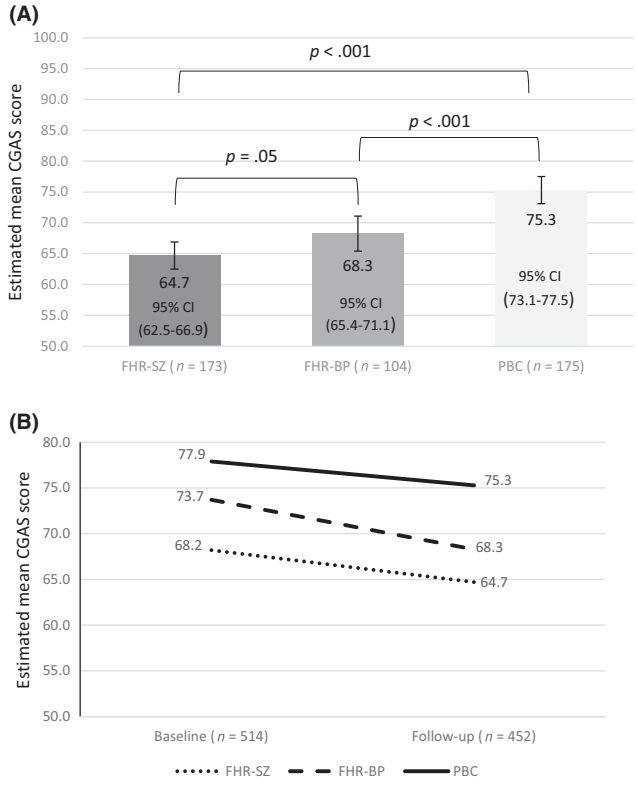

Figure 3 (A, B) Global functioning at baseline (age 7) and follow-up (age 11) in The Danish High Risk and Resilience Study, VIA 11. (A) Estimated mean CGAS score at age 11, adjusted for sex of the child. Error bars represent 95% CI. Observed means (*SD*) at age 11: FHR-SZ: 64.6 (15.6), FHR-BP: 68.1 (14.9), PBC: 75.2 (14.0). In the ANCOVA with FHR-group and sex there was a significant effect of sex on CGAS score. (B) Estimated mean CGAS score at age 7 and 11, adjusted for sex of the child. FHR-BP, Children at familial high-risk of bipolar disorder; FHR-SZ, Children at familial high-risk of schizophrenia spectrum disorders; PBC, Population-based controls. 95% CI at age 7: FHR-SZ: 66.3–70.2, FHR-BP: 71.2–76.3, PBC: 75.9–79.9. 95% CI at age 11: FHR-SZ: 62.5–66.9, FHR-BP: 65.4–71.1, PBC: 73.1–77.5

incidence of disorders increased equally across the three groups from early childhood to preadolescence, and global functioning did not change differentially, indicating that vulnerability in children at FHR manifests early and remains stable throughout childhood. Among children with current disorders, those at FHR-SZ had lower global functioning than PBC suggesting that children at FHR-SZ may experience more severe symptoms. Additionally, children at FHR-SZ were less likely to remit from any disorder in early childhood than children at FHR-BP and PBC, which may indicate a more severe clinical course in children at FHR-SZ at this early stage.

The seemingly high cumulative incidence in our control group is comparable to the rates found in early adolescence in two large, longitudinal general population studies (Caspi et al., 2020; Costello, Mustillo, Erkanli, Keeler, & Angold, 2003). Prevalence rates in longitudinal studies are usually higher than those found in single-wave, cross-sectional studies. In keeping with this these two studies reported a higher prevalence over the entire study period than at one point in time. Similarly, we found that the cumulative incidence over the entire study period was substantially higher than the current prevalence of disorders in all three groups of children underlining the importance of studying mental health over time to adequately capture the extent of mental disorders.

Our findings support evidence that offspring at FHR of schizophrenia and bipolar disorder are at increased risk of various mental disorders in childhood (Birmaher et al., 2009; de la Serna et al., 2011; De la Serna et al., 2020; Duffy et al., 2007; Garcia-Amador et al., 2013; Goetz et al., 2017; Hans et al., 2004; Henin et al., 2005; Keshavan et al., 2008; Maziade et al., 2008; Ross & Compagnon, 2001; Sanchez-Gistau et al., 2015; Shah et al., 2019; Singh et al., 2007; Vandeleur et al., 2012; Wals et al., 2001). All previous samples comprised both children and adolescents with wide age ranges precluding direct comparison with the prevalence observed in our study as rates are age-dependent. Previous FHR-studies found that ADHD, disruptive behavior disorders, and anxiety typically emerge first with onset in childhood followed by mood disorders and psychosis with onset in adolescence or early adulthood (Duffy et al., 2014; Shah et al., 2019). In keeping with this, we found that ADHD and anxiety disorders were more common in both FHR-groups than mood disorders and psychosis at this early stage. No mania was diagnosed which corroborates most previous FHR-studies where mania onsets in late adolescence (Duffy et al., 2014; Mesman, Nolen, Reichart, Wals, & Hillegers, 2013). One FHR-study (Henin et al., 2005), however, did find a small percentage with prepubertal onset. Our finding that children who had met criteria for a psychotic disorder by age 11 were all at FHR-SZ suggests early specificity for parental diagnosis in keeping with a review documenting a higher risk of schizophrenia in young (below age 20) offspring at FHR of schizophrenia compared with offspring at FHR of bipolar disorder and major depressive disorder (Rasic et al., 2014). In a study of offspring at FHR of bipolar disorder, only those of parents with lithium nonresponsive bipolar disorder, which is associated with worse course of illness (Hui et al., 2019), had developed psychotic disorders by early adulthood (Duffy et al., 2014).

Children at FHR-BP did not have a significantly higher cumulative incidence of ADHD than PBC in our study which, although consistent with our baseline findings (Ellersgaard et al., 2018) and some previous findings (Birmaher et al., 2009; Vandeleur et al., 2012), contrasts with other studies (Garcia-Amador et al., 2013; Sanchez-Gistau et al., 2015; Singh et al., 2007). The divergent findings may be attributable to heterogeneity of the samples regarding parental diagnoses and recruitment methods (Duffy et al., 2007). Parents in our study were recruited through registers and are likely better

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functioning than individuals drawn from in- or outpatient clinics. Elevated rates of ADHD may potentially only occur in offspring of parents with lithium nonresponsive bipolar disorder (Duffy, 2012). The findings of elevated rates of ADHD in children at FHR-SZ may also suggest a higher neurodevelopmental vulnerability in schizophrenia (Murray et al., 2004). The rates of ADHD and disruptive behavior disorders in our FHR-SZ group are notable as these children may represent a subgroup with increased liability to schizophrenia. This is supported by evidence of more symptoms of schizotypy in young offspring at FHR of schizophrenia with externalizing disorders (Keshavan et al., 2008), and associations between ADHD and psychosis proneness in young (9–22 years) first degree-relatives of patients with schizophrenia (Keshavan, Sujata, Mehra, Montrose, & Sweeney, 2003), and between childhood ADHD and schizophrenia in adulthood (Dalsgaard et al., 2014).

Childhood-onset depression in our FHR-groups is notable, since it is associated with an increased risk of later emergence of bipolar disorder in children from families with high rates of mood disorders (Geller, Zimerman, Williams, Bolhofner, & Craney, 2001). Similarly, adolescent-onset unipolar depression often precedes bipolar disorder in offspring at FHR of bipolar disorder (Duffy et al., 2014; Mesman et al., 2013). Our findings of elevated rates of anxiety in children at FHR-BP are also noteworthy as anxiety disorders in childhood are predictive of affective disorders in adolescence in this population (Duffy et al., 2014). Anxiety may thus, for some individuals, mark an early stage of a progressive course toward bipolar disorder (Duffy et al., 2014). Less is known of the predictive power of childhood affective and anxiety disorders in offspring at FHR of schizophrenia. In one study premorbid, dimensional affective and anxiety symptoms were significantly worse in young FHR-individuals (16–24 years) who later developed schizophrenia than in those who remained well (Johnstone, Ebmeier, Miller, Owens, & Lawrie, 2005). Another study found that childhood-onset anxiety and mood disorders were often comorbid with later schizophrenia spectrum disorders in young (12–22 years) offspring at FHR of schizophrenia (Hans et al., 2004). Thus, these disorders may represent early transdiagnostic antecedents of bipolar disorder and schizophrenia. Childhood Axis I disorders belong to clusters of risk factors predicting later transition to severe mental illness in both groups of offspring (Paccalet et al., 2016). Yet, considering the probabilistic nature of development, it is important to note that children in the current cohort are still young and that follow-up should examine how the early differences and similarities in their mental disorders, which we observed, evolve over time and how childhood mental disorders may be antecedents of severe mental illness within the current cohort.

Our findings point to a need for early prevention and intervention aimed at these children. A recent meta-analysis documented a substantial reduction in risk of mental disorders in offspring at FHR of mental illness following preventive interventions (Lannes, Bui, Arnaud, Raynaud, & Revet, 2021). There are ongoing efforts including children at FHR of severe mental illness from early childhood (Müller et al., 2019; Uher et al., 2014). Follow-up will elucidate their potential to reduce risk of severe mental illness in these children.

Strengths and limitations

A strength of our study is that we examined a large, nationwide sample prospectively in both early and middle childhood and included children of the same age increasing the reliability of risk estimates. We included both children at FHR-SZ, FHR-BP, and PBC and we assessed a range of mental disorders with a standardized, validated face-to-face interview conducted by trained mental health professionals blinded to parental illness and children's baseline data. Additionally, agreement upon diagnoses and global functioning was obtained at consensus meetings with an experienced specialist in child and adolescent psychiatry.

Some limitations should also be noted. Our FHR-BP group is smaller than the FHR-SZ group which weakens estimates of differences for this group. Additionally, we are unable to determine whether parents are lithium responders or nonresponders in children at FHR-BP, precluding identification of potentially homogeneous subgroups. Parental mental disorders in the coparents other than schizophrenia or bipolar disorder may also affect child psychopathology. These disorders were not included in this study, but it would be of relevance for future studies to examine their effects. Furthermore, stability of mental disorders was estimated from a binary measure of Any Axis I disorder obscuring potential changes in disorder categories. Due to the limited number of children in each disorder category at baseline and during follow-up, it was not meaningful to estimate stability for specific categories. We did not correct for multiple testing since data were highly overlapping as all occurrences of disorders (two-month and four-year prevalence) were contained in the cumulative incidence. Therefore, p values slightly below the traditional threshold of .05 should be interpreted conservatively. Consequently, in the current sample, no firm conclusions should be drawn regarding the differences in rates of disruptive behavior disorders between children at FHR-SZ and PBC and follow-up should clarify how these differences evolve. Finally, although the effect size was small, we cannot rule out that the lower global functioning in those who dropped out compared with those who remained in the study caused a bias towards less heterogeneity in the remaining sample.

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Conclusions

Preadolescent children at FHR-SZ and FHR-BP have a heightened risk of a range of mental disorders, mostly not diagnostically specific to parental disorders. Vulnerability manifests early and persists throughout childhood which demonstrates the importance of studying mental disorders in these children. These findings highlight the need for pre-emptive intervention and prevention, even from early childhood, to ameliorate current symptoms and to potentially improve their long-term outcome. Similar studies and follow-up in this cohort are important to determine the earliest stage at which reliable antecedents of schizophrenia and bipolar disorder can be identified and to increase knowledge on the role of childhood mental disorders in the pathogenesis of emerging illness.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Table S1. Four-year prevalence of DSM-IV and DSM-5 Axis I mental disorders in 452 children in The Danish High Risk and Resilience Study, VIA 11.

Table S2. Two-month prevalence of DSM-IV and DSM-5 Axis I mental disorders in 452 children in The Danish High Risk and Resilience Study, VIA 11.

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Key points

- Children at familial high-risk (FHR) of schizophrenia or bipolar disorder have an elevated risk of mental disorders, yet conjoint studies of same-aged children are lacking.
- This is the first study to examine mental disorders in these children conjointly throughout childhood in a same-aged sample.
- We found an elevated prevalence of mental disorders and lower global functioning in children at FHR of schizophrenia and bipolar disorder compared with controls.
- Cumulative incidence of mental disorders increased equally across the three groups from early childhood to preadolescence and global functioning did not change differentially, indicating that vulnerability in children at FHR manifests early and remains stable throughout childhood.
- Attention toward their mental health and identification of those in need of intervention is warranted.

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Supporting Information

Table S1. Four-year prevalence of DSM-IV and DSM-5 Axis I mental disorders in 452 children in The Danish High Risk and Resilience Study, VIA 11

	No. (%)			Pairwise comparisons					
				FHR-SZ Vs. PBC		FHR-BP Vs. PBC		FHR-SZ Vs. FHR-BP	
	FHR-SZ (*n* = 173)	FHR-BP (*n* = 104)	PBC (*n* = 175)	*p* Value	OR (95% CI)	*p* Value	OR (95% CI)	*p* Value	OR (95% CI)
Any Axis I disorder[a,b]	84 (48.6%)	41 (39.4%)	39 (22.3%)	**<.001**	3.4 (2.1-5.4)	**.003**	2.3 (1.3-3.9)	.12	1.5 (0.9-2.4)
Affective disorders	14 (8.1%)	10 (9.6%)	2 (1.1%)	**.008**	7.6 (1.7-33.9)	**.004**	9.4 (2.0-43.7)	.63	0.8 (0.3-1.9)
Psychotic disorders[c]	5 (2.9%)	0 (0.0%)	0 (0.0%)	NA	NA	NA	NA	NA	NA
Anxiety disorders	17 (9.8%)	15 (14.4%)	11 (6.3%)	.23	1.6 (0.7-3.6)	**.03**	2.5 (1.1-5.7)	.25	0.6 (0.3-1.4)
Disruptive behavior disorders	8 (4.6%)	3 (2.9%)	5 (2.9%)	.39	1.7 (0.5-5.2)	.99	1.0 (0.2-4.3)	.47	1.6 (0.4-6.3)
ADHD[b]	36 (20.8%)	11 (10.6%)	10 (5.7%)	**<.001**	4.5 (2.1-9.4)	.15	1.9 (0.8-4.7)	**.02**	2.3 (1.1-4.8)
Pervasive developmental disorders	12 (6.9%)	11 (10.6%)	8 (4.6%)	.34	1.6 (0.6-4.0)	.06	2.4 (0.9-6.3)	.31	0.6 (0.3-1.5)
Post-traumatic stress disorder[c]	1 (0.6%)	5 (4.8%)	0 (0.0%)	NA	NA	NA	NA	NA	NA
Stress and adjustment disorders	16 (9.2%)	11 (10.6%)	6 (3.4%)	**.03**	2.9 (1.1-7.6)	**.02**	3.3 (1.2-9.2)	.75	0.9 (0.4-2.0)
Tic disorders[d]	15 (8.7%)	6 (5.8%)	11 (6.3%)	.39	1.4 (0.6-3.2)	.84	0.9 (0.3-2.5)	.35	1.6 (0.6-4.3)

Significant *p* Values (<.05) in bold

FHR-BP, Children at familial high-risk of bipolar disorder; FHR-SZ, Children at familial high-risk of schizophrenia spectrum disorders; PBC, Population-based controls

[a]Any Axis I disorder excluding elimination disorders, transient and unspecified tics, and specific phobias, [b]In the logistic regression model with FHR-group and sex there was a significant effect of sex on Any Axis I disorder and ADHD, [c]Contained too few children to calculate confidence intervals, [d]Includes Tourette's disorder and chronic tic disorder

Table S2. Two-month prevalence of DSM-IV and DSM-5 Axis I mental disorders in 452 children in The Danish High Risk and Resilience Study, VIA 11

	No. (%)			Pairwise comparisons					
				FHR-SZ Vs. PBC		FHR-BP Vs. PBC		FHR-SZ Vs. FHR-BP	
	FHR-SZ (n = 173)	FHR-BP (n = 104)	PBC (n = 175)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)
Any Axis I disorder[a]	70 (40.5%)	32 (30.8%)	34 (19.4%)	**<.001**	2.8 (1.8-4.6)	**.03**	1.8 (1.0-3.2)	.10	1.6 (0.9-2.6)
Affective disorders	5 (2.9%)	4 (3.8%)	2 (1.1%)	.26	2.6 (0.5-13.5)	.16	3.5 (0.6-19.2)	.67	0.7 (0.2-2.8)
Psychotic disorders[b]	4 (2.3%)	0 (0.0%)	0 (0.0%)	NA	NA	NA	NA	NA	NA
Anxiety disorders	14 (8.1%)	12 (11.5%)	10 (5.7%)	.39	1.4 (0.6-3.4)	.08	2.2 (0.9-5.2)	.33	0.7 (0.3-1.5)
Disruptive behavior disorders	7 (4.0%)	3 (2.9%)	5 (2.9%)	.55	1.4 (0.4-4.6)	.99	1.0 (0.2-4.3)	.62	1.4 (0.4-5.6)
ADHD[c]	36 (20.8%)	11 (10.6%)	10 (5.7%)	**<.001**	4.5 (2.1-9.4)	.15	1.9 (0.8-4.7)	**.02**	2.3 (1.1-4.8)
Pervasive developmental disorders	12 (6.9%)	11 (10.6%)	8 (4.6%)	.34	1.6 (0.6-4.0)	.06	2.4 (0.9-6.3)	.31	0.6 (0.3-1.5)
Post-traumatic stress disorder[b]	1 (0.6%)	4 (3.8%)	0 (0.0%)	NA	NA	NA	NA	NA	NA
Stress and adjustment disorders	7 (4.0%)	2 (1.9%)	3 (1.7%)	.20	2.4 (0.6-9.6)	.91	1.1 (0.2-6.8)	.33	2.2 (0.4-10.9)
Tic disorders[d]	11 (6.4%)	6 (5.8%)	9 (5.1%)	.61	1.3 (0.5-3.1)	.84	1.1 (0.4-3.2)	.81	1.1 (0.4-3.2)

Significant p Values (<.05) in bold
FHR-BP, Children at familial high-risk of bipolar disorder; FHR-SZ, Children at familial high-risk of schizophrenia spectrum disorders; PBC, Population-based controls
[a]Any Axis I disorder excluding elimination disorders, transient and unspecified tics, and specific phobias, [b]Contained too few children to calculate confidence intervals, [c]In the logistic regression model with FHR-group and sex there was a significant effect of sex on ADHD, [d]Includes Tourette's disorder and chronic tic disorder

Paper 2

Developmental pathways and clinical outcomes of early childhood psychotic experiences in preadolescent children at familial high-risk of schizophrenia or bipolar disorder
A prospective, longitudinal cohort study - The Danish High Risk and Resilience Study, VIA 11

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Developmental pathways and clinical outcomes of early childhood psychotic experiences in preadolescent children at familial high-risk of schizophrenia or bipolar disorder

A prospective, longitudinal cohort study - The Danish High Risk and Resilience Study, VIA 11

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Abstract

Objective: Psychotic experiences are common in children and adolescents and are associated with concurrent and subsequent psychopathology. Most findings originate from general population studies whereas little is known of the clinical outcomes of psychotic experiences in children and adolescents at familial high-risk of psychosis. We examined the prevalence of psychotic experiences in middle childhood and whether early childhood psychotic experiences and developmental pathways of psychotic experiences predicted mental disorders in middle childhood in children at familial high-risk of schizophrenia (FHR-SZ), bipolar disorder (FHR-BP), and controls.

Methods: In a longitudinal population-based cohort study children at FHR-SZ (N=170), FHR-BP (N=103), and controls (N=174) were assessed for psychotic experiences and Axis I disorders with face-to-face interviews in early and middle childhood (at 7 and 11 years of age).

Results: Psychotic experiences were more prevalent in children at FHR-SZ (31.8%, odds ratio 2.1, 95% CI 1.3-3.4, p = .005) than controls (18.4%) in middle childhood. Early childhood psychotic experiences predicted mental disorders in middle childhood after adjusting for early childhood disorders and familial risk (odds ratio 2.0, 95% CI 1.2-3.1, p = .004). Having three or more psychotic experiences increased odds the most (odds ratio 2.5, 95% CI 1.1-5.7, p = .04). Persistent psychotic experiences were associated with increased odds of middle childhood disorders (odds ratio 4.1, 95% CI 2.1-8.4, p = <.001). Psychotic experiences were non-differentially associated with mental disorders across the three familial risk groups.

Conclusions: Early childhood psychotic experiences predict mental disorders in middle childhood. Psychotic experiences index vulnerability for psychopathology non-differentially in children at familial high-risk and controls. Psychotic experiences should be included in mental health screenings including children at familial high-risk.

Introduction

Psychotic experiences, including subclinical hallucinations and delusions in the absence of a diagnosable psychotic disorder, are common in children and adolescents from the general population and prevalence declines with age (1). Longitudinal studies show that in the general population psychotic experiences in children and adolescents predict both psychotic and non-psychotic disorders with the strongest evidence for psychotic disorders (2–6). Additionally, psychotic experiences are associated with concurrent mental disorders in childhood and adolescence (3, 7–9) and indicate increased severity of non-psychotic disorders (10).

Most psychotic experiences are transient whereas in a minority of individuals they persist over time (11). Persistent psychotic experiences are associated with higher levels of concurrent and subsequent psychopathology than non-persistent psychotic experiences (12, 13) and are considered part of an extended psychosis phenotype (11, 14). In one study a fifth of clinical psychosis cases were preceded by persistent psychotic experiences (14). The continuum between psychotic experiences and psychotic disorders is also demonstrated by their many shared risk factors including a family history of psychosis as elucidated in general population studies (15–17). Yet, findings are not unequivocal (8, 18) and one general population study found that although a family history of psychosis predicted persistence of psychotic experiences it did not predict psychotic experiences per se (19).

In spite of the associations between psychotic experiences and psychosis, relatively few studies have examined psychotic experiences in samples of children and adolescents at familial high-risk of psychosis. One familial high-risk study (mean age 21.2 years, range 16-25) documented that individuals with at least two first or second degree relatives with schizophrenia had a higher prevalence of psychotic symptoms than individuals without a family history of schizophrenia (20). Another study (mean age 11.8 years, range 6-21) not including a control group found that a family history of schizophrenia, bipolar disorder, and major depressive disorder was not differentially associated with the occurrence of psychotic experiences (21). Regarding prodromal symptoms, a study including offspring at familial high-risk of schizophrenia and bipolar disorder found higher scores in offspring at familial high-risk of schizophrenia with offspring at familial high-risk of bipolar disorder intermediate relative to controls at baseline (mean age 11.7 years, range 6-17) and at two-year follow-up (22). Elevated scores on prodromal symptoms were also reported in a sample including siblings (age 7-16 years) of individuals with schizophrenia within this study (23). In our baseline study, The Danish High Risk and Resilience Study, VIA 7, we found that psychotic experiences were more prevalent in 7-year-old children at familial high-risk of schizophrenia than in controls with children at familial high-risk of bipolar disorder intermediate (24).

Thus, there is evidence that psychotic experiences are more frequent in children and adolescents at familial high-risk of psychosis, yet there is a lack of familial high-risk studies examining the developmental pathways, i.e. the development over time, and clinical outcomes of psychotic experiences. One familial high-risk study examining clinical outcomes of psychotic experiences found that they predicted psychosis at two-year follow-up in young (mean age 16.1 years) first and second degree relatives of individuals with schizophrenia (25) whereas another found that childhood psychotic experiences belonged to clusters of risk factors predicting transition to severe mental illness in youth born to parents with schizophrenia or bipolar disorder (26).

In our baseline study we found that psychotic experiences in early childhood (measured at age 7 years) were associated with a higher occurrence of concurrent Axis I disorders (24). Since most studies have not measured psychotic experiences before middle childhood, there is little knowledge on early childhood psychotic experiences in relation to mental health later in childhood. One general population study documented that auditory vocal hallucinations at age 7-8 years predicted clinical psychopathology five years later (27). To our knowledge no study has examined clinical outcomes of early childhood psychotic experiences in children at familial high-risk of schizophrenia or bipolar disorder. Studying early childhood psychotic experiences in familial high-risk samples and elucidating whether they index risk of clinical outcomes is important to understand their potential as early vulnerability markers within this population.

The aims of the present study were 1) To examine the prevalence of psychotic experiences in middle childhood in children at familial high-risk of schizophrenia and bipolar disorder compared with controls 2) To examine whether early childhood psychotic experiences predict having psychotic experiences or an Axis I mental disorder in middle childhood 3) To examine associations between different developmental pathways of psychotic experiences and mental disorders in middle childhood 4) To examine whether early childhood psychotic experiences differentially predict psychotic experiences and mental disorders in middle childhood across the three groups of children 5) In exploratory analyses, to examine cross-sectional associations between psychotic experiences and mental disorders in middle childhood.

Method

Participants

The VIA 11 Study is the first follow-up of The Danish High Risk and Resilience Study, a Danish nationwide, longitudinal cohort study. The original cohort consisted of 522 seven-year-old children with at least one biological parent with a schizophrenia spectrum disorder (N=202, ICD 10-codes: F20, F22, F25 or ICD 8-codes: 295, 297, 298.29, 298.39, 298.89, 298.99), or bipolar disorder (N=120, ICD-10 codes: F30, F31 or ICD-8 codes: 296.19, 269.39), and population-based controls (hereafter controls) where neither parent was diagnosed with these disorders (N=200). The cohort was retrieved from the Danish national registers. Baseline data were obtained at face-to-face assessments between January 2013 and January 2016 (at age 7 years). Follow-up data were obtained at face-to-face assessments between March 2017 and June 2020 (at age 11 years). Controls were matched to children at familial high-risk of schizophrenia (FHR-SZ) on age, sex, and municipality. Children at familial high-risk of bipolar disorder (FHR-BP) were an unmatched sample comparable to the other groups regarding inclusion age and sex. Children had to be born in Denmark to be eligible and all participating children had Danish as their first language. Recruitment of the cohort is illustrated in section S1 of the online supplement. The cohort and study design are described in detail elsewhere (28).

The study was approved by the Danish Data Protection Agency. The study adheres to the guidelines of the Danish Committee on Health Research Ethics although this authority deemed ethical approval unnecessary due to the observational nature of the study. Written informed consent from the parent or other legal guardian and assent from the children were obtained upon explanation of all procedures.

Measures

Psychotic experiences

Psychotic experiences were assessed with the psychosis supplement of the Kiddie Schedule for Affective Disorders and Schizophrenia – Present and Lifetime Version (K-SADS-PL) (29). At baseline (age 7 years) children and the primary caregiver of each child were interviewed about psychotic experiences during the child's life, i.e. early childhood psychotic experiences, and at follow-up (age 11 years) they were re-interviewed about psychotic experiences during the four-year interim, i.e. middle childhood psychotic experiences. The interviews were conducted by formally trained psychologists, medical doctors, and research nurses. To ensure optimal information every child and primary caregiver was interviewed about all types of psychotic experiences regardless of their initial answers to the screening questions (for hallucinations and delusions). We inquired about 9 types of hallucinations and 13 types of delusions. Five types of

auditory hallucinations were subsequently collapsed into one. In case of a K-SADS-PL score of either a possible (score of 2) or definite (score of 3) psychotic symptom on either the child's or caregiver's answer the child or caregiver were asked additional questions about the symptom (frequency, duration, degree of conviction, distress, impact on functioning) and when it last occurred (current psychotic experiences were defined as occurring with the past six months). At follow-up all symptoms were consensus rated at clinical conferences by a psychotic experiences expert (professor of child and adolescent psychiatry, the last author) together with the interviewer and each symptom was given a final score on a seven point scale, ranging from 0 to 6 (0=absent, 1=possibly present, 2=mild, 3=moderate, 4=moderately severe, 5=severe but not psychotic, 6=severe and psychotic), to ensure consistent ratings and exclusion of uncertain symptoms. For the analyses scores were recoded into 0-1 = "absent or possible psychotic experiences" and 2-6 = "definite psychotic experiences". Only "definite psychotic experiences" were included in the analyses. Hypnagogic and hypnopompic hallucinations and symptoms attributed to fever were excluded at follow-up. The definition of psychotic experiences was slightly broader at baseline as these symptoms were not systematically excluded. Methods and results from the baseline study are described in detail elsewhere (24).

Having "any psychotic experiences" was defined as presence of any type of hallucination or delusion. A categorical predictor variable with number of differerent types of psychotic experiences divided into 0, 1, 2 or 3 and above was created to reflect severity. Using a categorical definition of presence or absence of psychotic experiences was chosen to increase comparability with other studies (2, 5, 6, 10, 30, 31). Number of different psychotic experiences was used to reflect severity in keeping with two large general population studies (5, 32). For developmental pathways of psychotic experiences a categorical predictor variable was created. Children not reporting any early childhood psychotic experiences nor any middle childhood psychotic experiences were classified as the "Never psychotic experiences" group. Children reporting any early childhood psychotic experiences but no middle childhood psychotic experiences were classified as the "Remittent psychotic experiences" group. Children not reporting any early childhood psychotic experiences but reporting any middle childhood psychotic experiences were classified as the "Incident psychotic experiences" group. Children reporting both any early childhood psychotic experiences and any middle childhood psychotic experiences were classified as the "Persistent psychotic experiences" group.

Mental disorders

DSM-IV and DSM-5 Axis I mental disorders were ascertained with K-SADS-PL. At age 7 years children and caregivers were interviewed about mental disorders during the child's life, i.e. early childhood mental disorders. At age 11 years

they were re-interviewed about symptoms during the four-year interim, i.e. middle childhood mental disorders. As per the K-SADS-PL manual all available information about the child was taken into consideration and summary ratings were based on the interviewers' best clinical judgment. All diagnoses were confirmed in consensus meetings with a child and adolescent psychiatrist (the last author). In the current cohort, diagnosed mental disorders included affective disorders, anxiety disorders, ADHD, disruptive behavior disorders, autism spectrum disorders, PTSD, stress and adjustment disorders, tic disorders, and psychotic disorders. "Any Axis I disorder" was defined as presence of any of these disorders. Elimination disorders, transient and unspecified tics, and specific phobias were excluded. Methods and results regarding mental disorders are described in detail elsewhere (33, 34). For supplementary analyses we constructed three disorder categories: internalizing (affective disorders and anxiety), externalizing (ADHD and disruptive behavior disorders), and other disorders, as detailed in section S5 of the online supplement.

Global functioning, IQ, and pubertal stage

Current global functioning was ascertained with Children's Global Assessment Scale (CGAS) (35). IQ was measured with Reynolds Intellectual Screening Test (36). Onset of puberty was assessed with self-reported Tanner Stages (37). For details, see section S2 of the online supplement.

Statistical analyses

Differences in demographic and clinical background characteristics between the three groups of children were analyzed with chi-square tests and one-way ANOVA. Dropout analyses were performed with chi-square.

For the main outcomes frequencies and percentages were calculated with crosstabs.

The aims of the study were examined as follows: 1) To ascertain the effects of familial high-risk group (FHR-group) on the prevalence of middle childhood psychotic experiences binary logistic regression analyses adjusted for sex of the child were conducted. FHR-group was used as predictor with any middle childhood psychotic experiences as outcome. Between-group comparisons were obtained by first using the controls as reference, then, for comparisons between children at FHR-SZ and FHR-BP, using children at FHR-BP as reference. Sensitivity analyses including three children (FHR-SZ, N=2, Controls, N=1) who provided data only at follow-up were conducted. 2) The effect of presence of any early childhood psychotic experiences as predictor on middle childhood psychotic experiences as outcome was ascertained with binary logistic regression adjusted for sex of the child. FHR-group was then added as covariate.

Similar models were run using number of early childhood psychotic experiences (0, 1, 2, 3 or above) as predictor. Children with no early childhood psychotic experiences were used as reference. Longitudinal relationship between any early childhood psychotic experiences as predictor and any middle childhood Axis I disorder as outcome was ascertained with binary logistic regression adjusted for sex of the child. Any early childhood Axis I disorder, and FHR-group were successively added as covariates. Models were repeated using number of early childhood psychotic experiences as predictor. 3) Similar analyses were carried out with developmental pathways of psychotic experiences as predictor using the "Never psychotic experiences" group as reference and any middle childhood Axis I disorder as outcome. 4) Analyses with psychotic experiences as predictor were checked for interaction effect by adding FHR-group as interaction term in the first model. Interaction analyses were conducted to examine whether associations between psychotic experiences and the examined outcomes differed across FHR-groups, therefore only p-values for the interaction terms are interpreted (estimates for the interaction terms are available from the authors upon request) 5) Exploratory cross-sectional analyses of associations between middle childhood psychotic experiences and mental disorders were conducted in the same way as the longitudinal analyses. Internalizing, externalizing, and other disorders were subsequently used as outcomes for aims 2) and 3) and 5) as detailed in section S5 of the online supplement.

Analyses were adjusted for sex to control for any effect of sex on outcome. Unadjusted models are included in all tables for information only. For relation between sex and the examined outcomes, see section S3 of the online supplement.

Sensitivity analyses excluding children with lifetime psychotic disorders were conducted as detailed in section S7 of the online supplement.

Due to the risk of overadjusting we did not adjust for socioeconomic status which is intrinsically associated with familial risk status.

Alpha was set to < .05. Data were analyzed using SPSS version 25.

Results

Sample characteristics

The three FHR-groups did not differ regarding sex, age at inclusion, IQ at age 7 years, or onset of puberty (Table 1). Children at FHR-SZ and FHR-BP had a significantly higher prevalence of Any Axis I disorder during early (age 7 years) and middle childhood (age 11 years) and lower current global functioning compared with controls. Children at FHR-SZ had a higher prevalence of early childhood psychotic experiences than controls. Children at FHR-SZ had significantly lower socioeconomic status reflected in lower levels of education of their primary caregivers than children at FHR-BP and controls (Table 1).

Data on psychotic experiences were provided for 513 children at age 7 years, for 450 children at age 11 years, and for 447 children (174 controls, 103 FHR-BP, 170 FHR-SZ) at both assessments (mean age 11.9 years at follow-up, SD 0.2, range 10.9-12.7). Retention was 87.1%. There were no significant differences between children who re-participated in the psychotic experiences assessment at age 11 years and dropouts regarding prevalence of any psychotic experiences ($X^2(1)=1.311$, $P = .25$), Any Axis I disorder ($X^2(1)=1.969$, $P = .16$) in early childhood, sex ($X^2(1)= .853$, $P = .36$), or FHR-group ($X^2(2)= .991$, $P = .61$).

Prevalence of middle childhood psychotic experiences

Significantly more children at FHR-SZ (31.8%) than controls (18.4%) experienced any middle childhood psychotic experiences (odds ratio 2.1, 95% CI 1.3-3.4, p = .005). No significant difference was found between children at FHR-BP (20.4%) and controls (Table 2). Children at FHR-SZ were significantly more likely than children at FHR-BP to have experienced any psychotic experiences. Similar results were found regarding current psychotic experiences (Table 2). Sensitivity analyses including three children with data at age 11 years only did not change these results (data not shown).

The prevalence of hallucinations and delusions in middle childhood is presented in section S4 of the online supplement. Children at FHR-SZ had a significantly higher prevalence of hallucinations than controls and children at FHR-BP as well as a higher prevalence of delusions than controls.

Longitudinal associations between early childhood psychotic experiences and middle childhood psychotic experiences and mental disorders

Children who reported any early childhood psychotic experiences were significantly more likely to report any middle

childhood psychotic experiences (30.7% reported psychotic experiences again) than children without early childhood psychotic experiences (19.0% reported middle childhood psychotic experiences) (Table 3). This effect was driven by children with multiple psychotic experiences, i.e. having more than one type of early childhood psychotic experiences predicted persistence of psychotic experiences whereas having one type did not (Table 3).

Presence of any early childhood psychotic experiences predicted any middle childhood Axis I disorder even after adjusting for early childhood disorders and familial risk (odds ratio 2.0, 95% CI 1.2-3.1, p = .004). Of children with any early childhood psychotic experiences 46.6% had an Axis I disorder in middle childhood whereas 28.3% of children with no early childhood psychotic experiences had a middle childhood disorder. The occurrence of three or more early childhood psychotic experiences was most strongly associated with having a middle childhood Axis I disorder (odds ratio 2.5, 95% CI 1.1-5.7, p = .04, Table 3).

Early childhood psychotic experiences predicted both internalizing, externalizing, and other disorders in middle childhood with stronger effects for more than one type of psychotic experiences. Not all associations survived adjustment for early childhood disorders (see section S5 of the online supplement).

Associations between developmental pathways of psychotic experiences and middle childhood mental disorders

Persistence of psychotic experiences into middle childhood was found in 36.1% (N=30) of those who reported early childhood psychotic experiences (N=83) in the FHR-SZ group, in 26.7% (12 out of 45) in the FHR-BP group, and in 26.2% (16 out of 61) among controls.

Across familial risk groups children with remittent, incident, and persistent psychotic experiences had a significantly higher risk of any middle childhood Axis I disorder than children in the never psychotic experiences group when only adjusting for sex. When taking into account early childhood mental disorders and familial risk only persistent psychotic experiences significantly predicted middle childhood mental disorders (odds ratio 4.1, 95% CI 2.1-8.4, p < .001, Table 4). There was some evidence that remittent psychotic experiences also predicted middle childhood Axis I disorders, as there was little attenuation of the association when adjusting for FHR-group, however, this fell just short of statistical significance (Table 4).

Developmental pathways of psychotic experiences are presented in Figure 1a-c.

Persistent psychotic experiences predicted both internalizing, externalizing, and other disorders after adjustment for early childhood disorders. However, after adjustment for FHR-group the association with other disorders fell just short of statistical significance (see section S5 of the online supplement).

Interaction between psychotic experiences and familial risk status

There was no interaction with FHR-group, i.e. early childhood psychotic experiences were not differentially associated with persistence of psychotic experiences or with any middle childhood Axis I disorder across the three familial risk groups. Developmental pathways of psychotic experiences were not differentially associated with any middle childhood Axis I disorder (p-values for test of interaction > .30).

Cross-sectional associations between PE and mental disorders in middle childhood

Occurrence of middle childhood psychotic experiences was associated with any concurrent Axis I disorder. Results are presented in section S6 of the online supplement. No differential associations between psychotic experiences and Any Axis I disorder were found between the three groups (p-values for test of interaction > .35).

Middle childhood psychotic experiences were cross-sectionally associated with both internalizing, externalizing, and other disorders (see section S5 of the online supplement).

Sensitivity analyses

Excluding 6 children with lifetime psychotic disorders rendered differences between children at FHR-SZ and FHR-BP in prevalence of any psychotic experiences non-significant. Associations between 2 early childhood psychotic experiences and persistence and between one type of early childhood psychotic experiences and any middle childhood Axis I disorder fell just short of statistical significance (see section S7 of the online supplement).

Discussion

Main findings

Psychotic experiences more often occurred in children at FHR-SZ in middle childhood than in controls whereas the prevalence in children at FHR-BP was not significantly higher than in controls. Across groups, having more than one type of early childhood psychotic experiences predicted persistence of psychotic experiences into middle childhood. Presence of any early childhood psychotic experiences predicted a two-fold increased risk of having an Axis I disorder in middle childhood after taking into account the effects of early childhood disorders and familial risk. Having three or

more types of psychotic experiences in early childhood was associated with the highest increase in odds (2.5-fold). When taking these risk factors into account, children with persistent psychotic experiences had a four-fold increased risk of having a mental disorder in middle childhood compared with children who never had psychotic experiences. Early childhood psychotic experiences were non-differentially associated with persistence and mental health outcomes across the three groups of children. Psychotic experiences in middle childhood were cross-sectionally associated with presence of mental disorders, with non-differential associations across groups. Excluding children who had met criteria for a psychotic disorder did not substantially change these results.

Interpretation

To our knowledge this is the first prospective study to examine early childhood psychotic experiences in relation to mental health outcomes in children at familial high-risk of schizophrenia or bipolar disorder.

The increased prevalence of psychotic experiences in children at FHR-SZ in the current sample is in keeping with the previously described evidence of the link between psychotic experiences and familial risk of psychosis from general population studies and familial high-risk studies (16, 20, 22). Our findings thus support the notion of psychotic experiences as a vulnerability marker of psychosis risk. The comparable prevalence of psychotic experiences in children at FHR-BP and controls aligns with findings from the previously mentioned study including both groups of offspring (22). In a general population sample of children assessed at age 11-12 years a family history of psychosis, including bipolar disorder, predicted occurrence of psychotic experiences whereas a family of nonpsychotic mental disorders did not. However, prediction from individual disorders was not reported (15).

The presence of more than one type of psychotic experiences in early childhood predicted persistence of psychotic experiences into middle childhood. Although a recent scoping review concluded that reliable predictors of persistence have not been sufficiently replicated across studies (38) our study lends support to the notion that higher severity of psychotic experiences predicts a higher risk of persistence, similarly to other studies (27, 32, 39, 40).

The finding of psychotic experiences as early markers for vulnerability to subsequent mental disorders align with the previously described meta-analytic findings from child and adolescent general population samples (3) and the limited longitudinal evidence on psychotic experiences measured as early as age 7-8 years (27, 41). Even when taking into account known risk factors, early childhood psychotic experiences predicted mental health in middle childhood in the current sample. This in keeping with a smaller study in an adolescent general population sample showing that

childhood psychotic experiences (age 11.7 years) predicted psychopathology in adolescence (age 15.7 years) after taking into consideration other risk factors (30). In the current cohort psychotic experiences appeared to increase risk across the diagnostic spectrum consistent with previous evidence (3, 6, 30). The higher increase in odds of having a disorder in middle childhood in children with three or more early childhood psychotic experiences is in keeping with a large, cross-sectional general population study of preadolescents documenting that higher severity of self-reported psychotic experiences corresponded with stronger associations with concurrent psychopathology (9). It should be noted that definitions of severity vary across studies, and while we used number of psychotic experiences, other indicators of increasing severity such as associated distress also confer increased risk of clinical outcomes and persistence (12, 42). The predictive value of early childhood psychotic experiences on middle childhood mental disorders in our population is important since childhood Axis I disorders may index an increased risk of transitioning to severe mental illness in children at familial high-risk (26, 43, 44). Although too few for quantitative analyses it is noteworthy that, in the current sample, 75% of children with incident psychotic disorders in middle childhood (N=4, all at FHR-SZ) reported psychotic experiences in early childhood.

Persistent psychotic experiences predicted later mental disorders in our cohort which extends findings from older populations. However, the strength of this association may potentially partly be explained by cross-sectional associations between middle childhood psychotic experiences and concurrent mental disorders. Persistent psychotic experiences relative to no psychotic experiences and transient psychotic experiences were associated with a greater risk of subsequent psychopathology in adolescent general population samples (13, 14, 31) as well as in a two-year follow-up of a general population sample of children first examined at age 9-11 years (45). In the study measuring hallucinations at age 7-8 years those with persistence had a higher risk of clinical psychopathology at five-year follow-up than those with no hallucinations (27). In the current cohort, a tentative case could be made that remittent psychotic experiences, albeit to a lesser extent than persistent, also predict having an Axis I disorder in middle childhood, suggesting that psychotic experiences, even when transient, may index increased risk of later psychopathology, in line with findings from an adolescent sample (30).

A meta-analysis including general population samples of various ages reported rates of persistent psychotic experiences of around 20% (11). The rates in the current sample were higher which corresponds to findings from other child and adolescent samples (14, 45). The study measuring hallucinations found decreasing prevalence of persistence with increasing age (23.5% from age 7-8 to 12-13 years vs. 18.5% from age 12-13 to age 18-19 years) (41).

The higher rates of persistence in the current sample are most likely attributable to the young age of the children, their familial high-risk, and the long follow-up period. We would expect a similar decrease at later follow-ups given the evidence of declining prevalence of psychotic experiences with advancing age (1).

In contrast with one previous study of a general population adolescent sample finding that parental psychosis predicted persistence of psychotic experiences (19), we found that familial risk was not differentially associated with persistence or remission of psychotic experiences. The same study, however, found that broadly defined parental psychopathology did not contribute to persistence of psychotic experiences. In our study, psychotic experiences and developmental pathways of psychotic experiences were not differentially associated with childhood Axis I disorders across the three groups. A general population study of adolescents found that psychotic experiences in conjunction with a parental history of mental illness was associated with a higher risk of subsequent disorders than psychotic experiences without parental mental illness. Yet, it only reported whether the risk was significantly different from a reference group without psychotic experiences and without parental mental disorder and the definition of parental mental disorder was broader than in the current study (6). Considering the evidence that psychotic experiences become more strongly associated with psychopathology with increasing age, as shown in general population samples (10), the predictive value of psychotic experiences is expected to increase at later follow-ups and cumulative effects with parental mental illness may then emerge.

Our findings suggest that those with several psychotic experiences in early childhood and those with persistent psychotic experiences may constitute a particularly vulnerable subgroup. This should warrant attention in light of meta-analytic evidence of a dose-response relationship between severity of psychotic experiences, including higher number of psychotic experiences and persistence, and risk of transitioning to clinical psychotic outcomes in adolescents and adults from the general population (46). Planned follow-up studies in our cohort will elucidate whether the severity of childhood psychotic experiences has similar predictive value.

Strengths and limitations

This study has several strengths. Attrition was low (12.9%) and equally distributed regarding those with psychotic experiences and mental disorders and those without at baseline. The same golden-standard interview, including information from both child and caregiver, carried out by trained mental health professionals, was used to ascertain psychotic experiences and mental disorders at both baseline and follow-up. Additionally, the design allowed us to examine developmental pathways and clinical outcomes of psychotic experiences in same-aged children and to adjust

for baseline mental health.

Some limitations should also be taken into consideration. Psychotic experiences defined as persistent may have occurred closely together in time since participants were interviewed about the entire interim. Ideally they would have been interviewed on several, shorter follow-ups to identify potential heterogeneous developmental pathways, e.g. to discern whether persistent psychotic experiences were time-limited continuations of early symptoms, continued over the entire interim, or were intermittent. However, in the current cohort, of children with early childhood psychotic experiences, 74.1% of those who reported middle childhood psychotic experiences reported symptoms within the past six months suggesting that for the majority of those classified as having persistent psychotic experiences symptoms were present in preadolescence. We are unable to subclassify children into those born to parents with bipolar disorder with and without psychotic illness features precluding examination of potential variations of psychotic experiences within these subgroups. Future studies may benefit from making such a distinction. Furthermore, considering the number of analyses in the current study and the defined alpha level of $< .05$, these findings should be independently replicated in future studies. The smaller sample size in the FHR-BP weakens estimates of differences for this group and may not have been fully conducive to detecting interaction effects hereby increasing the risk of type II errors. Therefore, no firm conclusions should be drawn regarding the non-differential associations between psychotic experiences and outcomes for this group. Additionally, potential confounding by other factors not examined in this study such as exposure to trauma and urbanicity which may moderate the associations between psychotic experiences and mental disorders (47) cannot be ruled out. Future studies in this cohort should examine their role.

Conclusions

This study extends previous knowledge on psychotic experiences to include early childhood psychotic experiences in children at familial high-risk of schizophrenia and bipolar disorder. The study demonstrates that early childhood psychotic experiences are markers for vulnerability to mental disorders in middle childhood and may characterize vulnerable subgroups within familial high-risk populations. Yet, the associations between psychotic experiences and mental health in the current sample were not unique to children at familial high-risk and are comparable to what has been found in the general population. As others have suggested, inquiring about psychotic experiences should be part of any mental health screening of children and adolescents (6, 30) and our findings suggest that this may meaningfully

begin in early childhood and should encompass children at familial high-risk. Occurrence of psychotic experiences, even in early childhood, although not necessarily cause for concern, should prompt identification of individual needs for early intervention and prevention with potential for reducing short and long term risk of mental disorders. Children who report several types of psychotic experiences and persistent psychotic experiences ought to warrant particular attention. Follow-up is crucial to elucidate the possible value of early childhood psychotic experiences in predicting psychotic disorders and other severe mental illness.

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Table 1. Demographic and clinical background characteristics of 447 children with data on Psychotic Experiences at age 7 and 11 years in The Danish High Risk and Resilience Study, VIA 11

	Familial risk group							*P* value for Pairwise Comparisons		
	FHR-SZ (n = 170*)		FHR-BP (n = 103)		Controls (n = 174*)					
	N/mean	%/SD	N/mean	%/SD	N/mean	%/SD	p	FHR-SZ vs Controls	FHR-BP vs Controls	FHR-SZ vs FHR-BP
Female, N, %	82	48.2	46	44.7	82	47.1	.85[a]	NA	NA	NA
Age at inclusion, years, mean, SD	12.0	0.3	11.9	0.2	11.9	0.2	.61[b]	NA	NA	NA
Baseline IQ[d], mean, SD[e]	103.0	11.3	105.3	8.8	105.2	9.8	.07[b]	NA	NA	NA
Onset of puberty[f], N, %[g]	137	87.3	87	90.6	151	94.4	.09[a]	NA	NA	NA
Any early childhood psychotic experiences (age 7 years), N, %	83	48.8	45	43.7	61	35.1	**.03**[a]	**.01**	.15	.41
Any early childhood Axis I disorder (K-SADS, age 7 years)[h], N, %	61	35.9	36	35.0	28	16.1	**<.001**[a]	**<.001**	**<.001**	.88
Any middle childhood Axis I disorder (K-SADS, age 11 years)[h], N, %	82	48.2	40	38.8	39	22.4	**<.001**[a]	**<.001**	**.003**	.13
Current global functioning[i], mean, SD	64.8	15.6	68.5	14.6	75.1	14.0	**<.001**[b]	**<.001**	**<.001**	.05
Educational level, primary caregiver[j,k],										
Primary/lower secondary, N,%	57	33.5	19	18.4	36	20.8				
Upper secondary, vocational, short-cycle tertiary, N,%	39	22.9	21	20.4	39	22.5	**.008**[c]	**.008**	.46	**.003**
Bachelor degree, equivalent or higher, N,%	74	43.5	63	61.2	98	56.6				

Abbreviations: FHR-BP, children at familial high risk of bipolar disorder; FHR-SZ, children at familial high risk of schizophrenia spectrum disorders; K-SADS-PL, Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime Version

[a]Chi square test, [b]One-way ANOVA test with post hoc Least Significant Difference, [c]Linear-by-Linear Association p value is reported when an ordinal variable has more than two categories, [d]Measured with Reynolds Intellectual Screening Test (RIST), [e]Includes 170 children at FHR-SZ, 103 children at FHR-BP, and 172 controls, [f]Measured with self-reported Tanner Stages. Onset of puberty defined as Tanner Stage 2-4 (vs Stage 1), [g]Includes 157 children at FHR-SZ, 96 children at FHR-BP, and 160 controls, [h]Includes affective disorders, anxiety disorders, ADHD, disruptive behavior disorders, autism spectrum disorders, PTSD, stress and adjustment disorders, tic disorders, and psychotic disorders, [i]Measured with Children's Global Assessment Scale (CGAS), [j]The primary caregiver is defined as the caregiver currently spending the most time with the child at the time of the VIA 11 assessment, [k]Includes 170 primary caregivers of children at FHR-SZ, 103 caregivers of children at FHR-BP, and 173 caregivers of controls

*At follow-up data on Psychotic Experiences were provided for 3 children (FHR-SZ=2, controls=1) who did not have data on Psychotic Experiences at baseline. Since the main analyses are on children with data at both baseline and follow-up (n = 447), those 3 children are not included in Table 1

Table 2. Psychotic experiences in middle childhood (age 11 years) in 447 children at FHR-SZ, FHR-BP, and controls in The Danish High Risk and Resilience Study, VIA 11

	N, %						Between-group comparisons								
	FHR-SZ (n = 170)		FHR-BP (n = 103)		Controls (n = 174)		FHR-SZ vs. controls			FHR-BP vs. controls			FHR-SZ vs. FHR-BP		
	N	%	N	%	N	%	Odds ratio	95% CI	p	Odds ratio	95% CI	p	Odds ratio	95% CI	p
Four-year prevalence, Any Psychotic Experiences															
Unadjusted	54	31.8	21	20.4	32	18.4	**2.1**	**1.3-3.4**	**.005**	1.1	0.6-2.1	.68	1.8	1.0-3.2	**.04**
Adjusted for sex							2.1	1.3-3.4	**.005**	1.1	0.6-2.1	.68	1.8	1.0-3.2	**.04**
Six-month prevalence, Any Psychotic Experiences															
Unadjusted	42	24.7	14	13.6	23	13.2	2.2	1.2-3.8	**.007**	1.0	0.5-2.1	.93	2.1	1.1-4.0	**.03**
Adjusted for sex							2.2	1.2-3.8	**.007**	1.0	0.5-2.1	.91	2.1	1.1-4.0	**.03**

Significant *P* values (<.05) in bold

Abbreviations: FHR-BP: Children at familial high-risk of bipolar disorder; FHR-SZ: Children at familial high-risk of schizophrenia spectrum disorders.

Table 3. Associations between early childhood psychotic experiences (age 7 years) and middle childhood psychotic experiences and mental disorders (age 11 years) in 447 children at FHR-SZ, FHR-BP, and controls in The Danish High Risk and Resilience Study, VIA 11

	Early childhood psychotic experiences											
	Any psychotic experiences (n = 189)			1 type of psychotic experiences (n = 104)			2 types of psychotic experiences (n = 48)			3 or more types of psychotic experiences (n = 37)		
	Odds ratio	95% CI	p	Odds ratio	95% CI	p	Odds ratio	95% CI	p	Odds ratio	95% CI	p
Any middle childhood psychotic experiences												
Unadjusted	1.9	1.2-2.9	**.004**	1.6	0.9-2.7	.10	2.1	1.1-4.2	**.03**	2.6	1.2-5.4	**.01**
Adjusted for sex	1.9	1.2-2.9	**.005**	1.6	0.9-2.7	.10	2.1	1.1-4.2	**.03**	2.6	1.2-5.4	**.01**
Any middle childhood Axis I disorder												
Unadjusted	2.2	1.5-3.3	**<.001**	1.6	1.0-2.6	.06	2.8	1.5-5.2	**.002**	4.2	2.0-8.5	**<.001**
Adjusted for sex	2.3	1.5-3.4	**<.001**	1.7	1.0-2.7	**.04**	2.8	1.5-5.3	**.001**	4.3	2.1-8.8	**<.001**
Adjusted for sex and any early childhood Axis I disorder	2.1	1.3-3.2	**.002**	1.7	1.0-3.0	**.05**	2.3	1.1-4.7	**.03**	3.1	1.4-7.0	**.007**
Adjusted for sex, any early childhood Axis I disorder, and familial risk	2.0	1.2-3.1	**.004**	1.8	1.0-3.1	**.04**	2.0	1.0-4.2	.06	2.5	1.1-5.7	**.04**

Note: Children with no early childhood psychotic experiences (n = 258) were used as reference.
Significant *P* values (<.05) in bold
Abbreviations: FHR-BP: Children at familial high-risk of bipolar disorder; FHR-SZ: Children at familial high-risk of schizophrenia spectrum disorders

Table 4. Associations between developmental pathways of psychotic experiences from early to middle childhood and middle childhood mental disorders in 447 children at FHR-SZ, FHR-BP, and controls in The Danish High Risk and Resilience Study, VIA 11

	Developmental pathways of psychotic experiences								
	Remittent psychotic experiences (n = 131)			Incident psychotic experiences (n = 49)			Persistent psychotic experiences (n = 58)		
	Odds ratio	95% CI	p	Odds ratio	95% CI	p	Odds ratio	95% CI	p
Any middle childhood Axis I disorder									
Unadjusted	2.0	1.2-3.2	**.004**	2.3	1.2-4.3	**.01**	4.9	2.7-9.1	**<.001**
Adjusted for sex	2.1	1.3-3.4	**.002**	2.3	1.2-4.5	**.01**	5.2	2.8-9.8	**<.001**
Adjusted for sex and any early childhood Axis I disorder	1.8	1.1-3.1	**.03**	2.1	1.0-4.3	.05	4.5	2.3-9.0	**<.001**
Adjusted for sex, any early childhood Axis I disorder, and familial risk	1.7	1.0-2.9	.06	1.8	0.9-3.9	.10	4.1	2.1-8.4	**<.001**

Note: The "Never psychotic experiences" group (n = 209) was used as reference
Significant *P* values (<.05) in bold
Abbreviations: FHR-BP: Children at familial high-risk of bipolar disorder; FHR-SZ: Children at familial high-risk of schizophrenia spectrum disorders

Figure titles and footnotes

Figure 1a-c. Developmental pathways of psychotic experiences from early to middle childhood in 447 children at FHR-SZ, FHR-BP, and controls in the Danish High Risk and Resilience Study, VIA 11

- **Figure 1a.** FHR-SZ (n = 170)
- **Figure 1b.** FHR-BP (n = 103)
- **Figure 1c.** Controls (n = 174)

Footnote:

Abbreviations: FHR-BP, Children at familial high-risk of bipolar disorder; FHR-SZ, Children at familial high-risk of schizophrenia spectrum disorde

Figure 1a. FHR-SZ (N=170)

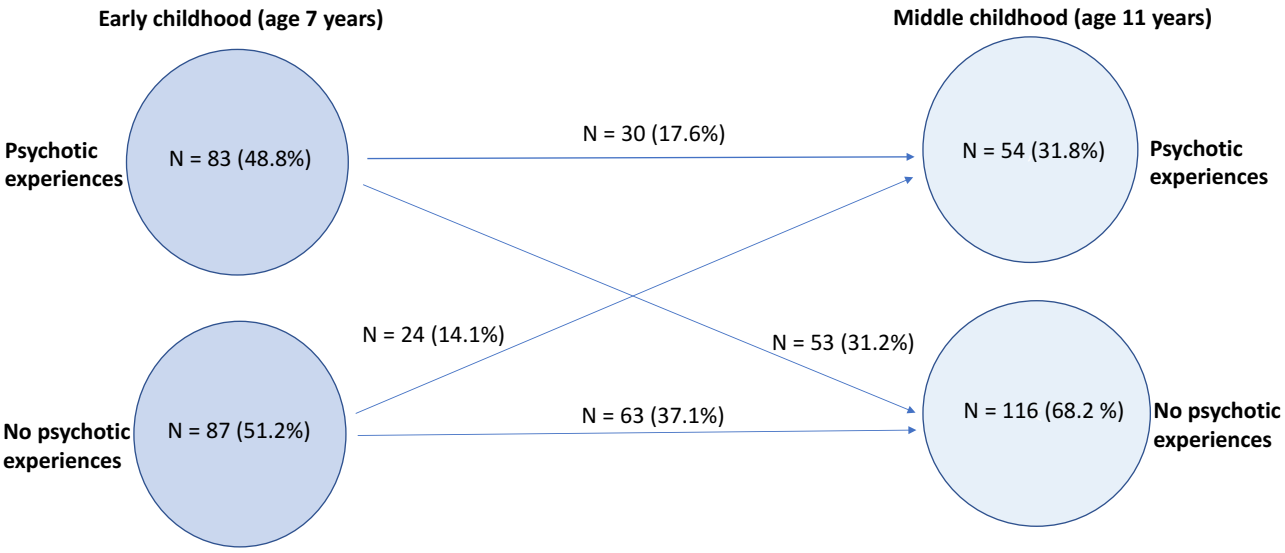


Figure 1b. FHR-BP (N=103)

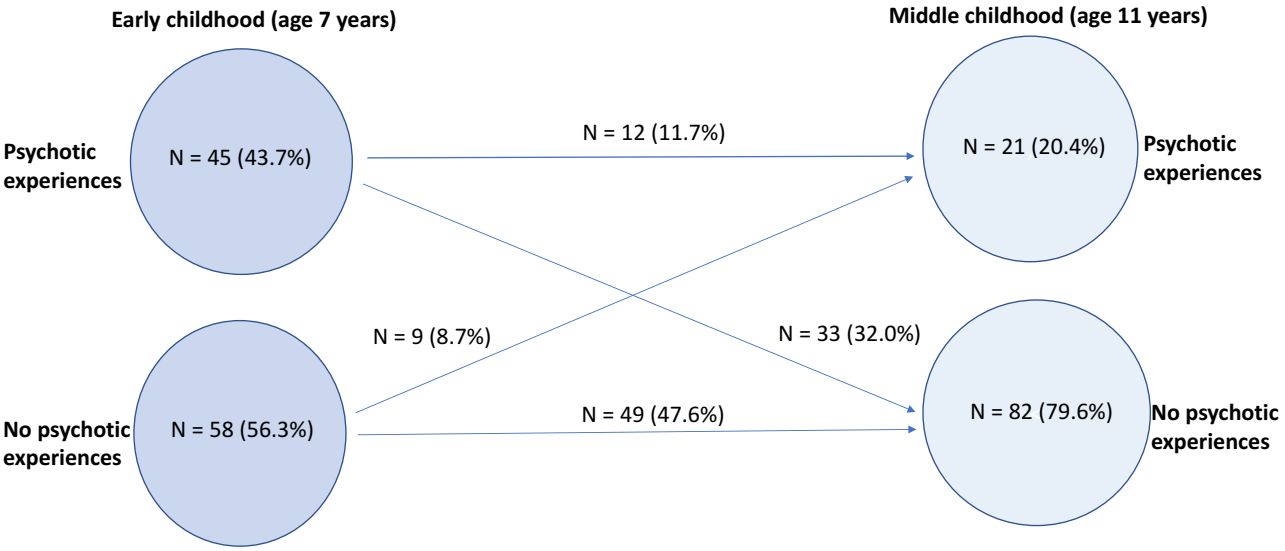
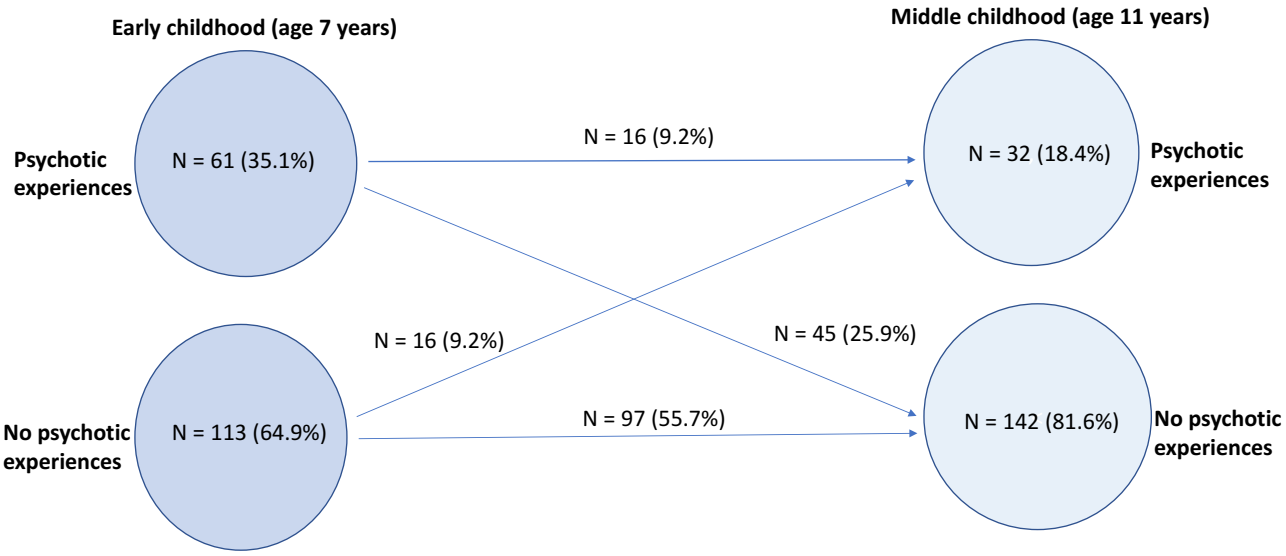


Figure 1c. Controls (N=174)



Online supplement

Section S1. Data extraction and recruitment procedure of the VIA 7 and VIA 11 cohort
- Figure S1

Section S2. Supplementary information for Children's Global Assessment Scale, Tanner Stages, and IQ

Section S3. Relation between sex, psychotic experiences, and mental disorders
- Table S1

Section S4. Hallucinations and delusions in middle childhood
- Table S2
- Figure S2a-b

Section S5. Supplementary analyses with internalizing, externalizing, and other mental disorders as outcome
- Table S3-S5

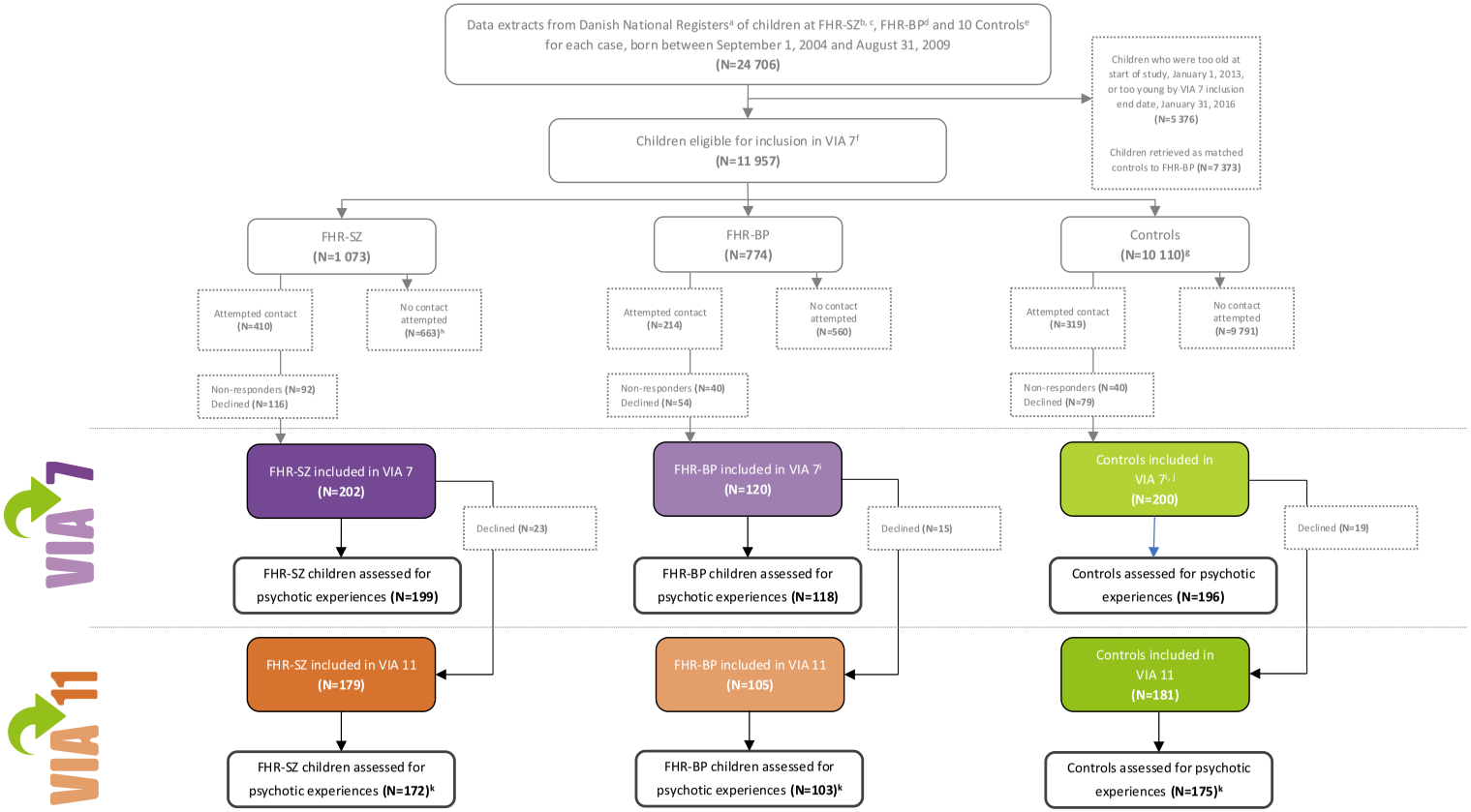
Section S6. Cross-sectional analyses
- Table S6

Section S7. Sensitivity analyses excluding 6 children with lifetime psychotic disorders
- Table S7-S10

eReferences

Section S1. Data extraction and recruitment procedure of the VIA 7 and VIA 11 cohort

Figure S1. Data extraction and recruitment procedure of the VIA 7 and VIA 11 cohort



Footnotes:

[a] Danish National Registers: Danish Civil Registration System and Danish Psychiatric Central Research Register.
[b] FHR-SZ: Children at familial high-risk of schizophrenia spectrum disorders.
[c] Double diagnosed parents: Parents with diagnoses of schizophrenia and bipolar disorder were assigned to the schizophrenia high-risk group as per the ICD-10 hierarchy.
[d] FHR-BP: Children at familial high-risk of bipolar disorder.
[e] Controls: Population-based control children of parents with no diagnoses of schizophrenia spectrum disorders or bipolar disorder.
[f] Research protection: As of May 2011, legislation was enacted to protect individuals´ phone numbers from being called for participation in scientific research. Therefore, there were eligible children who were not contacted and enrolled in VIA 7.
[g] Controls selection: Up to 10 controls were retrieved for each child in the FHR-SZ group and the FHR-BP group. Controls were matched to cases on sex, municipality, and exact age. The original intent was to only select control cases that were matched to children at FHR-SZ. However, there are 38 FHR-BP controls among the 200 total controls.
[h] Definition of contact: First through letters sent to the child´s address. If the family did not respond, contact by telephone was attempted (calls and text messages), if a phone number could be found.
[i] Re-assigned control parent: One control parent was found to have a diagnosis of bipolar disorder made by a private doctor, therefore the diagnosis was not present/visible in the National Register extract, as private doctors do not report to the National Register. This family/parent was therefore reassigned to the FHR-BP group. Therefore the N=201 for controls is now N=200.
[j] Control children not in the extract: Two younger siblings were included in VIA 7 by request of the parents. They were not in the original extract.
[k] Data on psychotic experiences were provided for 447 children at both assessments (FHR-SZ N=171, FHR-BP N=103, Controls N=174).

Section S2. Supplementary information for Children's Global Assessment Scale, Tanner Stages, and IQ

Children's Global Assessment Scale

The Children's Global Assessment Scale (CGAS) (1) is an interviewer based rating scale ranging from 1-100 used to assess global functioning taking into account all aspects of daily functioning, including the severity of symptoms. Higher scores indicate better functioning. In the current study CGAS scores were ascertained by the interviewer during the Kiddie Schedule for Affective Disorders and Schizophrenia – Present and Lifetime Version interview (2). All CGAS scores were subsequently confirmed in consensus meetings with a child and adolescent psychiatrist (the last author).

Tanner Stages

Tanner Stages is a commonly used and reliable indicator of pubertal development (3). In the current study, pubertal stage was assessed by the child pointing out which depictions of physical development from no sign of puberty onset to full puberty onset best corresponded with the child's physical development. In the current study scores were dichotomized into any sign of puberty onset or no sign of puberty onset based on whether the child had indicated any sign of puberty onset for either of the two depictions. For boys and girls respectively depictions were adapted from the original images as shown in the references by Marshall and Tanner (4, 5).

IQ

IQ was measured with Reynolds Intellectual Screening Test (RIST) which is an abbreviated version of Reynolds Intellectual Assessment Scales (6, 7). RIST consists of a verbal and a nonverbal scale combined into an overall, age adjusted RIST index score, which is an IQ estimate. RIST is used for individuals aged 3 to 94 years. In the current study tests were scored by trained psychology students blinded to the children's familial risk under supervision of a specialist in clinical child psychology (the second last author). Intraclass correlations were excellent (> 0.90) (8).

Section S3. Relation between sex, psychotic experiences, and mental disorders

Table S1. Frequencies and chi-square tests of the relation between sex and middle childhood psychotic experiences and mental disorders in 447 children at FHR-SZ, FHR-BP, and controls in The Danish High Risk and Resilience Study, VIA 11

	Boys		Girls		Pearson's Chi-Square
	N	%	N	%	p-value
Four-year prevalence, Any psychotic experiences	55	23.2	52	24.8	.70
Six-month prevalence, Any psychotic experiences	37	15.6	42	20.0	.23
Any middle childhood Axis I disorder	96	40.5	62	31.0	**.04**
Any middle childhood externalizing disorder	39	16.5	22	10.5	.07
Any middle childhood internalizing disorder	29	12.2	32	15.2	.36
Any other middle childhood disorder	55	23.2	32	15.2	**.03**

Significant *P* values (<.05) in bold
Abbreviations: FHR-BP: Children at familial high-risk of bipolar disorder; FHR-SZ: Children at familial high-risk of schizophrenia spectrum disorders

Section S4. Hallucinations and delusions in middle childhood

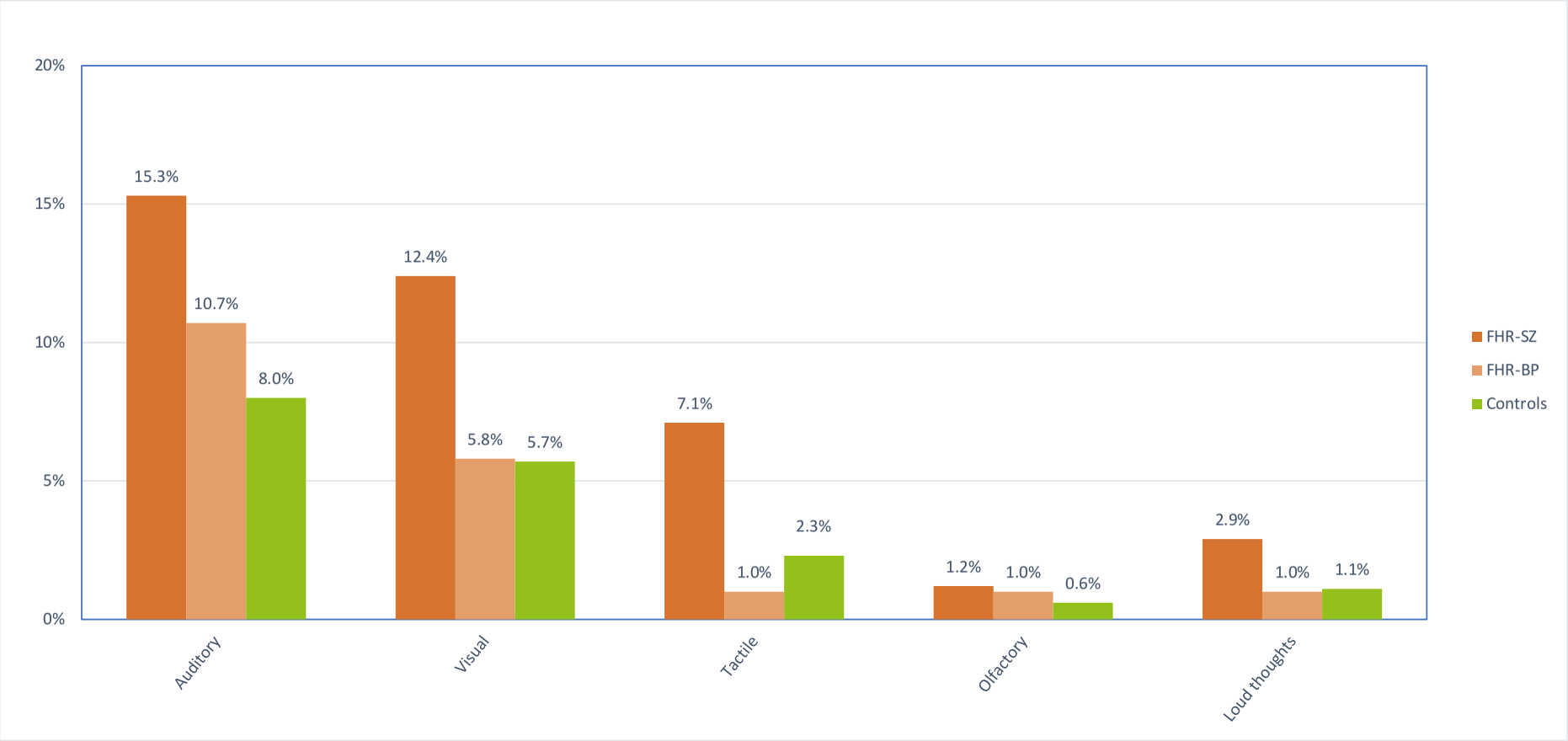
Table S2. Hallucinations and delusions in middle childhood (age 11 years) in 447 children at FHR-SZ, FHR-BP, and controls in The Danish High Risk and Resilience Study, VIA 11

	N, %						Between-group comparisons								
	FHR-SZ (n = 170)		FHR-BP (n = 103)		PBC (n = 174)		FHR-SZ vs. controls			FHR-BP vs. controls			FHR-SZ vs. FHR-BP		
	N	%	N	%	N	%	Odds ratio	95% CI	p	Odds ratio	95% CI	p	Odds ratio	95% CI	p
Four-year prevalence, hallucinations															
Unadjusted	42	24.7	14	13.6	23	13.2	2.2	1.2-3.8	**.007**	1.0	0.5-2.1	.93	2.1	1.1-4.0	**.03**
Adjusted for sex							2.2	1.2-3.8	**.007**	1.0	0.5-2.1	.92	2.1	1.1-4.0	**.03**
Four-year prevalence, delusions															
Unadjusted	33	19.4	14	13.6	17	9.8	2.2	1.2-4.2	**.01**	1.5	0.7-3.1	.33	1.5	0.8-3.0	.22
Adjusted for sex							2.2	1.2-4.2	**.01**	1.5	0.7-3.1	.32	1.5	0.8-3.0	.23
Six-month prevalence, hallucinations															
Unadjusted	33	19.4	10	9.7	15	8.6	2.6	1.3-4.9	**.005**	1.1	0.5-2.6	.76	2.2	1.1-4.8	**.04**
Adjusted for sex							2.6	1.3-4.9	**.005**	1.1	0.5-2.7	.75	2.2	1.0-4.7	**.04**
Six-month prevalence, delusions															
Unadjusted	25	14.7	9	8.7	12	6.9	2.3	1.1-4.8	**.02**	1.3	0.5-3.2	.58	1.8	0.8-4.0	.15
Adjusted for sex							2.3	1.1-4.8	**.02**	1.3	0.5-3.2	.55	1.8	0.8-4.0	.17

Significant *P* values (<.05) in bold
Abbreviations: FHR-BP: Children at familial high-risk of bipolar disorder; FHR-SZ: Children at familial high-risk of schizophrenia spectrum disorders

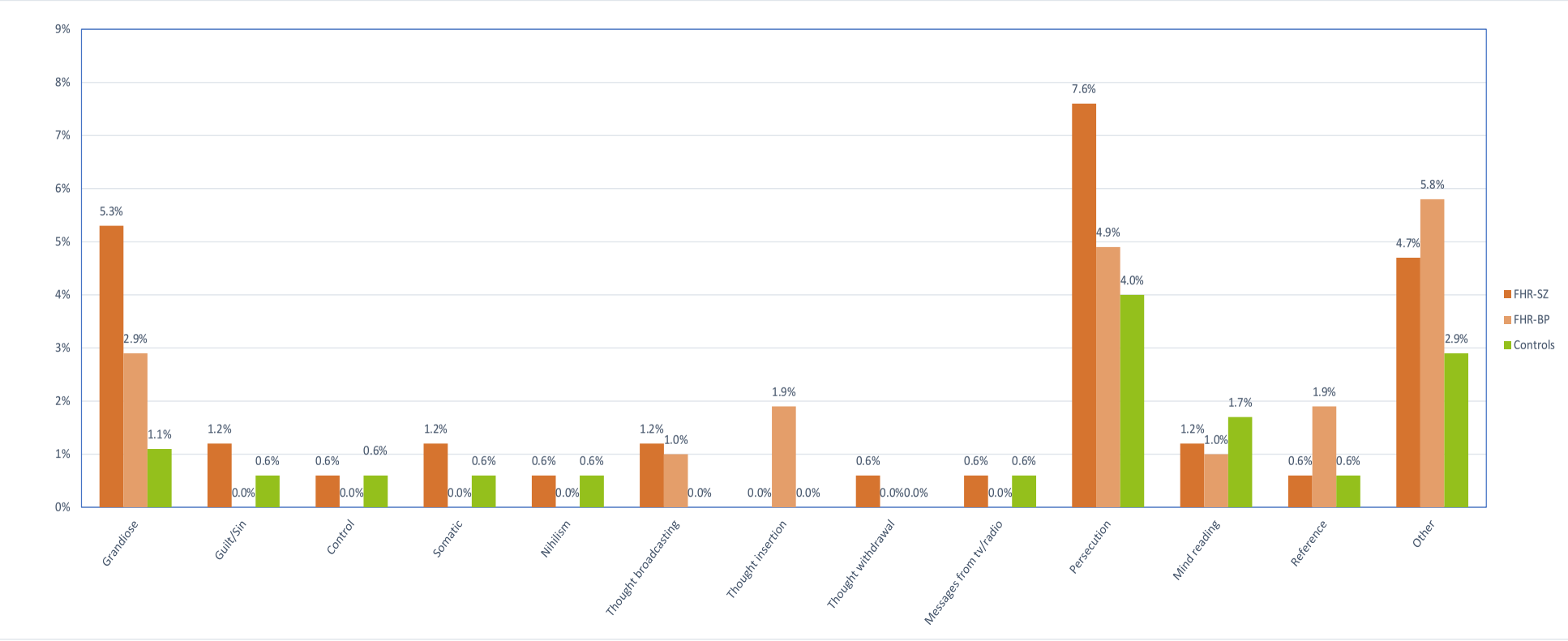
Figure S2a-b. Prevalence of different types of psychotic experiences in middle childhood in 447 children at FHR-SZ, FHR-BP, and controls in the Danish High Risk and Resilience Study, VIA 11

Figure S2a. Prevalence of different types of hallucinations in middle childhood (age 11 years) in 447 children at FHR-SZ, FHR-BP, and controls in The Danish High Risk and Resilience Study, VIA 11



Abbreviations: FHR-SZ: FHR-BP: Children at familial high-risk of bipolar disorder; Children at familial high-risk of schizophrenia spectrum disorders

Figure S2b. Prevalence of different types of delusions in middle childhood (age 11 years) in 447 children at FHR-SZ, FHR-BP, and controls in The Danish High Risk and Resilience Study, VIA 11



Abbreviations: FHR-BP: Children at familial high-risk of bipolar disorder; FHR-SZ: Children at familial high-risk of schizophrenia spectrum disorders

Section S5. Supplementary analyses with internalizing, externalizing, and other mental disorders as outcome

Binary logistic regression analyses were conducted with middle childhood internalizing disorders (yes/no), externalizing disorders (yes/no), and other mental disorders (yes/no) as outcomes in separate models to ascertain whether psychotic experiences predicted specific disorder categories. This statistical approach is similar to that used with other categories in Rimvall et al. 2020 (9).

Analyses were conducted in the same way as the main analyses, i.e. first using any early childhood psychotic experiences as predictor, then number of early childhood psychotic experiences, then developmental pathways of psychotic experiences in separate models. Similar analyses were carried out for cross-sectional associations between middle childhood psychotic experiences and concurrent internalizing, externalizing, and other mental disorders. Analyses were adjusted for sex, then for any early childhood Axis I disorder (due to the possibility of both homotypic and heterotypic continuity (10, 11)), and lastly familial high-risk group.

Mental disorders were categorized as follows.

Internalizing disorders: Affective disorders and anxiety disorders

Externalizing disorders: ADHD and disruptive behavior disorders

Other disorders: Autism spectrum disorders, PTSD, stress and adjustment disorders, tic disorders, and psychotic disorders

Table S3. Associations between early childhood psychotic experiences (age 7 years) and middle childhood (age 11 years) internalizing, externalizing, and other mental disorders in 447 children at FHR-SZ, FHR-BP, and controls in The Danish High Risk and Resilience Study, VIA 11

	Early childhood psychotic experiences											
	Any psychotic experiences (n = 189)			1 type of psychotic experiences (n = 104)			2 types of psychotic experiences (n = 48)			3 or more types of psychotic experiences (n = 37)		
	Odds ratio	**95% CI**	**p**	**Odds ratio**	**95% CI**	**p**	**Odds ratio**	**95% CI**	**p**	**Odds ratio**	**95% CI**	**p**
Any middle childhood internalizing disorder												
Unadjusted	2.4	1.4-4.1	**.002**	1.4	0.7-2.9	.37	3.6	1.7-7.8	**.001**	4.1	1.8-9.4	**.001**
Adjusted for sex	2.3	1.3-4.1	**.003**	1.4	0.7-2.8	.41	3.6	1.7-7.8	**.001**	4.1	1.8-9.4	**.001**
Adjusted for sex and any early childhood Axis I disorder	2.1	1.2-3.4	**.01**	1.3	0.6-2.7	.47	3.1	1.4-6.8	**.005**	3.2	1.4-7.5	**.007**
Adjusted for sex, any early childhood Axis I disorder, and familial risk	2.0	1.1-3.5	**.02**	1.3	0.6-2.8	.43	2.8	1.3-6.1	**.01**	3.0	1.2-7.1	**.02**
Any middle childhood externalizing disorder												
Unadjusted	2.0	1.2-3.5	**.01**	2.1	1.1-4.0	**.02**	1.3	0.5-3.3	.62	2.9	1.2-6.7	**.02**
Adjusted for sex	2.1	1.2-3.7	**.008**	2.3	1.2-4.3	**.01**	1.3	0.5-3.3	.60	2.9	1.2-7.0	**.01**
Adjusted for sex and any early childhood Axis I disorder	1.7	0.9-3.0	.09	2.4	1.2-4.8	**.02**	0.8	0.3-2.1	.62	1.6	0.6-4.2	.31
Adjusted for sex, any early childhood Axis I disorder, and familial risk	1.6	0.9-3.0	.12	2.5	1.2-5.1	**.01**	0.7	0.2-2.0	.50	1.3	0.5-3.6	.55
Any other middle childhood disorder												
Unadjusted	1.4	0.9-2.3	.13	1.0	0.6-1.9	.95	2.2	1.1-4.4	**.02**	1.8	0.8-4.0	.15
Adjusted for sex	1.5	0.9-2.4	.10	1.1	0.6-2.0	.81	2.3	1.1-4.5	**.02**	1.8	0.8-4.1	.14
Adjusted for sex and any early childhood Axis I disorder	1.2	0.7-2.0	.42	1.0	0.5-1.9	.96	1.7	0.8-3.7	.14	1.2	0.5-2.8	.70
Adjusted for sex, any early childhood Axis I disorder, and familial risk	1.2	0.7-2.0	.52	1.0	0.5-1.9	.94	1.6	0.8-3.4	.20	1.1	0.4-2.5	.88

Note: Children with no early childhood psychotic experiences (n = 258) were used as reference.
Significant *P* values (<.05) in bold
Abbreviations: FHR-BP: Children at familial high-risk of bipolar disorder; FHR-SZ: Children at familial high-risk of schizophrenia spectrum disorders

Table S4. Associations between developmental pathways of psychotic experiences from early to middle childhood and middle childhood internalizing, externalizing, and other mental disorders in 447 children at FHR-SZ, FHR-BP, and controls in The Danish High Risk and Resilience Study, VIA 11

	Developmental pathways of psychotic experiences								
	Remittent psychotic experiences (n = 131)			Incident psychotic experiences (n = 49)			Persistent psychotic experiences (n = 58)		
	Odds ratio	95% CI	p	Odds ratio	95% CI	p	Odds ratio	95% CI	p
Any middle childhood internalizing disorder									
Unadjusted	2.0	1.0-4.1	**.05**	2.4	1.0-5.9	.07	5.4	2.6-11.5	**<.001**
Adjusted for sex	2.0	1.0-4.1	.05	2.3	1.0-5.8	.07	5.4	2.5-11.4	**<.001**
Adjusted for sex and any early childhood Axis I disorder	1.8	0.9-3.7	.11	2.1	0.8-5.3	.12	4.5	2.1-9.7	**<.001**
Adjusted for sex, any early childhood Axis I disorder, and familial risk	1.7	0.8-3.6	.14	2.1	0.8-5.4	.12	4.4	2.0-9.8	**<.001**
Any middle childhood externalizing disorder									
Unadjusted	1.9	1.0-3.8	.07	2.5	1.1-6.1	**.04**	4.3	2.0-9.2	**<.001**
Adjusted for sex	2.0	1.0-4.1	.05	2.6	1.1-6.3	**.03**	4.5	2.1-9.8	**<.001**
Adjusted for sex and any early childhood Axis I disorder	1.5	0.7-3.2	.27	2.1	0.8-5.4	.12	3.3	1.5-7.7	**.004**
Adjusted for sex, any early childhood Axis I disorder, and familial risk	1.5	0.7-3.2	.30	1.9	0.7-5.0	.18	3.0	1.3-7.1	**.01**
Any other middle childhood disorder									
Unadjusted	1.4	0.8-2.5	.25	2.4	1.2-5.0	**.02**	2.7	1.4-5.3	**.004**
Adjusted for sex	1.5	0.8-2.7	.20	2.5	1.2-5.1	**.02**	2.8	1.4-5.6	**.003**
Adjusted for sex and any early childhood Axis I disorder	1.2	0.7-2.2	.55	2.1	1.0-4.6	.05	2.2	1.1-4.5	**.04**
Adjusted for sex, any early childhood Axis I disorder, and familial risk	1.2	0.6-2.2	.63	2.1	1.0-4.5	.07	2.1	1.0-4.3	.05

Note: The "Never psychotic experiences" group (n = 209) was used as reference
Significant *P* values (<.05) in bold
Abbreviations: FHR-BP: Children at familial high-risk of bipolar disorder; FHR-SZ: Children at familial high-risk of schizophrenia spectrum disorders

Table S5. Cross-sectional associations between psychotic experiences and internalizing, externalizing, and other mental disorders in middle childhood (age 11) in 447 children at FHR-SZ, FHR-BP, and controls in The Danish High Risk and Resilience Study, VIA 11

	Middle childhood psychotic experiences											
	Any psychotic experiences (n = 107)			1 type of psychotic experiences (n = 56)			2 types of psychotic experiences (n = 25)			3 or more types of psychotic experiences (n = 26)		
	Odds ratio	95% CI	p	Odds ratio	95% CI	p	Odds ratio	95% CI	p	Odds ratio	95% CI	p
Any middle childhood internalizing disorder												
Unadjusted	2.8	1.6-4.9	**<.001**	2.1	1.0-4.5	**.05**	2.2	0.8-6.2	.14	5.4	2.3-12.9	**<.001**
Adjusted for sex	2.8	1.6-4.9	**<.001**	2.1	1.0-4.5	**.05**	2.2	0.8-6.2	.14	5.3	2.2-12.6	**.001**
Adjusted for sex and any early childhood Axis I disorder	2.5	1.4-4.4	**.002**	2.1	1.0-4.5	.06	1.7	0.6-5.0	.32	4.5	1.8-10.9	**.001**
Adjusted for sex, any early childhood internalizing disorder, and familial risk	2.5	1.4-4.6	**.002**	2.2	1.0-4.7	.05	1.7	0.6-5.0	.35	4.6	1.8-11.5	**.001**
Any middle childhood externalizing disorder												
Unadjusted	2.6	1.5-4.5	**.001**	1.2	0.5-2.9	.67	5.6	2.4-13.5	**<.001**	3.8	1.5-9.2	**.004**
Adjusted for sex	2.6	1.5-4.6	**.001**	1.2	0.5-2.8	.69	5.7	2.4-13.7	**<.001**	4.2	1.7-10.5	**.002**
Adjusted for sex and any early childhood Axis I disorder	2.3	1.2-4.2	**.01**	1.2	0.5-2.9	.75	4.5	1.7-12.1	**.003**	3.1	1.1-8.5	**.03**
Adjusted for sex, any early childhood Axis I disorder, and familial risk	2.1	1.1-3.9	**.03**	1.1	0.4-2.8	.86	4.2	1.5-11.5	**.006**	2.7	1.0-7.7	.05
Any other middle childhood disorder												
Unadjusted	2.2	1.3-3.7	**.002**	1.4	0.7-2.8	.33	1.3	0.5-3.6	.62	7.1	3.1-16.2	**<.001**
Adjusted for sex	2.3	1.4-3.8	**.002**	1.4	0.7-2.8	.35	1.3	0.5-3.6	.64	8.2	3.5-19.1	**<.001**
Adjusted for sex and any early childhood Axis I disorder	2.0	1.2-3.4	**.01**	1.4	0.7-2.9	.38	0.9	0.3-2.6	.84	7.3	2.9-18.2	**<.001**
Adjusted for sex, any early childhood Axis I disorder, and familial risk	1.9	1.1-3.3	**.02**	1.4	0.7-2.9	.41	0.9	0.3-2.5	.78	7.1	2.8-17.7	**<.001**

Note: Children with no middle childhood psychotic experiences (n = 340) were used as reference.
Significant *P* values (<.05) in bold
Abbreviations: FHR-BP: Children at familial high-risk of bipolar disorder; FHR-SZ: Children at familial high-risk of schizophrenia spectrum disorders

Section S6. Cross-sectional analyses

Table S6. Cross-sectional associations between psychotic experiences and mental disorders in middle childhood (age 11 years) in 447 children at FHR-SZ, FHR-BP, and controls in The Danish High Risk and Resilience Study, VIA 11

	Middle childhood psychotic experiences											
	Any psychotic experiences (n = 107)			1 type of psychotic experiences (n = 56)			2 types of psychotic experiences (n = 25)			3 or more types of psychotic experiences (n = 26)		
	Odds ratio	**95% CI**	**p**	**Odds ratio**	**95% CI**	**p**	**Odds ratio**	**95% CI**	**p**	**Odds ratio**	**95% CI**	**p**
Any middle childhood Axis I disorder												
Unadjusted	2.6	1.7-4.0	**<.001**	1.6	0.9-2.8	.12	3.4	1.5-7.8	**.004**	6.2	2.5-15.1	**<.001**
Adjusted for sex	2.6	1.7-4.1	**<.001**	1.6	0.9-2.8	.12	3.4	1.5-8.0	**.004**	6.8	2.8-16.9	**<.001**
Adjusted for sex and any early childhood Axis I disorder	2.5	1.5-4.1	**<.001**	1.6	0.8-3.1	.15	2.7	1.0-6.9	**.04**	6.7	2.4-18.2	**<.001**
Adjusted for sex, any early childhood Axis I disorder, and familial risk	2.3	1.4-3.8	**.002**	1.5	0.8-2.9	.22	2.5	0.9-6.6	.07	5.8	2.1-16.0	**.001**

Note: children with no middle childhood psychotic experiences (N=340) were used as reference.
Significant *P* values (<.05) in bold
Abbreviations: FHR-BP: Children at familial high-risk of bipolar disorder; FHR-SZ: Children at familial high-risk of schizophrenia spectrum disorders

Section S7. Sensitivity analyses excluding 6 children with lifetime psychotic disorders

Analyses of the prevalence of any psychotic experiences in middle childhood and analyses with psychotic experiences as predictor and Any Axis I disorder as outcome were repeated excluding 6 children (all at FHR-SZ) who had met criteria for a psychotic disorder at some point during their lives, i.e. with lifetime psychotic disorders. P values which changed from significant (< .05) to non-significant are described in the footnotes of each table. All interaction analyses remained non-significant (data not shown).

Table S7. Psychotic experiences in middle childhood (age 11 years) in 441 children at FHR-SZ, FHR-BP, and controls in The Danish High Risk and Resilience Study, VIA 11. Excluding 6 children with lifetime psychotic disorders

	Between-group comparisons								
	FHR-SZ vs. controls			FHR-BP vs. controls			FHR-SZ vs. FHR-BP		
	Odds ratio	95% CI	p	Odds ratio	95% CI	p	Odds ratio	95% CI	p
Four-year prevalence, Any Psychotic Experiences									
Unadjusted	1.8	1.1-3.1	**.02**	1.1	0.6-2.1	.68	1.6	0.9-2.9	.11[1]
Adjusted for sex	1.8	1.1-3.1	**.02**	1.1	0.6-2.1	.68	1.6	0.9-2.9	.11[2]
Six-month prevalence, Any Psychotic Experiences									
Unadjusted	1.9	1.1-3.4	**.03**	1.0	0.5-2.0	.93	1.8	0.9-3.6	.07[3]
Adjusted for sex	1.9	1.1-3.4	**.03**	1.0	0.5-2.1	.91	1.8	0.9-3.6	.08[4]

Significant *P* values (<.05) in bold
Abbreviations: FHR-BP: Children at familial high-risk of bipolar disorder; FHR-SZ: Children at familial high-risk of schizophrenia spectrum disorders
[1] P value changed from .04 to .11 when removing 6 children with lifetime psychotic disorders
[2] P value changed from .04 to .11 when removing 6 children with lifetime psychotic disorders
[3] P value changed from .03 to .07 when removing 6 children with lifetime psychotic disorders
[4] P value changed from .03 to .08 when removing 6 children with lifetime psychotic disorders

Table S8. Associations between early childhood psychotic experiences (age 7 years) and middle childhood psychotic experiences and mental disorders (age 11 years) in 441 children at FHR-SZ, FHR-BP, and controls in The Danish High Risk and Resilience Study, VIA 11. Excluding 6 children with lifetime psychotic disorders

	Early childhood psychotic experiences											
	Any psychotic experiences (n = 184)			1 type of psychotic experiences (n = 102)			2 types of psychotic experiences (n = 46)			3 or more types of psychotic experiences (n = 36)		
	Odds ratio	**95% CI**	**p**	**Odds ratio**	**95% CI**	**p**	**Odds ratio**	**95% CI**	**p**	**Odds ratio**	**95% CI**	**p**
Any middle childhood psychotic experiences												
Unadjusted	1.8	1.1-2.8	**.01**	1.5	0.9-2.6	.15	1.9	0.9-3.8	.07[1]	2.5	1.2-5.2	**.02**
Adjusted for sex	1.8	1.1-2.7	**.01**	1.5	0.9-2.5	.16	1.9	0.9-3.8	.07[2]	2.5	1.2-5.2	**.02**
Any middle childhood Axis I disorder												
Unadjusted	2.1	1.4-3.1	**<.001**	1.5	0.9-2.5	.09	2.6	1.4-4.9	**.004**	4.0	2.0-8.3	**<.001**
Adjusted for sex	2.2	1.5-3.3	**<.001**	1.6	1.0-2.6	.06[3]	2.6	1.4-5.0	**.003**	4.2	2.0-8.6	**<.001**
Adjusted for sex and any early childhood Axis I disorder	2.0	1.3-3.2	**.002**	1.7	1.0-2.9	.07[4]	2.2	1.0-4.6	**.03**	3.1	1.3-7.0	**.008**
Adjusted for sex, any early childhood Axis I disorder, and familial risk	1.9	1.2-3.0	**.005**	1.7	1.0-3.0	.05[5]	2.0	1.0-4.2	.07	2.5	1.1-5.8	**.03**

Note: Children with no early childhood psychotic experiences (n = 257) were used as reference.
Significant *P* values (<.05) in bold
Abbreviations: FHR-BP: Children at familial high-risk of bipolar disorder; FHR-SZ: Children at familial high-risk of schizophrenia spectrum disorders
[1]P value changed from .03 to .07 when removing 6 children with lifetime psychotic disorders
[2]P value changed from .03 to .07 when removing 6 children with lifetime psychotic disorders
[3] P value changed from .04 to .06 when removing 6 children with lifetime psychotic disorders
[4] P value changed from .05 to .07 when removing 6 children with lifetime psychotic disorders
[5] P value changed from .04 to .05 (.053) when removing 6 children with lifetime psychotic disorders

Table S9. Associations between developmental pathways of psychotic experiences from early to middle childhood and middle childhood mental disorders in 441 children at FHR-SZ, FHR-BP, and controls in The Danish High Risk and Resilience Study, VIA 11. Excluding 6 children with lifetime psychotic disorders

	Developmental pathways of psychotic experiences								
	Remittent psychotic experiences (n = 131)			**Incident psychotic experiences** (n = 48)			**Persistent psychotic experiences** (n = 53)		
	Odds ratio	**95% CI**	**p**	**Odds ratio**	**95% CI**	**p**	**Odds ratio**	**95% CI**	**p**
Any middle childhood Axis I disorder									
Unadjusted	2.0	1.2-3.2	**.004**	2.2	1.1-4.1	**.02**	4.3	2.3-8.0	**<.001**
Adjusted for sex	2.1	1.3-3.4	**.002**	2.2	1.2-4.3	**.02**	4.5	2.3-8.5	**<.001**
Adjusted for sex and any early childhood Axis I disorder	1.8	1.1-3.1	**.03**	1.9	0.9-4.0	.09	4.1	2.0-8.2	**<.001**
Adjusted for sex, any early childhood Axis I disorder, and familial risk	1.7	1.0-2.9	.05	1.7	0.8-3.7	.15	3.8	1.9-7.8	**<.001**

Note: The "Never psychotic experiences" group (n = 209) was used as reference
Significant *P* values (<.05) in bold
Abbreviations: FHR-BP: Children at familial high-risk of bipolar disorder; FHR-SZ: Children at familial high-risk of schizophrenia spectrum disorders

Table S10. Cross-sectional associations between psychotic experiences and mental disorders in middle childhood (age 11 years) in 441 children at FHR-SZ, FHR-BP, and controls in The Danish High Risk and Resilience Study, VIA 11. Excluding 6 children with lifetime psychotic disorders

	Middle childhood psychotic experiences											
	Any psychotic experiences (n = 101)			1 type of psychotic experiences (n = 56)			2 types of psychotic experiences (n = 25)			3 or more types of psychotic experiences (n = 20)		
	Odds ratio	**95% CI**	**p**	**Odds ratio**	**95% CI**	**p**	**Odds ratio**	**95% CI**	**p**	**Odds ratio**	**95% CI**	**p**
Any middle childhood Axis I disorder												
Unadjusted	2.3	1.5-3.6	**<.001**	1.6	0.9-2.8	.12	3.4	1.5-7.8	**.004**	4.2	1.6-10.9	**.003**
Adjusted for sex	2.4	1.5-3.7	**<.001**	1.6	0.9-2.8	.13	3.4	1.5-7.9	**.004**	4.8	1.8-12.6	**.001**
Adjusted for sex, any early childhood Axis I disorder	2.2	1.3-3.8	**.002**	1.6	0.8-3.1	.15	2.7	1.0-6.9	**.04**	4.9	1.7-14.3	**.003**
Adjusted for sex, any early childhood Axis I disorder, and familial risk	2.1	1.3-3.5	**.005**	1.5	0.8-2.9	.22	2.5	0.9-6.6	.07	4.5	1.6-13.2	**.005**

Note: Children with no middle childhood psychotic experiences (N=340) were used as reference.
Significant *P* values (<.05) in bold
Abbreviations: FHR-BP: Children at familial high-risk of bipolar disorder; FHR-SZ: Children at familial high-risk of schizophrenia spectrum disorders

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Paper 3

Jumping to conclusions and its associations with psychotic experiences in preadolescent children at familial high-risk of schizophrenia or bipolar disorder - The Danish High Risk and Resilience Study, VIA 11

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Manuscript

Jumping to conclusions and its associations with psychotic experiences in preadolescent children at familial high-risk of schizophrenia or bipolar disorder

The Danish High Risk and Resilience Study, VIA 11

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Abstract

Background: The jumping to conclusions (JTC) bias, i.e. making decisions based on inadequate evidence, is associated with psychosis in adults and is believed to underlie the formation and maintenance of delusions. However, knowledge on the early manifestations of JTC and its associations with psychotic experiences (PE) in children and adolescents is lacking.

Method: Preadolescent children (mean age 11.9, SD 0.2) at familial high-risk of schizophrenia (FHR-SZ, *n* = 169), or bipolar disorder (FHR-BP, *n* = 101), and controls (*n* = 173) were assessed with the Beads Task to examine JTC. The continuous outcome from the Beads Task, number of beads drawn before making a decision, "draws to decision" (DTD), was used as primary outcome whereas the dichotomous outcome "extreme JTC", defined as deciding after a single bead, was examined as a secondary outcome. PE were ascertained in face-to-face interviews. General intelligence was measured with Reynolds Intellectual Screening Test.

Results: Children at FHR-SZ took fewer DTD, i.e. showed more JTC than controls (estimated mean 4.9 vs. 5.9, Cohen's *d* 0.31, *p* = .004). Differences were attenuated when adjusting for IQ (Cohen's *d* 0.24, *p* = .02). Higher IQ was associated with a higher number of DTD, i.e. less JTC (B = .073, 95% CI .046-.101, *p* < .001). Current subclinical delusions compared with no PE were associated with fewer DTD in children at FHR-SZ (*p* = .04) and controls (*p* < .05). Associations between delusions and DTD were nullified when accounting for IQ. The categorical, extreme JTC bias did not differentiate FHR-groups or PE-groups.

Conclusions: JTC marks familial risk of psychosis in preadolescence, not reducible to general intelligence. JTC is associated with subclinical delusions, supporting the continuum theory for psychosis, but this may be an expression of intellectual impairment. Future studies should establish causation and temporality between JTC and delusion formation within this cohort and examine JTC as a potential target for early intervention.

Introduction

Understanding the psychological underpinnings of psychotic experiences (PE), i.e. subclinical hallucinations and delusions thought to occur on a continuum with psychotic disorders [1], in children and adolescents, provides potential for early identification of at-risk individuals and for informing early prevention and intervention**.** The jumping to conclusions (JTC) bias, i.e. making decisions based on inadequate evidence, is reliably associated with psychosis in adults [2] whereas little is known of JTC and its association with PE in children and adolescents.

The JTC bias has consistently been found in adults with psychosis who require less information before reaching a decision than healthy individuals and individuals with nonpsychotic mental disorders [2–4]. It is also found in adult first degree relatives of individuals with psychosis [5, 6] suggesting that JTC is a trait marker of psychosis risk, associated with familial liability for psychosis. Whether JTC manifests as a marker of familial liability for psychosis as early as preadolescence is, to our knowledge, unexplored.

The majority of evidence suggests that the JTC bias is contingent upon the presence of delusional ideation. In clinical samples of individuals with psychosis those with current delusions show more JTC than those without current delusions [2, 3, 7, 8]. Additionally, JTC covaries with delusions across the diagnostic spectrum, i.e. in patients with other mental disorders, and with delusion proneness in nonclinical adult populations [6–12]. The aforementioned study of first degree relatives found that the association between sibling status and JTC was stronger in siblings with subthreshold delusions, but not in those with subthreshold hallucinations [5]. Longitudinal findings from clinical populations suggest that presence of JTC is implicated in persistence and worsening of delusions in individuals with psychosis [13, 14] which, along with meta-analytic evidence [2, 7] suggests that the JTC bias may be causal to the formation and maintenance of delusions. However, studies examining whether JTC precedes delusions in non-clinical populations are lacking. Findings regarding delusions are not entirely unequivocal as some studies have not found associations with JTC or have only found them in either individuals with clinical psychosis or in controls [3, 9, 15–18] or have instead found links between JTC and hallucinations [19].

There are only few reports on JTC and its relation to PE in childhood and adolescence. One study provided evidence that presence of PE increased the odds of JTC in a sample (*n* = 45) of children and adolescents (aged 5-14) referred to child and adolescent mental health services [20]. However, this study did not report subclinical hallucinations and delusions separately. In an overlapping sample (*n* = 40) of clinically referred children and adolescents (aged 8-14) JTC was associated with PE severity [21].

IQ is the most commonly examined neurocognitive factor in relation to JTC and appears to be linked with JTC in both clinical and nonclinical populations. The previously mentioned study of children and adolescents found that lower IQ increased the odds of JTC [20]. Similarly, evidence from adult populations suggests that IQ deficits are associated with the JTC bias. In a study of adults with first-episode psychosis, IQ accounted for a large part of the variance in JTC suggesting that JTC may be understood as part of a general cognitive impairment in psychosis [15]. In keeping with this, another study found that lower IQ was associated with JTC in both individuals with first-episode psychosis and controls and that associations between clinical status and JTC were rendered non-significant when including IQ and working memory in the model [3].

To our knowledge, no prior study has examined the JTC bias in relation to subclinical hallucinations and delusions and IQ in children at familial high-risk of schizophrenia or bipolar disorder. The aims of the present study were to 1. Examine the occurrence of the JTC bias in 11-year-old children at familial high-risk of schizophrenia and bipolar disorder compared with population-based controls 2. Examine whether PE with and without delusions are associated with JTC in this population 3. Investigate potential differential associations between PE and JTC across familial high-risk groups 4. Ascertain whether IQ affects the associations between familial high-risk group, PE, and JTC.

Method

Participants

The current study is a part of the VIA 11 Study which is the first follow-up of an ongoing, longitudinal cohort study, The Danish High Risk and Resilience Study. The original cohort consisted of 522 seven-year-old children with at least one biological parent with a schizophrenia spectrum disorder (FHR-SZ), (*n* = 202, ICD-10 codes: F20, F22, F25 or ICD-8 codes: 295, 297, 298.29, 298.39, 298.89, 298.99), or bipolar disorder (FHR-BP), (*n* = 120, ICD-10 codes: F30, F31 or ICD-

8 codes: 296.19, 269.39), and population-based controls (hereafter controls) where neither parent was diagnosed with these disorders (*n* = 200). The cohort was retrieved from the Danish national registers. The first face-to-face assessments took place between January 2013 and January 2016 when the children were seven years old, the VIA 7 Study. Data for the current study stem from the first face-to-face follow-up which took place between March 2017 and June 2020 when the children were 11 years old. Child assessors were blinded to the children's familial risk status. The cohort and study design are described in detail elsewhere [22].

The study was approved by the Danish Data Protection Agency. The study follows the guidelines of the Danish Committee on Health Research Ethics although ethical approval was deemed unnecessary due to the observational nature of the study. Written informed consent from the parent or other legal guardian and assent from the children were obtained following explanation of the study procedures.

Measures

Jumping to conclusions

The JTC bias was assessed with a modified version of the Beads Task [23, 24] which has been employed in several different versions in previous studies and is the most commonly used paradigm for assessing JTC [2]. A previous study has demonstrated the suitability of the Beads Task for assessing JTC in children and adolescents [20].

The Danish instructions with the principles chosen for the current study were devised by the first and the third authors (MG and JRMJ). In the current study children were presented with two jars containing 100 beads each, of two different colors in equal but opposite ratios. To ensure task comprehension children were first presented with a practice trial with two jars of beads with ratios of 85:15 and 15:85, before completing four trials with two jars of beads with ratios of 60:40 and 40:60, and instructions were repeated before each trial. Including practice and several trials has been shown to reduce miscomprehension and to elicit a better reflection of representative performance in adults [2]. We employed the harder 60:40/40:60 version as it has been shown to better distinguish between individuals with schizophrenia and controls as well as between individuals with attenuated biases, e.g. at risk groups, and controls than the easier 85:15/15:85 version [4, 25, 26].

For the current study, the sequence of beads for the 85:15/15:85 trial was taken from the Hassanali et al. study [20] whereas the sequences for the four 60:40/40:60 trials were made using a random number generator to construct four sequences, of 20 beads each, corresponding with the ratio of beads in one of the jars, i.e. sequences with 60% of one color and 40% of the other color or vice versa. All children were presented with the same five sequences.

On each of the five trials the child was informed of the number and ratio of beads in each jar and told that the beads would be drawn consecutively from one of the jars in a random order. However, the beads were actually presented in the prespecified sequences. The child was instructed to guess which jar the beads were being drawn from when it felt certain. After the instructions were given the jars were hidden and the child was presented with the first bead. The child was asked whether it wished to see more beads or to make a guess. The bead was then hidden from the child's view. This was repeated with the following beads until the child made a guess as to where the beads were being drawn from. When the child made a guess it was noted how many beads the child had seen. If the child had not made a guess after seeing 20 beads the child was prompted to make a decision.

The main outcome variable indexing the JTC bias for this study is the number of beads drawn, usually referred to as "draws to decision" (DTD), operationalizing the amount of evidence gathered, i.e. the lower the DTD, the more pronounced the JTC bias [2]. For this study DTD is defined as the average number of beads drawn before making a decision across the four 60:40/40:60 trials. As a secondary outcome we also examine a categorical, binary JTC variable, hereafter referred to as "extreme JTC". We used a cutoff of guessing after seeing a single bead, in keeping with a previous FHR-study showing that this cutoff better distinguishes between groups with different degrees of psychosis liability than using less stringent cutoffs [6]. In the current study extreme JTC was defined as guessing after a single bead on either of the four 60:40/40:60 trials.

Psychotic experiences

Psychotic experiences at age 11 (PE) were assessed with the psychosis supplement from the Kiddie Schedule for Affective Disorders and Schizophrenia – Present and Lifetime Version (K-SADS-PL) [27]. Children were asked about 9 different types of hallucinations and 13 types of delusions. In case a symptom was endorsed and given a score of 2 "possible" or 3 "definite" on K-SADS-PL additional questions were asked (frequency, duration, degree of conviction,

distress, impact on functioning) to assess the severity of the symptom. Finally the symptom was given a score on a 7-point scale from 0=absent to 6=severe and psychotic. For the analyses scores were recoded into 0-1=absent or possible PE and 2-6=definite PE. Only definite PE were considered in the analyses. All PE were consensus rated with a senior research child and adolescent psychiatrist (the second last author, AAET). Current PE were defined as occurring within the past six months. Methods and results regarding PE are described in detail elsewhere [28]. PE-groups for the current study were defined as children with no current PE, children with current hallucinations only, and children with current delusions.

General intelligence, pubertal stage, global functioning, and dimensional psychopathology

General intelligence (IQ) was measured with Reynolds Intellectual Screening Test [29]. Methods and results are described in detail elsewhere [30]. Onset of puberty was ascertained with self-reported Tanner Stages [31]. Global functioning was assessed with Children's Global Assessment Scale (CGAS) [32]. Dimensional psychopathology was measured with the Child Behavior Check List (CBCL) [33] completed by the child's primary caregiver.

Statistical analyses

Between-group differences in background characteristics were analyzed with chi-square tests and one-way ANOVA. Dropout analyses were performed with chi-square tests and t-tests.

Crosstabs were used for calculating frequencies and percentages. Differences in mean DTD were analyzed through ANCOVA, with familial high-risk group (FHR-group) as independent variable and DTD as the dependent variable. Analyses were adjusted for sex of the child, then adding IQ.

Associations between no current PE (used as reference), current hallucinations only, and current delusions (PE-group) and DTD were ascertained with ANCOVA with DTD as the dependent variable. Analyses were adjusted for sex of the child, then to control for effect of group, adding FHR-group, and lastly IQ. To check for interaction effects an interaction term with FHR-group x PE-group was added to the unadjusted model. However, due to the relatively low number of children within each PE-group we also report stratified analyses, adjusted for sex then IQ, to avoid type II errors if the interaction analyses are underpowered to detect differential associations.

In exploratory analyses similar multivariable logistic regressions were conducted using the dichotomous measure extreme JTC as outcome.

Alpha was set to < .05. Data were analyzed using SPSS version 25.

Results

Sample characteristics

Four hundred forty-three children (FHR-SZ, *n* = 169, FHR-BP, *n* = 101, controls, *n* = 173) participated in the Beads Task at age 11 corresponding with 84.7% of the original cohort (*n* = 522) included at age 7.

There were no significant differences between those who participated in the Beads Task and those who did not regarding sex ($X^2(1)= .023$, $p = .88$), FHR-group ($X^2(2)= .689$, $p = .71$) or prevalence of any Axis I mental disorder at age 7 ($X^2(1)=2.644$, $p = .10$). Those who did not participate in the Beads Task had significantly lower global functioning at age 7 (CGAS 69.5, *SD* 15.9) than those who participated (CGAS 73.6, *SD* 15.0, t(512)=-2.164, Cohen's *d* 0.27, $p = .03$) and significantly higher levels of dimensional psychopathology at age 7 measured with CBCL (mean 28.1, *SD* 25.0 vs. mean 21.5, *SD* 17.7, t(492)=2.738, Cohen's *d* 0.35, $p = .006$).

Within the sample participating in the Beads Task there were no differences between the three FHR-groups regarding age at inclusion, sex, or onset of puberty. Children at FHR-SZ had significantly lower IQ than controls and a significantly higher occurrence of PE than children at FHR-BP and controls. Children at FHR-SZ and FHR-BP had significantly lower current global functioning than controls. Children at FHR-SZ had lower functioning than children at FHR-BP. Children at FHR-SZ and FHR-BP had significantly higher levels of current dimensional psychopathology measured with CBCL than controls (Table 1).

Draws to decision across familial risk groups

Children at FHR-SZ took significantly fewer DTD (estimated mean 4.9, 95% CI 4.5-5.4) to reach a decision compared with controls (estimated mean 5.9, 95% CI 5.4-6.3, Cohen's *d* 0.31, *p* = .004), whereas children at FHR-BP did not (estimated mean 5.4, 95% CI 4.8-6.0, Cohen's *d* 0.16, *p* = .18, Figure 1, Table 2). The difference between children at FHR-SZ and FHR-BP was non-significant (Cohen's *d* 0.15, *p* = .26). Differences between children at FHR-SZ and controls were attenuated but remained significant when adding IQ to the model (Table 2). IQ significantly predicted DTD in the adjusted model (B = .073, 95% CI .046-.101, *p* < .001), meaning that higher IQ was associated with a higher number of DTD.

Draws to decision and psychotic experiences with and without delusions

Across the cohort delusions were associated with fewer DTD whereas hallucinations were not. Differences remained when adjusting for FHR-group. Adding IQ rendered this association non-significant (Table 3a) and higher IQ predicted a higher number of DTD (B = .069, 95% CI .041-.097, *p* < .001). There was no interaction between PE-group and FHR-group (*p* = .33). However, in stratified analyses, the associations between PE and DTD were only significant in children at FHR-SZ and controls (Table 3b). Children with current delusions in the FHR-SZ group took significantly fewer DTD (estimated mean 3.9, 95% CI 2.9-5.0) than those without PE (estimated mean 5.2, 95% CI 4.7-5.6, Cohen's *d* = 0.46, *p* = .04). This was not the case for children with current hallucinations (estimated mean 4.8, 95% CI 3.6-6.1) compared with those without PE (Cohen's *d* = 0.14, *p* = .68, Table 3b). In the FHR-BP group there were no differences between children with delusions (estimated mean 5.8, 95% CI 3.8-7.8) or hallucinations (estimated mean 5.8, 95% CI 2.8-8.8) and those without PE (estimated mean 5.3, 95% CI 4.7-6.0, Cohen's *d* = 0.17, *p* = .64 and Cohen's *d* =0.17, *p* = .75, respectively). Among controls, having delusions was associated with a lower number of DTD (estimated mean 4.2, 95% CI 2.2-6.1) than having no PE (estimated mean 6.2, 95% CI 5.6-6.7, Cohen's *d* = 0.60, , *p* = .05) whereas having hallucinations was not (estimated mean 4.6, 95%CI 2.7-6.5, Cohen's *d* = 0.47, *p* = .12, Table 3b). Differences between children with delusions and those with no PE were rendered non-significant both among FHR-SZ and in the control group when adding IQ to the model (Table 3b), and higher IQ significantly predicted a higher number of DTD in children at FHR-SZ and controls (FHR-SZ = B = .073, 95% CI .034-.111, *p* < .001, controls = B = .074, 95%CI .023-.124, *p* = .004, Table 3b). In the FHR-BP group differences between PE groups remained non-significant in the model adjusted for IQ which was not significantly associated with DTD within this group (Table 3b).

Exploratory analyses of extreme JTC

Of children at FHR-SZ, 21.9% showed the extreme JTC-bias (i.e. guessing after a single bead). The same was true of 17.8% of children at FHR-BP and 14.5% of controls. Between-group differences were non-significant (Table S1). There was no interaction between PE-group and FHR-group (p = .98). Extreme JTC was not associated with PE across the cohort or in stratified analyses (Table S2a-b). Results remained non-significant when adding IQ (Table S1 and S2a-b).

Discussion

Main findings

In the current cohort, children at FHR-SZ had a more hasty decision making style, i.e. they showed more JTC, measured with the continuous outcome from the Beads Task, than controls. This was not the case for children at FHR-BP. Differences were attenuated when adjusting for general intelligence. In the model with FHR-group, higher general intelligence predicted less JTC.

When examining the entire cohort, having delusions predicted more JTC. Interaction between FHR-group and PE-group was non-significant. Yet, stratified analyses revealed that JTC and presence of delusions were only significantly associated in the FHR-SZ group and among controls. In these groups, presence of PE with subclinical delusions was associated with a more hasty decision making than no PE. Presence of subclinical hallucinations only was not. Associations between delusions and JTC became non-significant when adjusting for general intelligence. In the stratified analyses higher general intelligence predicted less JTC in children at FHR-SZ and controls.

In exploratory analyses, the higher occurrence of the extreme JTC bias in the FHR-SZ group compared with the control group did not reach significance. Extreme JTC was not significantly associated with PE with or without delusions compared with no PE. Adjusting for general intelligence did not change these results.

Interpretation

To our knowledge, this is the first study to examine the JTC bias and its associations with subclinical delusions and hallucinations and general intelligence in children at FHR of schizophrenia or bipolar disorder. We found that JTC is a vulnerability marker for familial risk of psychosis in preadolescence extending previous findings from older

populations [5, 6]. JTC does not appear to be an early vulnerability marker for familial risk of bipolar disorder which is expected given the evidence of its specificity to psychotic disorders [2, 4, 7]. Of the few studies on JTC including individuals with bipolar disorder, one did not find more JTC in adults with bipolar disorder than controls [34]. Another, examining affective disorders broadly, found that JTC was more frequent only if affective disorders and PE co-occurred and that JTC increased with number of PE and psychosis-related help-seeking behavior supporting the specificity with psychosis [35]. In light of this, studies on JTC in children born to parents with lithium responsive vs. lithium nonresponsive bipolar disorder, the latter being associated with psychotic illness features and elevated rates of psychosis in offspring [36], would be relevant to examine JTC as an early marker of psychosis risk in bipolar disorder.

Corroborating the previous sparse evidence from children and adolescents [20, 21] we found that JTC was associated with PE in preadolescence. Further, we provide evidence that JTC is contingent upon delusional ideation in both children at FHR-SZ and controls, suggesting that the presence of a hasty decision making style may serve as a vulnerability marker of delusion proneness both inside and outside the context of familial risk of psychosis in preadolescence. This extends previous finding of JTC and subclinical delusions in older populations [5, 6, 9, 11] and these findings support the hypothesis that PE lie on a continuum with psychotic disorders [1]. In line with this, factors usually associated with psychosis in adults, including JTC, accounted for a substantial part of the variance in PE in adolescence in the previously mentioned sample of children and adolescents [37].

In the current cohort, higher IQ was linked with less JTC across models, similarly to the findings of others [3, 6, 15, 20]. When taking IQ into account, differences between FHR-groups were attenuated in accordance with the reduced associations between clinical status and JTC observed in other studies when including general intelligence, adding to the proposition that JTC may be part of a broader cognitive impairment [3, 6, 15]. Although differences between FHR-groups were attenuated, they remained significant, suggesting that the more hasty decision making among children at FHR-SZ was not entirely attributable to between-group differences in general intelligence. Associations with subthreshold delusions were rendered non-significant when adding IQ. Previous findings are inconsistent as to whether associations between delusions and JTC remain [3] or are reduced or nullified [6, 38] when adding IQ. There is evidence that low IQ is associated with a higher risk of PE in preadolescence [39], thus our findings may suggest that

JTC in children with subthreshold delusions denotes underlying impairments in general intelligence which are also associated with increased risk of schizophrenia [40].

We did not find the extreme JTC bias to be associated with FHR-group or PE at this early stage, suggesting that the continuous measure of JTC may be better suited for detecting early, subtle differences. In the smaller sample of children and adolescents [20] where a binary JTC outcome was associated with PE, only PE causing distress and impairment were considered. Considering the evidence that the bias may be stronger toward the severe end of the delusion continuum [7, 8] we may speculate that restricting to more severe PE rather than relying on presence or non-presence of PE would have resulted in associations with a more pronounced JTC bias in the current sample.

Interventions targeting the JTC bias show some promise for delusion reduction in individuals with psychosis [41–45]. Evidence for the efficacy of psychological interventions for psychosis in children and adolescents is sparse [46] and to our knowledge no intervention studies have included JTC. Considering the associations documented in the current cohort, future studies should examine the efficacy of including JTC in preventive interventions in children and adolescents with PE and at FHR of psychosis to ameliorate current symptoms and improve long-term outcome. However, since JTC is also associated with other neurocognitive impairments, e.g. in working memory, in older populations [19, 47] studies on these associations in preadolescence may elucidate the relevance of examining interventions including JTC over general cognitive training. Finally, the continuum between PE and psychosis within this FHR-population should be explored further by examining JTC along with other putative risk factors for psychosis as predictors of PE. Longitudinal follow-up should establish causation and temporality between JTC and delusion formation and conversion to clinical psychosis within the current cohort.

Strengths and limitations

Our findings should be interpreted in light of the strengths and limitations of the study. Same-aged children were examined by trained mental health professionals using commonly employed methods for measuring JTC and PE. Interviewers were blinded to children's FHR-status and prior data. The study design allowed for examination of hallucinations and delusions separately and the examination of current symptoms, which enabled extension of previous findings of JTC and specific associations with current delusional ideation. We employed several trials of the

Beads Task to increase task comprehension and representativity of the findings. However, some limitations should also be considered. The FHR-BP group was smaller than the other two groups which weakens estimates of differences for this group and no firm conclusions should be drawn regarding this group. The discrepancy between the non-significant interaction analyses and the stratified analyses suggests that the interaction analyses were underpowered to detect differential associations between PE and JTC across FHR-groups. Further, the number of children with current hallucinations or delusions were low across groups, and we cannot rule out that the small group sizes may have affected the results. Thus, ideally, future studies should replicate our findings in a larger preadolescent FHR-sample. The design did not enable distinction between children of parents with lithium responsive vs. lithium nonresponsive bipolar disorder potentially constituting subgroups with varying psychosis liability and varying JTC. Moreover, since very few children had more than one type of current delusion, which could be used as a proxy for delusion severity, it was not possible to examine the relation between JTC and delusion severity. Additionally, PE were measured dichotomously, not taking into account the resulting distress or impairment which could potentially have enabled restriction to more severe symptoms. Data for this study were cross-sectional precluding causal inferences about the relation between JTC and delusion formation. Dropout was skewed toward those with better functioning and less dimensional psychopathology remaining in the study making it plausible that the remaining sample was less heterogeneous than the original sample.

Conclusions

This study provides the first evidence that the JTC bias is a marker of familial liability for psychosis in preadolescence and extends previous findings of the link between JTC and subthreshold delusions to include a preadolescent FHR-population, supporting the continuum theory for psychosis. Future studies should further explore the underpinnings of PE in preadolescence within this population and examine the potential causal role of the JTC bias in relation to delusion formation and conversion to clinical psychosis with the potential for informing early prevention and intervention.

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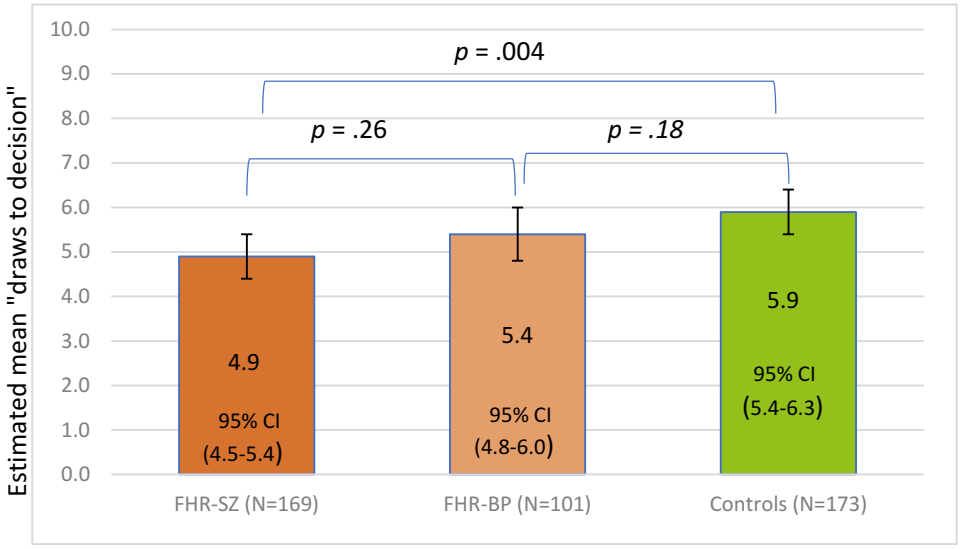
Table 1. Demographic and clinical background characteristics of 443 children with data on the Beads Task in The Danish High Risk and Resilience Study, VIA 11

	Familial risk group				*P* value for Pairwise Comparisons		
	FHR-SZ (n = 169)	**FHR-BP** (n = 101)	**Controls** (n = 173)	***P* value**	**FHR-SZ vs Controls**	**FHR-BP vs Controls**	**FHR-SZ vs FHR-BP**
Female, No. (%)	81 (47.9%)	45 (44.6%)	80 (46.2%)	.86[a]	NA	NA	NA
Age at inclusion, years, mean (SD)	12.0 (0.3)	11.9 (0.2)	11.9 (0.2)	.46[b]	NA	NA	NA
IQ[c], mean (SD)	95.0 (10.5)	97.3 (9.7)	98.0 (10.4)	**.03**[b]	.009	.64	.07
Onset of puberty[d], No. (%)[e]	138 (87.3%)	87 (90.6%)	152 (94.4%)	.09[a]	NA	NA	NA
Any current psychotic experiences, No. (%)[f]	44 (26.0%)	13 (13.0%)	24 (14.1%)	**.005**[a]	**.006**	.80	**.01**
CBCL[g] total score, mean (SD)	23.2 (20.6)	20.2 (19.8)	12.6 (12.5)	**<.001**[b]	**<.001**	**.001**	.19
Current global functioning[h], mean (SD)[i]	64.5 (15.6)	68.6 (14.7)	75.0 (14.1)	**<.001**[b]	**<.001**	**.001**	**.03**

Abbreviations: CBCL – Child Behavior Check List School-age version; FHR-BP, children at familial hig- risk of bipolar disorder. FHR-SZ, children at familial high-risk of schizophrenia spectrum disorders.
[a]Chi square test
[b]One-way ANOVA test with post hoc Least Significant Difference
[c]Measured with Reynolds Intellectual Screening Test (RIST)
[d]Measured with self-reported Tanner Stages. Onset of puberty defined as Tanner Stage 2-4 (vs Stage 1)
[e]Includes 158 children at FHR-SZ, 96 children at FHR-BP, and 161 controls
[f]Includes 169 children at FHR-SZ, 100 children at FHR-BP, and 170 controls
[g]Includes 160 children at FHR-SZ, 99 children at FHR-BP, and 167 controls
[h]Measured with Children's Global Assessment Scale
[i]Includes 169 children at FHR-SZ, 101 children at FHR-BP, and 170 controls

Figure 1. Draws to decision on the Beads Task in 443 children at FHR-SZ, FHR-BP, and controls in the Danish High Risk and Resilience Study, VIA 11



Error bars represent 95% CI.
FHR-BP, Children at familial high-risk of bipolar disorder; FHR-SZ, Children at familial high-risk of schizophrenia.

Table 2. Draws to decision on the Beads Task in 443 children at FHR-SZ, FHR-BP, and controls in The Danish High Risk and Resilience Study, VIA 11

	Pairwise comparisons					
	FHR-SZ vs. controls		FHR-BP vs. controls		FHR-SZ vs. FHR-BP	
Mean draws to decision	***P* value**	**Cohen's D**	***P* value**	**Cohen's D**	***P* value**	**Cohen's D**
Adjusted for sex[a]	**.004**	0.31	.18	0.16	.26	0.15
Adjusted for sex and IQ[ab]	**.02**	0.24	.20	0.15	.49	0.09

Abbreviations: FHR-BP, children at familial high-risk of bipolar disorder; FHR-SZ, children at familial high-risk of schizophrenia spectrum disorders;
[a]A significant effect of sex was found on draws to decision in this model. Being female was associated with a higher number of draws to decision.
[b]A significant effect of IQ was found on draws to deicision in this model. Having higher IQ was associated with a higher number of draws to decision.

Table 3a-b. Draws to decision on the Beads Task in children with psychotic experiences in The Danish High Risk and Resilience Study, VIA 11

Table 3a. Full cohort

	All (*n* = 439)			
	Psychotic experiences without delusions (*n* = 34)		**Psychotic experiences with delusions** (*n* = 47)	
Mean draws to decision	***P* value**	**Cohen's D**	***P* value**	**Cohen's D**
Adjusted for sex[a]	.15	0.25	**.01**	0.45
Adjusted for sex and FHR-group[b]	.20	0.22	**.03**	0.34
Adjusted for sex, FHR-group and IQ[c]	.26	0.19	.16	0.22

Children with no psychotic experiences during the past six months (n = 358) were used as reference
Abbreviations: FHR-BP, children at familial high-risk of bipolar disorder; FHR-SZ, children at familial high-risk of schizophrenia spectrum disorders.
[a]A significant effect of sex was found on draws to decision in this model. Being female was associated with a higher number of draws to decision.
[b]A significant effect of sex and FHR-group was found on draws to decision in this model. Being female was associated with a higher number of draws to decision. Being at FHR-SZ was associated with a lower number of draws to decision.
[c]A significant effect of sex, FHR-group and IQ was found on draws to decision in this model. Being female and having higher IQ was associated with a higher number of draws to decision. Being at FHR-SZ was associated with a lower number of draws to decision.

Table 3a-b. Draws to decision on the Beads Task in children with psychotic experiences in The Danish High Risk and Resilience Study, VIA 11

Table 3b. Stratified by familial high-risk-group

	FHR-SZ (*n* = 169)				**FHR-BP** (*n* = 100)				**Controls** (*n* = 170)			
	Psychotic experiences without delusions (*n* = 18)		**Psychotic experiences with delusions** (*n* = 26)		**Psychotic experiences without delusions** (*n* = 4)		**Psychotic experiences with delusions** (*n* = 9)		**Psychotic experiences without delusions** (*n* = 12)		**Psychotic experiences with delusions** (*n* = 12)	
Mean draws to decision	***P* value**	**Cohen's D**	***P* value**	**Cohen's D**	***P* value**	**Cohen's D**	***P* value**	**Cohen's D**	***P* value**	**Cohen's D**	***P* value**	**Cohen's D**
Adjusted for sex[a]	.68	0.14	**.04**	0.46	.75	0.17	.64	0.17	.12	0.47	**.05**	0.60
Adjusted for sex and IQ[a,b]	.66	0.10	.14	0.32	.68	0.20	.52	0.23	.15	0.41	.17	0.42

Children with no psychotic experiences during the past six months in each group (FHR-SZ, *n* = 125, FHR-BP, *n* = 87, controls, *n* = 146) were used as reference
Significant *p* values (<.05) in bold.
Abbreviations: FHR-BP, children at familial high-risk of bipolar disorder; FHR-SZ, children at familial high-risk of schizophrenia spectrum disorders.
[a]A significant effect of sex was found on draws to decision in children at FHR-SZ in this model. Being female was associated with a higher number of draws to decision.
[b]A significant effect of IQ was found on draws to decision in children at FHR-SZ and controls in this model. Having higher IQ was associated with a higher number of draws to decision.

Table S1. Extreme JTC on the Beads Task in 443 children at FHR-SZ, FHR-BP, and controls in The Danish High Risk and Resilience Study, VIA 11

	Pairwise comparisons					
	FHR-SZ vs. controls		FHR-BP vs. controls		FHR-SZ vs. FHR-BP	
Extreme JTC	***P* value**	**OR (95%CI)**	***P* value**	**OR (95%CI)**	***P* value**	**OR (95%CI)**
Adjusted for sex	.07	1.7 (1.0-2.9)	.47	1.3 (0.7-2.5)	.39	1.3 (0.7-2.5)
Adjusted for sex and IQ[b]	.25	1.4 (0.8-2.5)	.54	1.2 (0.6-2.5)	.70	1.1 (0.6-2.2)

Abbreviations: FHR-BP, children at familial high-risk of bipolar disorder; FHR-SZ, children at familial high-risk of schizophrenia spectrum disorders; JTC, jumping to conclusions

[c]A significant effect of IQ was found on extreme JTC in this model. Having higher IQ was associated with lower odds of extreme responding

Table S2a-b. Extreme JTC on the Beads Task in children with psychotic experiences in The Danish High Risk and Resilience Study, VIA 11

Table S2a. Full cohort

	All (*n* = 439)			
	Psychotic experiences without delusions (n = 34)		**Psychotic experiences with delusions** (n = 47)	
Extreme JTC	***P* value**	**OR (95% CI)**	***P* value**	**OR (95% CI)**
Adjusted for sex[a]	.06	2.1 (1.0-4.7)	.15	1.7 (0.8-3.6)
Adjusted for sex and FHR-group	.09	2.0 (0.9-4.5)	.22	1.6 (0.8-3.4)
Adjusted for sex, FHR-group and IQ[a]	.12	1.9 (0.8-4.4)	.79	1.1 (0.5-2.5)

Children with no psychotic experiences during the past six months (n = 358) were used as reference

Abbreviations: FHR-BP, children at familial high-risk of bipolar disorder; FHR-SZ, children at familial high-risk of schizophrenia spectrum disorders; JTC, jumping to conclusions

[a]A significant effect of IQ was found on extreme JTC in this model. Having higher IQ was associated with lower odds of extreme responding

Table S2a-b. Extreme JTC on the Beads Task in children with psychotic experiences in The Danish High Risk and Resilience Study, VIA 11

Table S2b. Stratified by familial high-risk-group

	FHR-SZ (*n* = 169)				**FHR-BP** (*n* = 100)				**Controls** (*n* = 170)			
	Psychotic experiences without delusions (*n* = 18)		**Psychotic experiences with delusions** (*n* = 26)		**Psychotic experiences without delusions** (*n* = 4)		**Psychotic experiences with delusions** (*n* = 9)		**Psychotic experiences without delusions** (*n* = 12)		**Psychotic experiences with delusions** (*n* = 12)	
Extreme JTC	***P* value**	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**	**OR (95% CI)**
Adjusted for sex	.26	1.9 (0.6-5.6)	.21	1.9 (0.7-5.4)	NA	NA[b]	.75	1.3 (0.2-7.0)	.05	3.7 (1.0-13.7)	.68	1.4 (0.3-7.0)
Adjusted for sex and IQ[a]	.27	1.9 (0.6-5.6)	.33	1.7 (0.6-4.8)	NA	NA	.86	0.8 (0.1-6.3)	.08	3.5 (0.9-14.2)	.63	0.6 (0.1-5.1)

Children with no psychotic experiences during the past six months in each group (FHR-SZ, *n* = 125, FHR-BP, *n* = 87, controls, *n* = 146) were used as reference
Significant *p* values (<.05) in bold.
Abbreviations: FHR-BP, children at familial high-risk of bipolar disorder; FHR-SZ, children at familial high-risk of schizophrenia spectrum disorders; JTC, jumping to conclusions
[a]A significant effect of IQ was found on extreme responding in this model in children at FHR-BP and controls. Having higher IQ was associated with lower odds of extreme responding
[b]Contained too few children to calculate confidence intervals