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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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 a population-based control group.

Methods: In a longitudinal population-based cohort study children at FHR-SZ (N=170), FHR-BP (N=103), and the control group (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) than in the control group (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). Having three or more psychotic experiences increased odds the most (odds ratio 2.5, 95% CI 1.1–5.7). Persistent psychotic experiences were associated with increased odds of middle childhood disorders (odds ratio 4.1, 95% CI 2.1–8.4). Psychotic experiences were nondifferentially 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 nondifferentially in children at familial high risk and the control group. Psychotic experiences should be included in mental health screenings including children at familial high risk.

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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 nonpsychotic 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 nonpsychotic disorders (10).

While most psychotic experiences are transient, in a minority of individuals they persist over time (11). Persistent psychotic experiences are associated with higher levels of

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concurrent and subsequent psychopathology than nonpersistent 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 the control group at baseline (mean age 11.7 years, range 6–17) and at 2-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 the control group 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 2-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 5 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 the control group; 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.

METHODS

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 7-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 a population-based control group (hereafter control group) 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). Children in the control group 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 reinterviewed about psychotic experiences during the 4-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 nine 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 within the past 6 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. 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 different 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, with four categories: children not reporting any early childhood psychotic experiences, nor any middle childhood psychotic experiences (never psychotic experiences); children reporting any early childhood psychotic experiences, but no middle childhood psychotic experiences (remittent psychotic experiences); children not reporting any early childhood psychotic experiences but reporting any middle childhood psychotic experiences (incident psychotic experiences); children reporting both any early childhood psychotic experiences and any middle childhood psychotic experiences (persistent psychotic experiences).

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 reinterviewed about symptoms during the 4-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 the control group 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; control group: 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 the 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 over-adjusting we did not adjust for socioeconomic status which is intrinsically associated with familial risk status. Alpha was set to <0.05. 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). FHR-SZ and FHR-BP groups 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 the control group. Children at FHR-SZ had a higher prevalence of early childhood psychotic experiences than the control group. 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 the control group (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 (FHR-SZ: N=170; FHR-BP: N=103; control group: N=174) at both assessments (mean age at follow-up, 11.9 years [SD=0.2, range=10.9–12.7]). Retention was 87.1%. There were no significant differences between children who participated in the psychotic experiences assessment at age 11 years and dropouts regarding prevalence of any psychotic experiences (X^2 (1)= 1.311, p=0.25), any axis I disorder (X^2 (1)=1.969, p=0.16) in early childhood, sex (X^2 (1)=0.853, p=0.36), or FHR-group (X^2 (2)=0.991, p=0.61).

Prevalence of Middle Childhood Psychotic Experiences

Significantly more children at FHR-SZ (31.8%) than children in the control group (18.4%) experienced any middle childhood psychotic experiences (odds ratio 2.1, 95% CI=1.3–3.4, p=0.005). No significant difference was found between children at FHR-BP (20.4%) and the control group (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 the control group and children at FHR-BP, as well as a higher prevalence of delusions than the control group.

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

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[a]

	Familial risk group							p Value for pairwise comparisons		
	FHR-SZ (N=170[b])		FHR-BP (N=103)		Control group (N=174[b])					
	N/mean	%/SD	N/mean	%/SD	N/mean	%/SD	p	FHR-SZ vs. control group	FHR-BP vs. control group	FHR-SZ vs. FHR-BP
Female, N, %	82	48.2	46	44.7	82	47.1	0.85[c]	NA	NA	NA
Age at inclusion, years, mean, SD	12.0	0.3	11.9	0.2	11.9	0.2	0.61[d]	NA	NA	NA
Baseline IQ[e], mean, SD[f]	103.0	11.3	105.3	8.8	105.2	9.8	0.07[d]	NA	NA	NA
Onset of puberty[g], N, %[h]	137	87.3	87	90.6	151	94.4	0.09[c]	NA	NA	NA
Any early childhood psychotic experiences (age 7 years), N, %	83	48.8	45	43.7	61	35.1	0.03[c]	0.01	0.15	0.41
Any early childhood axis I disorder (K-SADS, age 7 years)[i], N, %	61	35.9	36	35.0	28	16.1	<0.001[c]	<0.001	<0.001	0.88
Any middle childhood axis I disorder (K-SADS, age 11 years)[i], N, %	82	48.2	40	38.8	39	22.4	<0.001[c]	<0.001	0.003	0.13
Current global functioning[j], mean, SD	64.8	15.6	68.5	14.6	75.1	14.0	<0.001[d]	<0.001	<0.001	0.05
Educational level, primary caregiver[k,l]										
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	0.008[m]	0.008	0.46	0.003
Bachelor degree, equivalent or higher, N, %	74	43.5	63	61.2	98	56.6				

[a] K-SADS-PL=Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime Version; FHR-SZ=children at familial high risk of schizophrenia spectrum disorders; FHR-BP=children at familial high risk of bipolar disorder.
[b] At follow-up data on Psychotic Experiences were provided for three children (FHR-SZ=2, control group=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 three children are not included in Table 1.
[c] Chi square test.
[d] One-way ANOVA test with post hoc Least Significant Difference.
[e] Measured with Reynolds Intellectual Screening Test (RIST).
[f] Includes 170 children at FHR-SZ, 103 children at FHR-BP, and 172 children in the control group.
[g] Measured with self-reported Tanner Stages. Onset of puberty defined as Tanner Stage 2–4 (vs. Stage 1).
[h] Includes 157 children at FHR-SZ, 96 children at FHR-BP, and 160 children in the control group.
[i] Includes affective disorders, anxiety disorders, ADHD, disruptive behavior disorders, autism spectrum disorders, PTSD, stress and adjustment disorders, tic disorders, and psychotic disorders.
[j] Measured with Children's Global Assessment Scale (CGAS).
[k] The primary caregiver is defined as the caregiver currently spending the most time with the child at the time of the VIA 11 assessment.
[l] Includes 170 primary caregivers of children at FHR-SZ, 103 caregivers of children at FHR-BP, and 173 caregivers of children in the control group.
[m] Linear-by-Linear Association p value is reported when an ordinal variable has more than two categories.

ratio 2.0, 95% CI=1.2–3.1, p=0.004). 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=0.04, 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 the control group.

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

TABLE 2. Psychotic experiences in middle childhood (age 11 years) in 447 children at FHR-SZ, FHR-BP, and control group in The Danish High Risk and Resilience Study, VIA 11[a]

	N, %						Between-group comparisons								
	FHR-SZ (N=170)		FHR-BP (N=103)		Control group (N=174)		FHR-SZ vs. control group			FHR-BP vs. control group			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	0.005	1.1	0.6–2.1	0.68	1.8	1.0–3.2	0.04
Adjusted for sex							2.1	1.3–3.4	0.005	1.1	0.6–2.1	0.68	1.8	1.0–3.2	0.04
Six-month prevalence, any psychotic experiences															
Unadjusted	42	24.7	14	13.6	23	13.2	2.2	1.2–3.8	0.007	1.0	0.5–2.1	0.93	2.1	1.1–4.0	0.03
Adjusted for sex							2.2	1.2–3.8	0.007	1.0	0.5–2.1	0.91	2.1	1.1–4.0	0.03

[a] FHR-SZ=Children at familial high risk of schizophrenia spectrum disorders; FHR-BP=Children at familial high risk of bipolar disorder.

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 control group in The Danish High Risk and Resilience Study, VIA 11[a]

	Early childhood psychotic experiences											
	Any psychotic experiences (N=189)			One type of psychotic experiences (N=104)			Two types of psychotic experiences (N=48)			Three 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	0.004	1.6	0.9–2.7	0.10	2.1	1.1–4.2	0.03	2.6	1.2–5.4	0.01
Adjusted for sex	1.9	1.2–2.9	0.005	1.6	0.9–2.7	0.10	2.1	1.1–4.2	0.03	2.6	1.2–5.4	0.01
Any middle childhood axis I disorder												
Unadjusted	2.2	1.5–3.3	<0.001	1.6	1.0–2.6	0.06	2.8	1.5–5.2	0.002	4.2	2.0–8.5	<0.001
Adjusted for sex	2.3	1.5–3.4	<0.001	1.7	1.0–2.7	0.04	2.8	1.5–5.3	0.001	4.3	2.1–8.8	<0.001
Adjusted for sex and any early childhood axis I disorder	2.1	1.3–3.2	0.002	1.7	1.0–3.0	0.05	2.3	1.1–4.7	0.03	3.1	1.4–7.0	0.007
Adjusted for sex, any early childhood axis I disorder, and familial risk	2.0	1.2–3.1	0.004	1.8	1.0–3.1	0.04	2.0	1.0–4.2	0.06	2.5	1.1–5.7	0.04

[a] Children with no early childhood psychotic experiences (N=258) were used as reference. FHR-SZ=Children at familial high risk of schizophrenia spectrum disorders; FHR-BP=Children at familial high risk of bipolar disorder.

significantly predicted middle childhood mental disorders (odds ratio 4.1, 95% CI=2.1–8.4, p<0.001, 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, 1b, and 1c.

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 >0.30).

Cross-sectional Associations Between Psychotic Experiences 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 >0.35).

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

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 control group in The Danish High Risk and Resilience Study, VIA 11[a]

	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	0.004	2.3	1.2–4.3	0.01	4.9	2.7–9.1	<0.001
Adjusted for sex	2.1	1.3–3.4	0.002	2.3	1.2–4.5	0.01	5.2	2.8–9.8	<0.001
Adjusted for sex and any early childhood axis I disorder	1.8	1.1–3.1	0.03	2.1	1.0–4.3	0.05	4.5	2.3–9.0	<0.001
Adjusted for sex, any early childhood axis I disorder, and familial risk	1.7	1.0–2.9	0.06	1.8	0.9–3.9	0.10	4.1	2.1–8.4	<0.001

[a] Children in the never psychotic experiences group (N=209) were used as reference. FHR-SZ=Children at familial high risk of schizophrenia spectrum disorders; FHR-BP=Children at familial high risk of bipolar disorder.

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 nonsignificant. Associations between two types of 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 the control group, whereas the prevalence in children at FHR-BP was not significantly higher than in the control group. 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 twofold 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 fourfold increased risk of having a mental disorder in middle childhood compared with children who never had psychotic experiences. Early childhood psychotic experiences were nondifferentially 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 nondifferential 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 the control group 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).

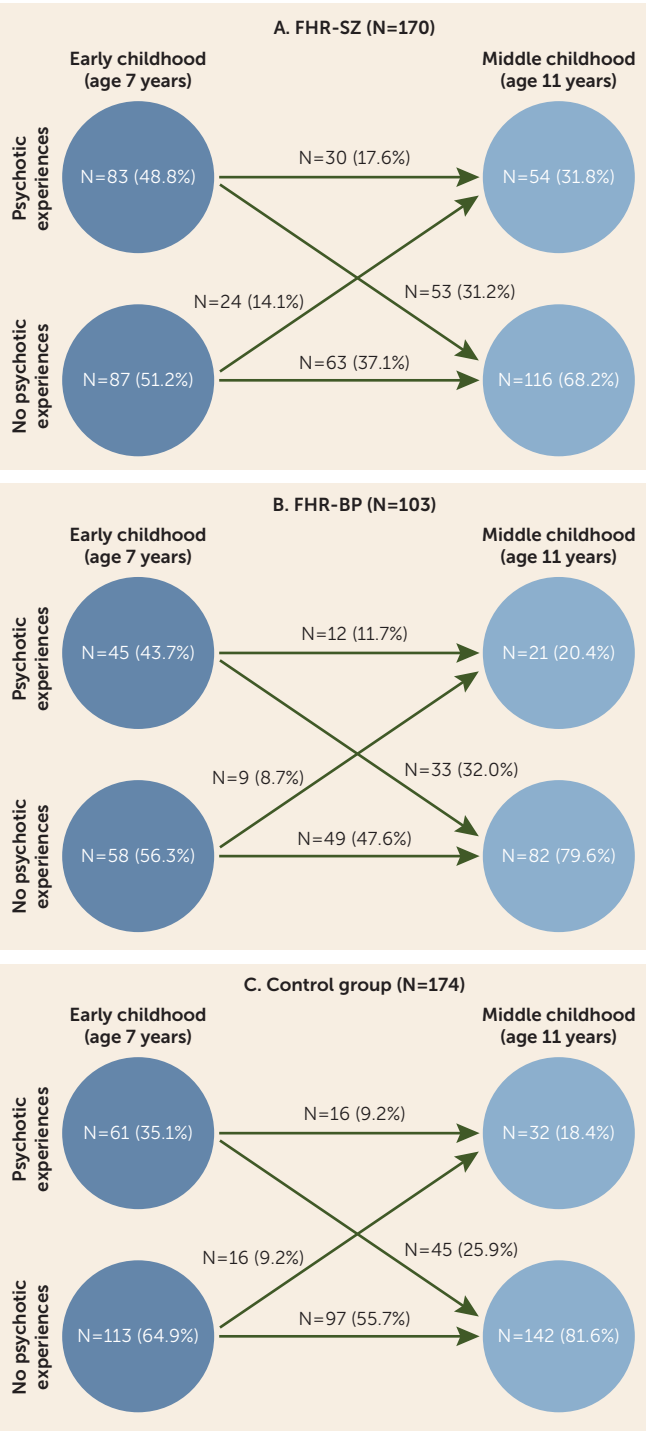
The finding of psychotic experiences as early markers for vulnerability to subsequent mental disorders aligns with the previously described meta-analytic findings from child and adolescent general population samples (3), and the limited longitudinal evidence on psychotic experiences measured as early 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 is 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 2-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 5-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).

FIGURE 1. Developmental pathways of psychotic experiences from early to middle childhood in 447 children at FHR-SZ, FHR-BP, and control group in the Danish High Risk and Resilience Study, VIA 11[a]



[a] FHR-SZ=Children at familial high risk of schizophrenia spectrum disorders; FHR-BP=Children at familial high risk of bipolar disorder.

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 gold-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 6 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 <0.05, these findings should be independently replicated in future studies. The smaller sample size in the FHR-BP group weakens estimates of differences for this group and may not have been fully conducive to detecting interaction effects, thereby increasing the risk of type II errors. Therefore, no firm conclusions should be drawn regarding the nondifferential 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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REFERENCES

1. Kelleher I, Connor D, Clarke MC, et al: Prevalence of psychotic symptoms in childhood and adolescence: a systematic review and meta-analysis of population-based studies. Psychol Med 2012; 42:1857–1863
2. Fisher HL, Caspi A, Poulton R, et al: Specificity of childhood psychotic symptoms for predicting schizophrenia by 38 years of age: a birth cohort study. Psychol Med 2013; 43:2077–2086
3. Healy C, Brannigan R, Dooley N, et al: Childhood and adolescent psychotic experiences and risk of mental disorder: a systematic review and meta-analysis. Psychol Med 2019; 49:1589–1599
4. Poulton R, Caspi A, Moffitt TE, et al: Children's self-reported psychotic symptoms and adult schizophreniform disorder: a 15-year longitudinal study. Arch Gen Psychiatry 2000; 57:1053–1058
5. Zammit S, Kounali D, Cannon M, et al: Psychotic experiences and psychotic disorders at age 18 in relation to psychotic experiences at age 12 in a longitudinal population-based cohort study. Am J Psychiatry 2013; 170:742–750
6. Rimvall MK, van Os J, Verhulst F, et al: Mental health service use and psychopharmacological treatment following psychotic experiences in preadolescence. Am J Psychiatry 2020; 177:318–326
7. Jeppesen P, Clemmensen L, Munkholm A, et al: Psychotic experiences co-occur with sleep problems, negative affect and mental disorders in preadolescence. J Child Psychol Psychiatry 2015; 56: 558–565
8. Karcher NR, Loewy RL, Savill M, et al: Replication of associations with psychotic-like experiences in middle childhood from the Adolescent Brain Cognitive Development (ABCD) study. Schizophr Bull Open 2020; 1:sgaa009
9. Laurens KR, Tzoumakis S, Dean K, et al: Population profiles of child-reported psychotic-like experiences and their differential association with other psychopathologies. Br J Clin Psychol 2020; 59:22–38
10. Kelleher I, Keeley H, Corcoran P, et al: Clinicopathological significance of psychotic experiences in non-psychotic young people: evidence from four population-based studies. Br J Psychiatry 2012; 201:26–32
11. Linscott RJ, van Os J: An updated and conservative systematic review and meta-analysis of epidemiological evidence on psychotic experiences in children and adults: on the pathway from proneness to persistence to dimensional expression across mental disorders. Psychol Med 2013; 43:1133–1149
12. Havers L, Taylor MJ, Ronald A: Genetic and environmental influences on the stability of psychotic experiences and negative symptoms in adolescence. J Child Psychol Psychiatry 2019; 60: 784–792
13. Wigman JT, van Winkel R, Raaijmakers QA, et al: Evidence for a persistent, environment-dependent and deteriorating subtype of subclinical psychotic experiences: a 6-year longitudinal general population study. Psychol Med 2011; 41:2317–2329
14. Dominguez MD, Wichers M, Lieb R, et al: Evidence that onset of clinical psychosis is an outcome of progressively more persistent subclinical psychotic experiences: an 8-year cohort study. Schizophr Bull 2011; 37:84–93
15. Jeppesen P, Larsen JT, Clemmensen L, et al: The CCC2000 birth cohort study of register-based family history of mental disorders and psychotic experiences in offspring. Schizophr Bull 2015; 41: 1084–1094
16. Kelleher I, Cannon M: Psychotic-like experiences in the general population: characterizing a high-risk group for psychosis. Psychol Med 2011; 41:1–6
17. Polanczyk G, Moffitt TE, Arseneault L, et al: Etiological and clinical features of childhood psychotic symptoms: results from a birth cohort. Arch Gen Psychiatry 2010; 67:328–338
18. Zammit S, Horwood J, Thompson A, et al: Investigating if psychosis-like symptoms (PLIKS) are associated with family history of schizophrenia or paternal age in the ALSPAC birth cohort. Schizophr Res 2008; 104:279–286
19. Wigman JT, van Winkel R, Ormel J, et al: Early trauma and familial risk in the development of the extended psychosis phenotype in adolescence. Acta Psychiatr Scand 2012; 126:266–273
20. Johnstone EC, Abukmeil SS, Byrne M, et al: Edinburgh high risk study—findings after four years: demographic, attainment and psychopathological issues. Schizophr Res 2000; 46:1–15
21. MacKenzie LE, Abidi S, Fisher HL, et al: Stimulant medication and psychotic symptoms in offspring of parents with mental illness. Pediatrics (Epub ahead of print, Dec 30, 2015)
22. De la Serna E, Ilzarbe D, Sugranyes G, et al: Lifetime psychopathology in child and adolescent offspring of parents diagnosed with schizophrenia or bipolar disorder: a 2-year follow-up study. Eur Child Adolesc Psychiatry 2021; 30:117–129
23. de la Serna E, Baeza I, Andrés S, et al: Comparison between young siblings and offspring of subjects with schizophrenia: clinical and neuropsychological characteristics. Schizophr Res 2011; 131:35–42
24. Ellersgaard D, Gregersen M, Spang KS, et al: Psychotic experiences in seven-year-old children with familial high risk of schizophrenia or bipolar disorder in: The Danish High Risk and Resilience Study - VIA 7; a population-based cohort study. Schizophr Res 2021; 228: 510–518
25. Tandon N, Montrose D, Shah J, et al: Early prodromal symptoms can predict future psychosis in familial high-risk youth. J Psychiatr Res 2012; 46:105–110

26. Paccalet T, Gilbert E, Berthelot N, et al: Liability indicators aggregate many years before transition to illness in offspring descending from kindreds affected by schizophrenia or bipolar disorder. Schizophr Res 2016; 175:186–192
27. Bartels-Velthuis AA, van de Willige G, Jenner JA, et al: Course of auditory vocal hallucinations in childhood: 5-year follow-up study. Br J Psychiatry 2011; 199:296–302
28. Thorup AAE, Hemager N, Søndergaard A, et al: The Danish High Risk and Resilience Study-VIA 11: study protocol for the first follow-up of the VIA 7 cohort -522 children born to parents with schizophrenia spectrum disorders or bipolar disorder and controls being re-examined for the first time at age 11. Front Psychiatry 2018; 9:661
29. Kaufman J, Birmaher B, Brent D, et al: Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. J Am Acad Child Adolesc Psychiatry 1997; 36:980–988
30. Healy C, Gordon AA, Coughlan H, et al: Do childhood psychotic experiences improve the prediction of adolescent psychopathology? A longitudinal population-based study. Early Interv Psychiatry 2019; 13:1245–1251
31. De Loore E, Gunther N, Drukker M, et al: Persistence and outcome of auditory hallucinations in adolescence: a longitudinal general population study of 1800 individuals. Schizophr Res 2011; 127:252–256
32. Rimvall MK, van Os J, Rask CU, et al: Psychotic experiences from preadolescence to adolescence: when should we be worried about adolescent risk behaviors? Eur Child Adolesc Psychiatry 2020; 29: 1251–1264
33. Ellersgaard D, Jessica Plessen K, Richardt Jepsen J, et al: Psychopathology in 7-year-old children with familial high risk of developing schizophrenia spectrum psychosis or bipolar disorder - The Danish High Risk and Resilience Study - VIA 7, a population-based cohort study. World Psychiatry 2018; 17:210–219
34. Gregersen M, Søndergaard A, Brandt JM, et al: 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. J Child Psychol Psychiatry (Epub ahead of print, Dec 15, 2021)
35. Shaffer D, Gould MS, Brasic J, et al: A children's global assessment scale (CGAS). Arch Gen Psychiatry 1983; 40:1228–1231
36. Reynolds CR, Kamphaus RW: Reynolds Intellectual Assessment Scales (RIAS). Lutz, FL, Psychological Assessment Resources Inc, 2003
37. Coleman L, Coleman J: The measurement of puberty: a review. J Adolesc 2002; 25:535–550
38. Kalman JL, Bresnahan M, Schulze TG, et al: Predictors of persisting psychotic like experiences in children and adolescents: a scoping review. Schizophr Res 2019; 209:32–39
39. Calkins ME, Moore TM, Satterthwaite TD, et al: Persistence of psychosis spectrum symptoms in the Philadelphia Neurodevelopmental Cohort: a prospective two-year follow-up. World Psychiatry 2017; 16:62–76
40. Steenkamp LR, Tiemeier H, Blanken LME, et al: Predicting persistence of hallucinations from childhood to adolescence. Br J Psychiatry 2021; 219:670–677
41. Bartels-Velthuis AA, Wigman JT, Jenner JA, et al: Course of auditory vocal hallucinations in childhood: 11-year follow-up study. Acta Psychiatr Scand 2016; 134:6–15
42. Sullivan SA, Kounali D, Cannon M, et al: A population-based cohort study examining the incidence and impact of psychotic experiences from childhood to adulthood, and prediction of psychotic disorder. Am J Psychiatry 2020; 177:308–317
43. Duffy A, Horrocks J, Doucette S, et al: The developmental trajectory of bipolar disorder. Br J Psychiatry 2014; 204:122–128
44. Nurnberger JI, McInnis M, Reich W, et al: A high-risk study of bipolar disorder. Childhood clinical phenotypes as precursors of major mood disorders. Arch Gen Psychiatry 2011; 68:1012–1020
45. Downs JM, Cullen AE, Barragan M, et al: Persisting psychotic-like experiences are associated with both externalising and internalising psychopathology in a longitudinal general population child cohort. Schizophr Res 2013; 144:99–104
46. Kaymaz N, Drukker M, Lieb R, et al: Do subthreshold psychotic experiences predict clinical outcomes in unselected non-help-seeking population-based samples? A systematic review and meta-analysis, enriched with new results. Psychol Med 2012; 42:2239–2253
47. Guloksuz S, van Nierop M, Lieb R, et al: Evidence that the presence of psychosis in non-psychotic disorder is environment-dependent and mediated by severity of non-psychotic psychopathology. Psychol Med 2015; 45:2389–2401

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Examination Questions for 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

1. **What was the prevalence of any psychotic experiences in middle childhood across the three groups?**
   - A. Children at familial high risk of bipolar disorder had a higher prevalence of psychotic experiences than the other two groups
   - B. Children in the control group had a higher prevalence than children at familial high risk of bipolar disorder
   - C. Children at familial high risk of schizophrenia had a higher prevalence than the other two groups
   - D. There were no between-group differences
2. **Which developmental pathway of psychotic experiences from early to middle childhood was associated with having an axis I mental disorder during middle childhood after adjustment?**
   - A. Never having any psychotic experiences
   - B. Having remittent psychotic experiences
   - C. Having incident psychotic experiences
   - D. Having persistent psychotic experiences
3. **Which recommendation for early mental health screenings follows from this study?**
   - A. Mental health screenings should include psychotic experiences from middle childhood
   - B. Mental health screenings should include psychotic experiences from early childhood
   - C. Mental health screenings should not include psychotic experiences
   - D. No recommendation