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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

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).

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

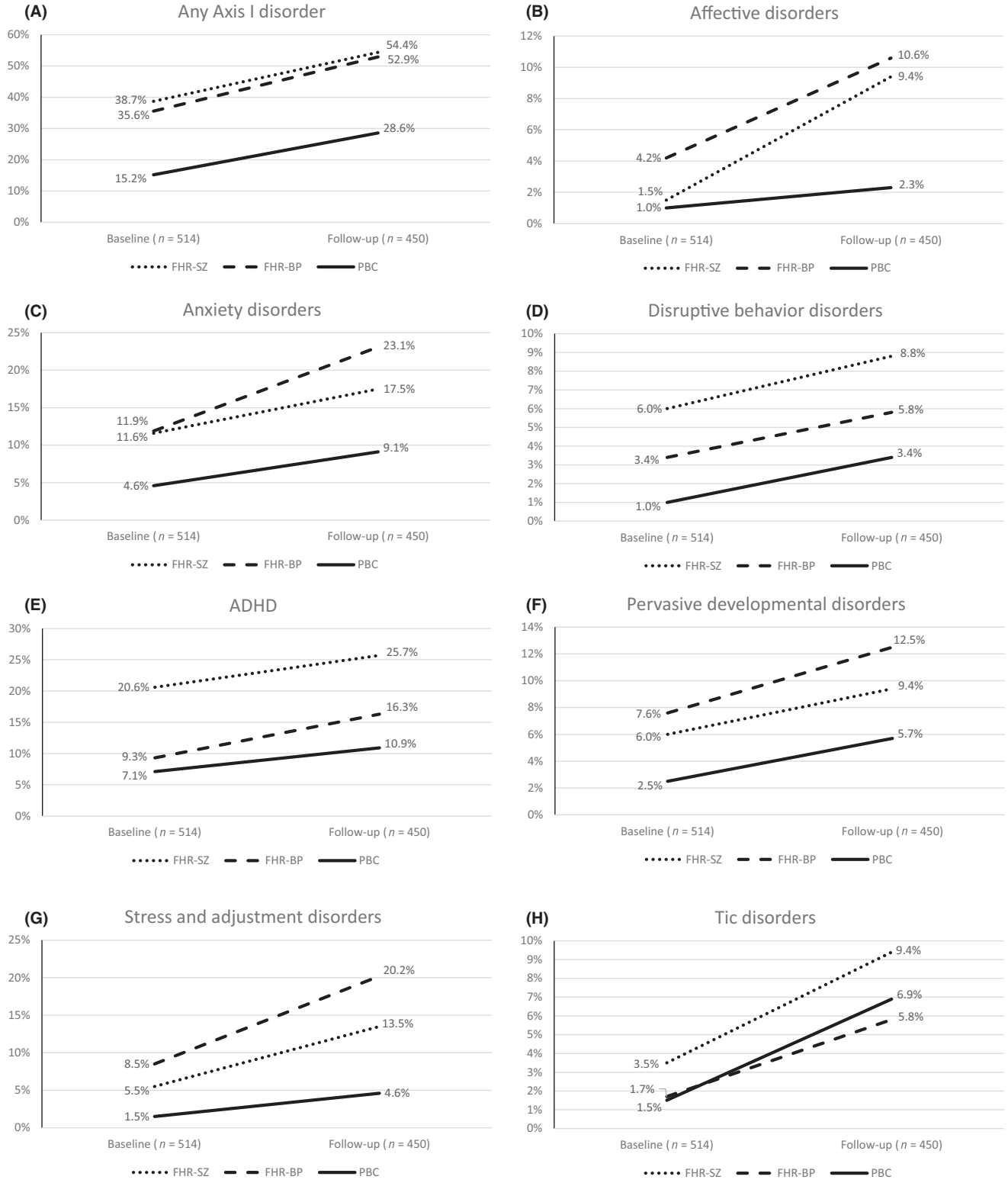

Figure 1 (A–H) Cumulative incidence of DSM-IV and DSM-5 mental disorders at baseline (age 7) and follow-up (age 11) in The Danish High Risk and Resilience Study, VIA 11. FHR-BP, Children at familial high-risk of bipolar disorder; FHR-SZ, Children at familial high-risk of schizophrenia spectrum disorders;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

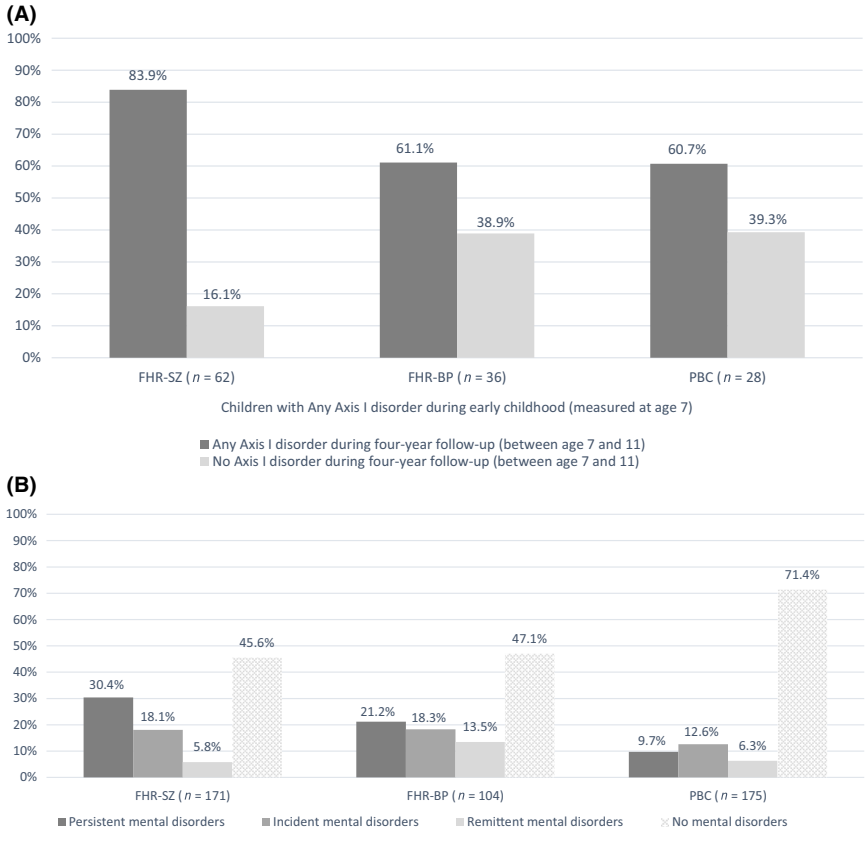

Figure 2 (A, B) Stability of mental disorders from early to middle childhood in The Danish High Risk and Resilience Study, VIA 11. (A) Stability of mental health in children with early childhood mental disorders. (B) Percentage of children with persistent, incident, remittent, and no mental disorders 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

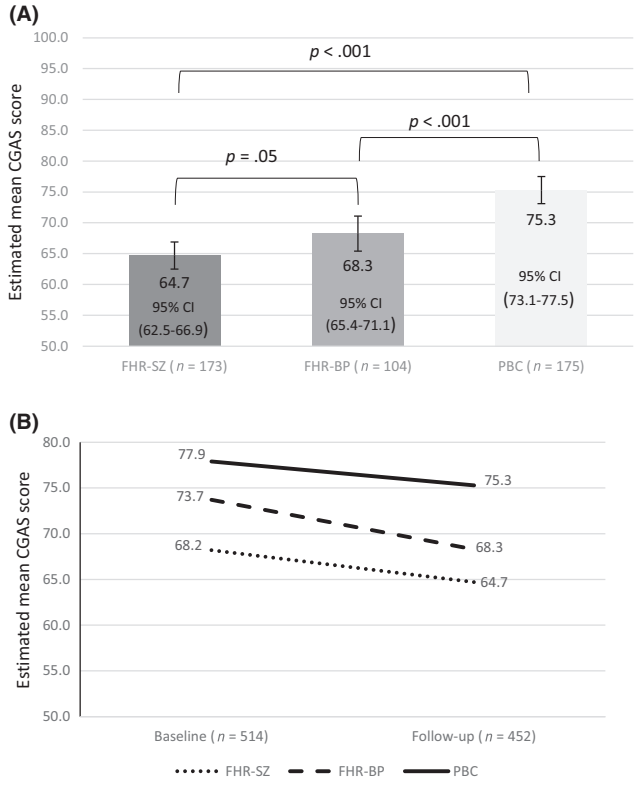

Figure 3 (A, B) Global functioning at baseline (age 7) and follow-up (age 11) in The Danish High Risk and Resilience Study, VIA 11. (A) Estimated mean CGAS score at age 11, adjusted for sex of the child. Error bars represent 95% CI. Observed means (*SD*) at age 11: FHR-SZ: 64.6 (15.6), FHR-BP: 68.1 (14.9), 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

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.

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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