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ARTICLE

Childhood trauma in children at familial high risk of schizophrenia or bipolar disorder: A longitudinal study. The Danish High Risk and Resilience Study – VIA 7 and VIA 11

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Abstract

Objectives: Childhood trauma increases the risk of developing mental illness as does being born to parents with schizophrenia or bipolar disorder. We aimed to compare prevalence of lifetime childhood trauma among 11-year-old

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children at familial high risk of schizophrenia (FHR-SZ) or bipolar disorder (FHR-BP) compared with population-based controls (PBCs).

Design: The study is a longitudinal, prospective cohort study of children at FHR-SZ, FHR-BP, and PBCs.

Methods: A cohort of 512 children at FHR-SZ (N = 199), FHR-BP (N = 118), and PBCs (N = 195) were examined at baseline (mean age 7.8, SD 0.2) and 451 children at FHR-SZ (N = 172), FHR-BP (N = 104), and PBCs (N = 175) were examined at four-year follow-up (mean age 11.9, SD 0.2, retention rate 87.3%). Childhood trauma was measured with a semi-structured interview.

Results: Children at FHR-BP had an elevated risk of exposure to any lifetime trauma (age 0–11 years) compared with PBCs (OR 2.082, 95%CI 1.223–3.545, p = .007) measured with binary logistic regression. One-way ANOVA revealed that both FHR-groups had a higher lifetime prevalence of exposure to a greater number of types of trauma compared with PBCs (FHR-SZ: observed mean: 1.53, 95%CI 1.29–1.77; FHR-BP: observed mean: 1.56, 95%CI 1.26–1.85; PBCs: observed mean: 0.99, 95%CI 0.82–1.17; p < .001). Binary logistic regression showed that the lifetime risk of exposure to interpersonal trauma (age 0–11 years) was elevated for both FHR-groups (FHR-SZ: OR 3.773, 95%CI 2.122–6.710, p < .001; FHR-BP: OR 3.602, 95%CI 1.913–6.783, p < .001).

Conclusions: Children at FHR-SZ and FHR-BP are at increased risk for being exposed to childhood trauma compared with PBCs. This study underscores the need for early detection, support, and prevention of childhood trauma in children at FHR-SZ and FHR-BP.

KEYWORDS
Childhood trauma, familial high risk, schizophrenia, bipolar disorder, follow-up

INTRODUCTION

Exposure to childhood trauma is a well-known environmental risk factor for the later development of schizophrenia spectrum disorder or bipolar disorder (Haahr et al., 2018; McKay et al., 2020; Morelli et al., 2019; Read et al., 2005; Sandstrom et al., 2019; Trotta et al., 2015; Varese et al., 2012). Being born to parents with schizophrenia or bipolar disorder also constitutes a genetic risk for developing not only

Practitioner Points

- Children at familial high risk of bipolar disorder are at increased risk of exposure to any lifetime trauma compared with population-based controls.
- Both children at familial high risk of schizophrenia and bipolar disorder are at increased risk of exposure to any lifetime interpersonal trauma and multiple types of trauma compared with population-based controls.
- In daily treatment of patients suffering from schizophrenia or bipolar disorder, early attention towards childhood trauma in their children is warranted.
- Further studies are needed to investigate the correlation of trauma exposure and onset of mental illness among children at both genetically and environmental risk for severe mental illness.

these disorders, but also other mental illnesses in adulthood (Hameed & Lewis, 2016; Rasic et al., 2014). Thus, when exposed to childhood trauma, children at familial risk of schizophrenia spectrum disorder or bipolar disorder are exposed to at least two risk determinants (Koenders et al., 2020; Mayo et al., 2017).

While the risk of severe mental illness following childhood trauma and the association between familial high risk of schizophrenia or bipolar disorder and later development of mental illness is well-documented, not all children exposed to these risk factors will be adversely affected (Hosman et al., 2009). Development of mental illness is a complex interaction between genetic vulnerability, neurodevelopmental factors, and environmental exposures (Goldstein et al., 2010; Morelli et al., 2019; Reupert & Maybery, 2016). It has been evidenced that parental psychopathology including psychosis and bipolar disorder along with genetic propensity may contribute to adverse environments with higher stress reactivity, more frequent exposure to high-conflict levels, child abuse, and low level of control (Fisher et al., 2014; Hosman et al., 2009; Koenders et al., 2020).

Individual factors within the child may also influence reaction to childhood trauma (Fisher et al., 2014). The neural diathesis-stress model proposes that pre-existing vulnerability of inherited and acquired factors interacts with later exposure to stressors as childhood trauma (Quidé et al., 2020). Furthermore, exposure to childhood trauma may cause dysregulation of stress hormones potentially causing structural changes in the brain, increasing the risk for psychopathology (Aas et al., 2019; Morelli et al., 2019; Popovic et al., 2019; Quidé et al., 2020; Walker et al., 2004).

In continuation of this, an individual's susceptibility may affect the reaction to trauma exposure, suggesting that more susceptible individuals react more poorly to adverse environments but also are more prone to positively adapt to supportive environment (Belsky, 2013; Belsky & Pluess, 2009; Quidé et al., 2020). These factors can be a result of exposure to or independent from parental illness (Reupert & Maybery, 2016).

Studies investigating the relationship between being at familial high risk of schizophrenia or bipolar disorder and occurrence of childhood trauma are limited. A few studies report that children of parents with bipolar disorder have a higher prevalence of trauma exposure compared with controls (Goldstein et al., 2010; Koenders et al., 2020; Schreuder et al., 2016). One study examining childhood trauma retrospectively during adulthood found that offspring of parents with bipolar (mean age 27.7 years) had a higher number of trauma exposures during childhood compared with controls (Schreuder et al., 2016). Although not directly comparable, retrospective studies of the association between childhood trauma and illness severity in adult bipolar patients have shown childhood trauma is associated with a more severe course of illness, more depressive episodes, and increased severity of mania (Watson et al., 2014). Moreover, there is robust evidence for an association between occurrence of childhood trauma and later development of psychotic illnesses (Haahr et al., 2018; Morelli et al., 2019; Read et al., 2005; Varese et al., 2012) and for childhood trauma predicting increase in positive symptoms among patients with schizophrenia (Kline et al., 2016). A dose-response effect is also evident, where increase in number of different

types of trauma (e.g., physical, emotional, and sexual abuse) during childhood elevates the risk for both psychosis and bipolar disorder in adult life (Aas et al., 2019; Croft et al., 2019; Kline et al., 2016; McKay et al., 2020; Schreuder et al., 2016; Varese et al., 2012; Wigman et al., 2012). The necessity of studying specific types of childhood trauma is supported by meta-analytic evidence that interpersonal trauma, that is, trauma characterized by intention to harm, (Wigman et al., 2012) are more strongly associated with later development of psychopathology than non-interpersonal trauma such as unintentional injury, natural disaster, or accidents (Croft et al., 2019; Gibson et al., 2016; Varese et al., 2012). Furthermore, a previous study reported a high prevalence of sexual and physical abuse among individuals with bipolar disorder (female patients: 49%; male patients: 36%) (Leverich et al., 2002). In addition to this, sexual- and physical abuse have a stronger association with onset of psychosis and bipolar disorder than other types of interpersonal trauma such as bullying, (Aas et al., 2019; Croft et al., 2019; Wigman et al., 2012) and interpersonal trauma can trigger or worsen development of psychotic symptoms in individuals at clinical high risk for psychosis (Kline et al., 2016).

Some studies have investigated sensitive periods of risk during childhood for being exposed to trauma; however, findings are inconclusive and vary according to trauma type (Arseneault et al., 2011; Croft et al., 2019; Fisher et al., 2010). One study identified the age before 7 to have the strongest association between childhood trauma and later development of psychosis, (Arseneault et al., 2011) another before the age 12 (Fisher et al., 2010), whereas a recent study identified the ages between 11 and 17 years to be the most critical period of risk for later development of psychotic symptoms (Croft et al., 2019). Moreover, previous studies have found post-traumatic stress disorder to be associated with an increased risk of schizophrenia spectrum or bipolar disorder among adults (Okkels et al., 2017). Our own previous findings examining mental health disorders among children at familial high risk of schizophrenia or bipolar disorder showed, that children at familial high risk of schizophrenia and bipolar disorder have a higher prevalence of stress- and adjustment disorder and post-traumatic stress disorder at both early childhood, age 0–7 years (Ellersgaard et al., 2018) and middle childhood, age 7–11 years (Gregersen et al., 2021). Future follow-up studies will determine if there is an association between childhood trauma and psychopathology among children of parents with schizophrenia or bipolar disorder.

Studying childhood trauma in children who are at familial high risk for schizophrenia or bipolar disorder can enhance the understanding of vulnerability, predictors, and risk factors of severe mental illness and may subsequently help guide early intervention strategies to reduce trauma exposure and potentially risk of mental illness (Morelli et al., 2019). Previous studies have small samples sizes, wide age ranges, and most studies uses questionnaires for assessment of childhood trauma and studies using semi-structured diagnostic interviews for trauma assessment are rare (Croft et al., 2019; Kelleher et al., 2008; Morelli et al., 2019). Finally, with a few exceptions, childhood trauma are studied retrospectively during adulthood in individuals with schizophrenia or bipolar disorder, increasing the risk of inaccuracies in memory recall (Kelleher et al., 2008; Morelli et al., 2019; Sandstrom et al., 2019).

To date, only a few studies have examined occurrence of childhood trauma in children at familial high risk of bipolar disorder (Duffy et al., 2007; Morelli et al., 2019; Schreuder et al., 2016). Further, to our knowledge, no other studies have examined childhood trauma in children at familial high risk of schizophrenia. Therefore, we aimed to examine the prevalence of any childhood trauma, frequency of trauma exposure to number of different types of trauma as well as prevalence of interpersonal- and non-interpersonal trauma among children at familial high risk of schizophrenia spectrum disorder (FHR-SZ) or bipolar disorder (FHR-BP) compared with population-based controls (PBCs) during their lifetime (age 0–11 years), and at distinct age periods, from age 0 to 7 (baseline) and from age 7 to 11 years (follow-up).

METHODS

Participants

This study is a part of the Danish High Risk and Resilience Study – VIA, a population-based cohort study of 522 children born and living in Denmark (Thorup et al., 2015, 2018). The study is prospective

and longitudinal, with baseline assessment at age 7 (VIA 7) and first follow-up at age 11 (VIA 11). The cohort consists of children at FHR-SZ (N = 202, defined as children born to parents with a register-based diagnosis of schizophrenia spectrum disorder), children at FHR-BP (N = 120, defined as children born to parents with a register-based diagnosis of bipolar affective disorder), and PBCs (N = 200). See online Appendix S1 for details of ICD-10 and ICD-8 codes. Children at FHR had at least one parent with schizophrenia or bipolar disorder. PBCs were born to parents with neither schizophrenia nor bipolar disorder and were matched to children at FHR-SZ on age, sex, and municipality. Parents in the PBC group could have other mental illness reflecting background population. Children at FHR-BP were unmatched, but comparable to the other two groups on age at inclusion and sex.

Procedures

Identification of the cohort was made through The Danish Psychiatric Central Research Register (Mors et al., 2011) and the Danish Civil Registration System (Pedersen et al., 2006). Approval from the Danish Data Agency was obtained. Formal approval from the Danish Committee on Health Research Ethics was applied for, but deemed unnecessary by this authority, due to the observational nature of the study. Informed oral and written consent was obtained from the child's parent or custody holder.

The baseline assessment took place from January 1, 2013 to January 31, 2016 and the follow-up from March 1, 2017 to June 30, 2020. Assessments were conducted at research units in Copenhagen and Aarhus and to a small extent in the homes of the children.

The study design, cohort, and full assessment battery are described elsewhere (Thorup et al., 2015, 2018).

Measures

Childhood trauma was examined with the Kiddie Schedule for Affective Disorders and Schizophrenia – Present and Lifetime Version PTSD-section (K-SADS-PL) (Kaufman et al., 1997), a semi-structured clinical interview assessing present and previous psychopathology in children and adolescents, including post-traumatic stress disorder (PTSD). Participants were asked about 13 different predefined categories of trauma and one 'other' category for trauma types not listed. The instrument did not allow registration of frequency, duration or, severity of exposure.

Interviews with first the primary caregiver and afterwards the child were conducted separately. Afterwards their responses were combined. Each item was scored dichotomously as yes/no, with exception of the 'other' category (Kline et al., 2016; Morelli et al., 2019). The interview was carried out by psychologists, medical doctors, or research nurses, all formally trained in the use of the instrument. All assessors were blinded to familial high-risk status and at follow-up also to prior data concerning the child.

All diagnoses were discussed at consensus meetings with a specialist in child and adolescent psychiatry, blinded to familial high-risk status of the child as well as prior diagnoses. At baseline, age 7, diagnoses were based on DSM-IV criteria, and at follow-up, at age 11, DSM-IV as well as DSM-V were used (Ellersgaard et al., 2018; Gregersen et al., 2021).

Assessment at baseline, age 7, rated exposure to childhood trauma from age 0 to age 7. Assessment at follow-up rated the preceding four years, from baseline at age 7 to age 11.

Variables derived from K-SADS-PL PTSD-section were (1) exposure to any childhood trauma, (2) number of types of trauma, (3) exposure to interpersonal trauma (victim of violent crime, witness to domestic violence, physical abuse, sexual abuse), and (4) non-interpersonal trauma (car accident, other accident, fire, witness of disaster, witness to a violent crime, confronted with traumatic news, terrorism-related trauma, witness of war, victim of war). Variables concerning any trauma and any interpersonal/non-interpersonal trauma were coded as binary outcomes. Variables regarding number of types of trauma the children were exposed to were coded as discrete numerical variables ranging from

0 to 14 to calculate mean. Furthermore, number of types of trauma was coded as a categorical variable with 0, 1, 2, and ≥3 types of trauma exposure to report prevalence of exposure to ≥3 types of trauma. All variables were coded as lifetime (age 0–11 years), including children participating at both times of assessment, and specific age periods; age 0–7 years (baseline assessment) and age 7–11 years (follow-up assessment), respectively.

Statistical analyses

Data analyses were carried out in IBM SPSS Statistical software (version 25).

Background characteristics were analysed using chi-square test for categorical data and one-way analyses of variance (one-way ANOVA) for continuous data.

For binary outcomes, that is, any trauma, any interpersonal- and non-interpersonal trauma, cross tabulation was used to calculate frequencies and percentages. Between-group differences were analysed using binary logistic regression.

To calculate between-group differences in changes in risk for any trauma from baseline to follow-up, repeated measures mixed-effects binary logistic regression with FHR-group, sex, and interaction time x group as fixed variables were made.

Number of types of trauma were analysed with one-way ANOVA. As data were not normally distributed, analyses were repeated using negative binomial regression. As this did not alter the results, only results from ANOVA are reported.

To calculate the mean changes of number of types of trauma from baseline to follow-up, linear mixed-model with repeated measures were conducted with FHR-group, sex, and interaction time x group as fixed variables.

Alpha-level was set to .05 for all analyses.

RESULTS

Background characteristics

At baseline, age 7 (mean age 7.8, SD 0.2, range 6.9–8.4), a total of 512 children (FHR-SZ, N = 199; FHR-BP, N = 118 and PBC, N = 195) and at follow-up, age 11 (mean age 11.9, SD 0.2, 10.9–12.7), 451 children (FHR-SZ, N = 172; FHR-BP, N = 104, PBC, N = 175) were assessed with the K-SADS-PL PTSD-section. A total of 447 children participated both at age 7 and at age 11 (FHR-SZ, N = 170, FHR-BP, N = 104; PBC, N = 173), totalling a retention rate at 87.3%. Retention rates across the three groups were similarly high, FHR-SZ = 170 (85.4%), FHR-BP = 104 (88.1%) and PBC = 173 (88.7%) (Table 1).

Analyses on drop-out from first assessment to follow-up revealed no statistically significant differences in those who participated at age 11 and those who dropped out regarding any trauma experienced from age 0–7 years (X^2 (1) = 0.571, p = .450), FHR-group (X^2 (2) = 1.058, p = .589) or sex (X^2 (1) = 0.676, p = .411).

No significant differences regarding age at inclusion or sex were found at baseline or follow-up (Table 1).

Lifetime trauma from age 0–11 years

Any childhood trauma

Between age 0 and 11 years, 67.1% of the children at FHR-SZ, 74.0% of the children at FHR-BP and 57.8% of PBCs reported exposure to any childhood trauma (Table 2). Children at FHR-BP had twofold

TABLE 1 Background characteristics of children participating in K-SADS-PL PTSD-section in the Danish High Risk and Resilience Study – VIA7 and VIA11. Age 0–11 years (lifetime), age 0–7 years (baseline), and age 7–11 years (follow-up)

					Pairwise comparisons (*p*-value)		
	FHR-SZ†	**FHR-BP‡**	**PBCs§**	***p*-value**	**FHR-SZ vs. PBCs**	**FHR-BP vs. PBCs**	**FHR-SZ vs. FHR-BP**
Children, N (%)[c]							
Lifetime, 0–11 years	170 (38.0%)	104 (23.3%)	173 (38.7%)	-	-	-	-
Baseline, age 7	199 (38.9%)	118 (23.0%)	195 (38.1%)	-	-	-	-
Follow-up, age 11	172 (38.1%)	104 (23.1%)	175 (38.8%)	-	-	-	-
Female, N (%)							
Lifetime, 0–11 years	82 (48.2%)	46 (44.2%)	82 (47.2%)	.804[a]			
Baseline, age 7	92 (46.2%)	55 (46.6%)	90 46.2%)	.997[a]	-	-	-
Follow-up, age 11	83 (48.3%)	46 (44.2%)	82 (46.9%)	.810[a]	-	-	-
Age at inclusion, mean (SD)							
Baseline, age 7	7.84 (0.22)	7.87 (0.20)	7.81 (0.20)	.084[b]	-	-	-
Follow-up, age 11	11.96 (0.27)	11.94 (0.22)	11.93 (0.22)	.558[b]	-	-	-
CBCL†† total score, mean (SD)[d]							
Baseline, age 7[e]	27.20 (21.05)	23.41 (14.64)	17.14 (14.74)	**<.001**[b]	**<0.001**	**0.005**	0.087
Follow-up, age 11[f]	23.41 (20.53)	21.61 (21.24)	12.54 (12.48)	**<.001**[b]	**<0.001**	**<0.001**	0.428
C-GAS‡‡ score, mean (SD)[g]							
Baseline, age 7[h]	68.07 (15.40)	73.55 (14.91)	77.56 (13.47)	**<.001**[b]	**<0.001**	**0.019**	**0.001**
Follow-up, age 11[i]	64.70 (15.62)	68.12 (14.94)	75.17 (13.97)	**<.001**[b]	**<0.001**	**<0.001**	0.065
Stress and adjustment disorders, N (%)							
Lifetime, age 0–11 years**	23 (13.5%)	21 (20.2%)	8 (4.6%)	**<.001**[a]	**0.004**	**<0.001**	0.145
Age 0–7 years*	11 (5.5%)	10 (8.5%)	3 (1.5%)	**.015**[a]	**0.032**	**0.003**	0.308
Age 7–11 years**	16 (9.3%)	11 (10.6%)	6 (3.4%)	**.038**[a]	**0.025**	**0.016**	0.730

(Continues)

TABLE 1 (Continued)

	FHR-SZ†	FHR-BP‡	PBCs§	*p*-value	Pairwise comparisons (*p*-value)		
					FHR-SZ vs. PBCs	FHR-BP vs. PBCs	FHR-SZ vs. FHR-BP
Post-traumatic stress disorder[i]							
Lifetime, age 0–11 years ¶¶	5 (2.9%)	6 (5.8%)	0 (0.0%)	-	-	-	-
Age 0–7 years §§	4 (2.0%)	3 (2.5%)	0 (0.0%)	-	-	-	-
Age 7–11 years ¶¶	1 (0.6%)	5 (4.8%)	0 (0.0%)	-	-	-	-

Note: Abbreviations: †FHR-SZ: Children born to familial high risk of schizophrenia; ‡FHR-BP: Children born to familial high risk of bipolar disorder; §PBCs: Population-based controls. ¶ K-SADS-PL: Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime Version; ††CBCL: Child Behaviour Checklist; †FHR-SZ: Children born to familial high risk of schizophrenia; ‡‡C-GAS: Children's Global Assessment Scale; ‡FHR-BP: Children born to familial high risk of bipolar disorder.

Significant *p*-values (<.05) in bold.

[a]Chi square test.

[b]One-way ANOVA test.

[c]Participants included in this sample were those who were assessed with K-SADS-PL PTSD section. Five hundred twelve children participated at baseline and 451 children participated at follow-up. Sixty-five children participated at baseline, but not at follow-up. Four children participated at follow-up but not at baseline. Lifetime analyses are made with those participating at both assessments; baseline and at follow-up ($N = 447$).

[d]CBCL total score range: 0–226. Higher score indicates more problem behaviour. Range of total score in this cohort: Baseline: 0–103; Follow-up: 0–106.

[e]CBCL total score at baseline includes 192 children at FHR-SZ, 111 children at FHR-BP, and 189 PBCs.

[f]CBCL total score at follow-up includes 162 children at FHR-SZ, 102 children at FHR-BP, and 170 PBCs.

[g]C-GAS score ranges from 1 to 100. Higher score indicates higher level of function. Range in this cohort: Baseline: 35–100; Follow-up: 33–98.

[h]C-GAS at baseline includes 199 children at FHR-SZ, 118 children at FHR-BP, and 195 PBCs.

[i]C-GAS at follow-up includes 172 children at FHR-SZ, 104 children at FHR-BP, and 175 PBCs.

[j]Too small sample for pairwise comparisons.

[§§]Ellersgaard et al. (2018).

[¶¶]Gregersen et al. (2021).

TABLE 2 Prevalence of childhood trauma in children at FHR-SZ, FHR-BP, and PBCs in The Danish High Risk and Resilience Study - VIA7 and VIA11. Age 0–11 years (lifetime), age 0–7 years (baseline), and age 7–11 years (follow-up)

	FHR-SZ † Lifetime, *N* = 170 Age 0–7 years, *N* = 199 Age 7–11 years, *N* = 172	FHR-BP ‡ Lifetime, *N* = 104 Age 0–7 years, *N* = 118 Age 7–11 years, *N* = 104	PBCs § Lifetime, *N* = 173 Age 0–7 years, *N* = 195 Age 7–11 years, *N* = 175	Pairwise comparisons					
				FHR-SZ vs. PBCs		FHR-BP vs. PBCs		FHR-SZ vs. FHR-BP	
	N (%)	*N* (%)	*N* (%)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)
Any trauma									
Lifetime, age 0–11 years[a]	114 (67.1%)	77 (74.0%)	100 (57.8%)	.077	1.486 (0.957–2.307)	**.007**	2.082 (1.223–3.545)	.223	1.401 (0.814–2.410)
Age 0–7 years[b]	85 (42.7%)	51 (43.2%)	55 (28.2%)	**.003**	1.898 (1.247–2.888)	**.007**	1.938 (1.200–3.130)	.930	1.021 (0.645–1.617)
Age 7–11 years[c]	91 (52.9%)	61 (58.7%)	74 (42.3%)	**.048**	1.533 (1.004–2.343)	**.009**	1.936 (1.184–3.167)	.353	1.263 (0.772–2.065)
Any interpersonal trauma									
Lifetime, age 0–11 years	54 (31.8%)	32 (30.8%)	19 (11.0%)	**<.001**	3.773 (2.122–6.710)	**<.001**	3.602 (1.913–6.783)	.863	0.955 (0.564–1.617)
Age 0–7 years	53 (26.6%)	24 (20.3%)	10 (5.1%)	**<.001**	6.716 (3.303–13.656)	**<.001**	4.723 (2.169–10.287)	.208	0.703 (0.407–1.216)
Age 7–11 years	28 (16.3%)	17 (16.3%)	11 (6.3%)	**.004**	2.899 (1.394–6.031)	**.009**	2.913 (1.307–6.495)	.988	1.005 (0.520–1.942)
Any non-interpersonal trauma									
Lifetime, age 7–11 years	90 (52.9%)	58 (55.8%)	80 (46.2%)	.215	1.308 (0.856–1.99)	.125	1.466 (0.899–2.390)	.649	1.830 (0.686–1.830)
Age 0–7 years	56 (28.1%)	31 (26.3%)	43 (22.1%)	.164	1.384 (0.875–2.189)	.395	1.260 (0.740–2.143)	.718	0.910 (0.545–1.520)
Age 7–11 years	65 (37.8%)	48 (46.2%)	58 (33.1%)	.366	1.225 (0.789–1.904)	**.031**	1.729 (1.051–2.844)	.172	1.411 (0.861–2.311)

Note: Abbreviations: † FHR-SZ: Children born to familial high risk of schizophrenia; ‡ FHR-BP: Children born to familial high risk of bipolar disorder; § PBCs: Population-based controls.

Significant *p*-values (<.05) in bold.

[a]Lifetime, age 0–11 years: Children participating in both assessments (*N* = 447).

[b]Age 0–7 years: Children participating in assessment at baseline, age 7 (*N* = 512).

[c]Age 7–11 years: Children participating in assessment at follow-up, age 11 (*N* = 451).

higher risk (OR 2.082, 95% CI 1.223–3.545, $p = .007$) of any experienced trauma compared with PBCs. Children at FHR-SZ were at an intermediate level, but not significantly higher than PBCs (OR 1.486, 95% CI 0.957–2.307, $p = .077$). The FHR-SZ and FHR-BP groups did not differ significantly ($p = .223$) (Table 2, Figure S1). Adjusting for sex did not alter the significant between-group differences ($p = .910$, Table S1).

Number of types of trauma

Children at FHR-SZ (observed mean: 1.53, 95% CI 1.29–1.77, $p < .001$; mean diff: 0.54, 95% CI 0.23–0.84, $p = .001$) and FHR-BP (observed mean: 1.56, 95% CI 1.26–1.85, $p < .001$; mean diff: 0.56, 95% CI: 0.22–0.91, $p = .001$) reported exposure to a greater number of different types of trauma compared with PBCs (observed mean: 0.99, 95% CI 0.82–1.17, $p < .001$, Figure 1a, Table S2). The mean difference of trauma exposure was non-significant between FHR-SZ and FHR-BP children

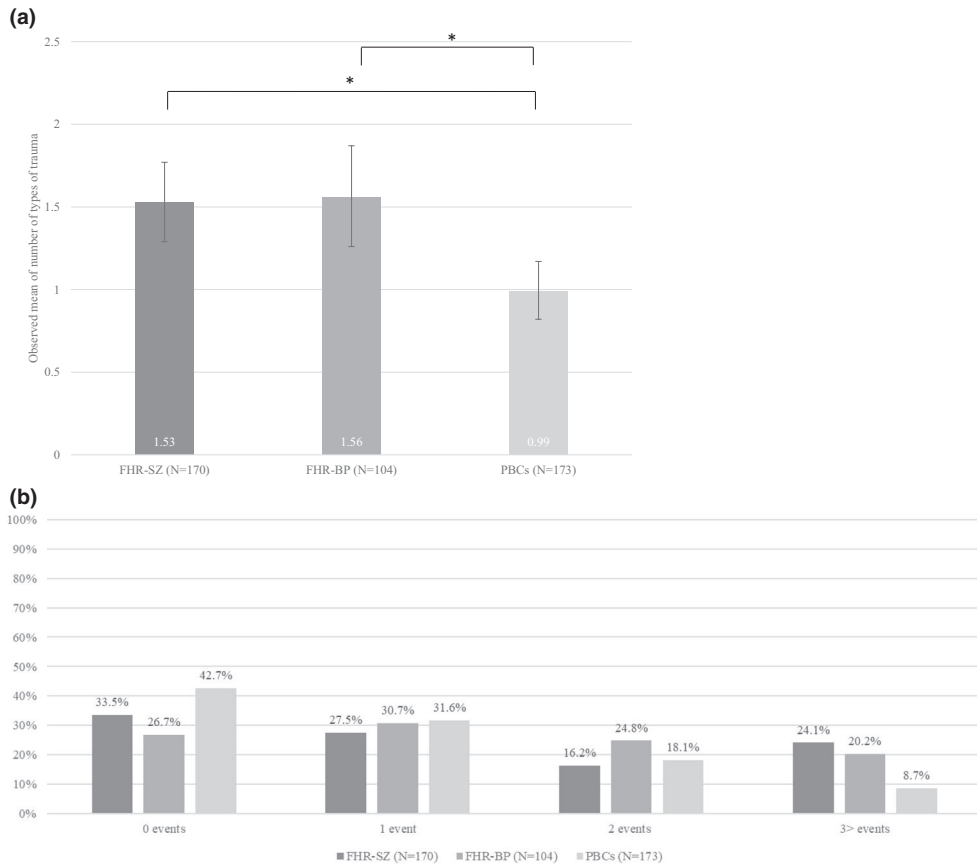

FIGURE 1 (a–b) Prevalence of number of types of trauma exposure in children at FHR-SZ, FHR-BP, and PBCs in the Danish High Risk and Resilience Study – VIA7 and VIA11. Age 0–11 years (lifetime). *Note*: (a) Observed mean of number of types of trauma from age 0 to 11 years (lifetime). Lifetime, age 0–11 years: Children participating in both assessments ($N = 447$). *Significant (<0.05) p-value. 95% CI represented by error bars. Mean (95% CI) at age 0–11 years (lifetime): FHR-SZ: 1.53 (1.29–1.77); FHR-BP: 1.56 (1.26–1.85); PBCs: 0.99 (0.82–1.17). (b) Prevalence of number of types of trauma from age 0 to 11 years (lifetime). Abbreviations: FHR-SZ, Children born to familial high risk of schizophrenia; FHR-BP, Children born to familial high risk of bipolar disorder; PBCs, Population-based controls. Lifetime, age 0–11 years: Children participating in both assessments ($N = 447$). Too few children to calculate OR

(Figure 1a, Table S2). Children at both FHR-groups reported a higher prevalence of three or more types of trauma exposure compared with PBCs (FHR-SZ: 24.1%; FHR-BP: 20.2%; PBC: 8.7%). Odds ratio could not be calculated due to lack of power (Figure 1b).

Interpersonal- and non-interpersonal trauma

Both high risk groups had a more than three times higher risk (FHR-SZ: OR 3.773, 95% CI 2.122–6.710, $p < .001$; FHR-BP: OR 3.602, 95% CI 1.913–6.783, $p < .001$, Table 2) of experiencing interpersonal trauma from age 0 to 11 years compared with PBCs. More children at FHR had experienced physical abuse (FHR-SZ: 8.2%; FHR-BP; 7.7%; PBC: 3.5%) towards themselves or witnessed to domestic violence (FHR-SZ: 24.1%; FHR-BP: 20.2%; PBC: 5.2%) compared with PBCs. Only children at FHR reported sexual abuse (FHR-SZ: 4.7%; FHR-BP: 4.8%; PBC: 0%, Figure 2a). Due to lack of power, odds ratio could not be calculated.

There were no significant differences between any of the groups regarding any non-interpersonal trauma (Table 2, Figure 2b). All three groups had a high prevalence of receiving traumatic news from age 0 to 11 years (FHR-SZ: 39.6%; FHR-BP: 40.4%; PBC: 34.1%, Figure 2b).

Age periods of risk

Any childhood trauma

From age 0 to 7 years, both high risk groups had a nearly two-fold higher risk of trauma exposure compared with PBCs (FHR-SZ: OR 1.898, 95% CI 1.247–2.888, $p = .003$; FHR-BP: OR 1.938, 95% CI 1.200–3.130, $p = .007$, Table 2). From age 7 to 11, children at FHR-SZ had a 1.5 times higher risk (OR 1.533, 95% CI: 1.004–2.343, $p = .048$) of experiencing trauma compared with PBCs, whereas FHR-BP children had a nearly two-fold higher risk (OR 1.936, 95% CI 1.184–3.167, $p = .009$) of experiencing trauma compared with PBCs.

There was no significant difference between the two high-risk groups, in any trauma experienced from age 0 to 7 years ($p = .930$) nor at age 7–11 years ($p = .353$). No differences were found adjusting for sex at age 0–7 years ($p = .380$, Table S1) nor at 7–11 years ($p = .480$, Table S1).

The prevalence of any lifetime trauma experienced from age 0 to 7 and from age 0 to 11 years, increased equally for all three groups and no significant time x group interaction was found ($p = .676$, Figure S2).

Number of types of trauma

The mean of number of types of trauma was at age 0–7 as well as age 7–11 years significantly higher for both high risk groups compared with PBCs ($p = .001$; $p = .003$, Table S2).

The mean of number of types of trauma experienced from age 0 to 7 and from age 0 to 11 years, increased equally over time for the three groups, as no time x group interaction was found ($p = .398$, Figure S3).

Interpersonal- and non-interpersonal trauma

Exposure to interpersonal trauma was higher for both high risk groups at each age period, but with the highest risk in early childhood, age 0 to 7 years (0–7 years: FHR-SZ: OR 6.716, 95% CI 3.303–13.656, $p < .001$; FHR-BP OR 4.723, 95% CI 2.169–10.287, $p < .001$; 7–11 years: FHR-SZ: OR 2.899,95% CI

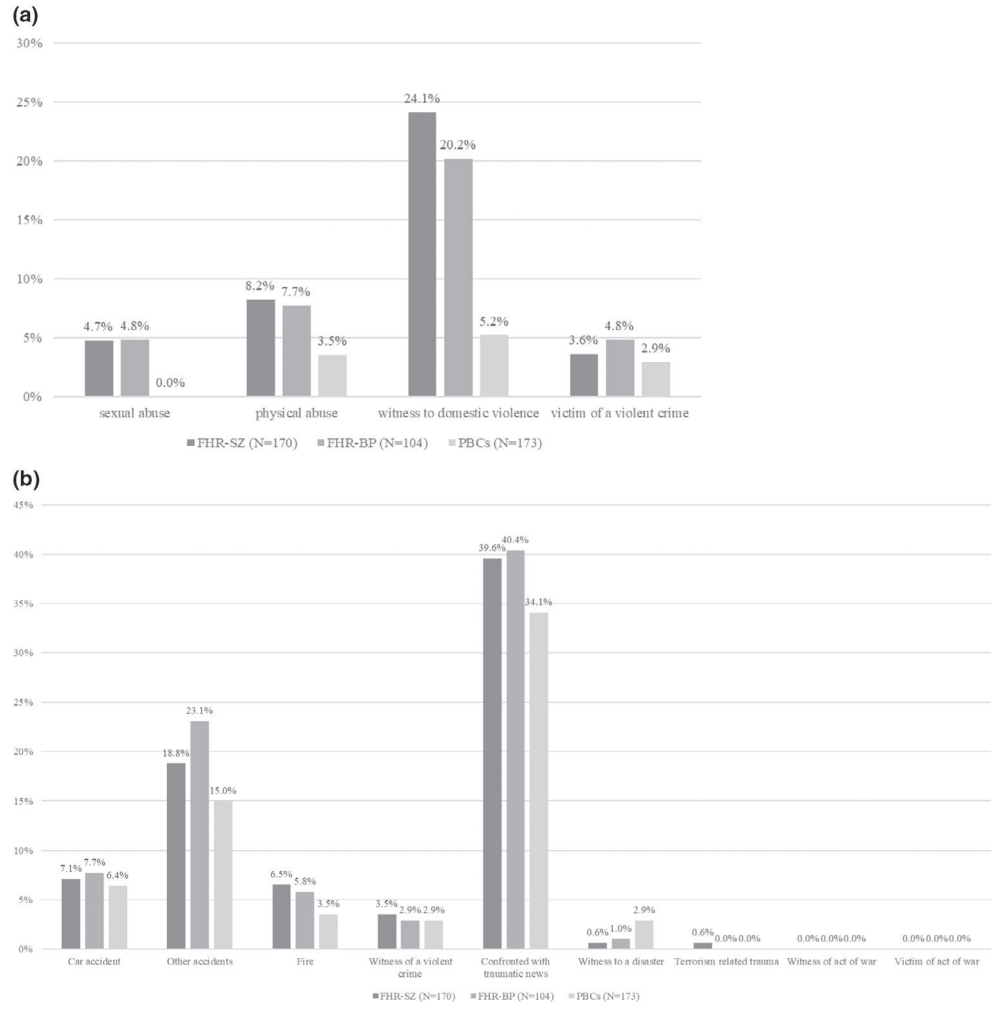

FIGURE 2 (a–b) Prevalence of types of interpersonal and non-interpersonal trauma in children at FHR-SZ, FHR-BP, and PBCs in the Danish High Risk and Resilience Study – VIA7 and VIA11. Age 0–11 years (lifetime). *Note*: (a) Prevalence of types of interpersonal trauma from age 0 to 11 years (lifetime). Interpersonal trauma: sexual abuse, physical abuse, witness to domestic violence, victim of violent crime. Lifetime, age 0–11 years: Children participating in both assessments (N = 447). (b) Prevalence of types of non-interpersonal trauma events from age 0–11 years (lifetime). Non-interpersonal trauma: car accident, other accidents, fire, witness to a violent crime, confronted with traumatic news, witness of disaster, terrorism related trauma, witness of war, victim of war. Abbreviations: FHR-SZ, Children born to familial high risk of schizophrenia; FHR-BP, Children born to familial high risk of bipolar disorder; PBCs: Population-based controls. Lifetime, age 0–11 years: Children participating in both assessments (N = 447)

1.394–6.031, p = .004; FHR-BP: OR 2.913, 95% CI 1.307–6.495, p = .009, Table 2, Figure S4a–d). Regarding non-interpersonal trauma, children at FHR-BP had almost 2-fold higher risk between age 7 and 11 years compared with PBCs (OR 1.729; 95% CI: 1.051–2.844, p = .031). Besides that, no statistically significant differences were found regarding non-interpersonal trauma between the three groups at any periods (Table 2, Figure S4a–d).

DISCUSSION

This is the first longitudinal study to examine the relationship between childhood trauma and familial high risk in both children at FHR-SZ and FHR-BP compared with controls.

Based on thorough interviews, our study revealed that children at FHR-BP had a two-fold increased risk of any trauma exposure from age 0 to 11 years compared with PBCs and both children at FHR-SZ and FHR-BP had an increased risk of experiencing any trauma in early childhood, age 0–7 years, and middle childhood, age 7–11 years. The risk of exposure for a greater number of types of trauma were higher for both FHR-groups compared with PBCs at all age periods, and both FHR-groups reported a higher prevalence of three or more different types of trauma compared with PBCs. Moreover, children at FHR-SZ and FHR-BP did not differ from each other in risk of exposure to any trauma or to number of types of trauma at any age period. Of note, the risk of any lifetime trauma and mean of number of types of trauma increased equally across the three groups from baseline to follow-up. Furthermore, children at FHR-SZ and FHR-BP were more likely to experience interpersonal trauma compared with PBCs at all age periods, and the FHR-groups did not differ from each other regarding risk of any interpersonal trauma at any age period. Additionally, sexual abuse was only reported in the FHR-groups and both children at FHR-SZ and FHR-BP had a higher prevalence of physical abuse and domestic violence compared with PBCs.

Any childhood trauma

The findings of elevated risk of any childhood trauma during all age periods among children at FHR-BP and between age 0–7 and 7–11 years for children at FHR-SZ, are in line with previous FHR-BP-studies and studies of adults with psychotic illness or bipolar disorder (Gibson et al., 2016; Mayo et al., 2017; Morelli et al., 2019; Pedrini et al., 2021; Schreuder et al., 2016; Varese et al., 2012; Wigman et al., 2012). Children at FHR-SZ were not at elevated risk for any lifetime trauma compared with controls, however the trend significant result regarding age 0–11 years may be due to a slight, undetected attrition bias, or reduced power due to the somewhat smaller sample size at follow-up. Additionally, as ratings are based on parents and child reports, it could be hypothesized that parental illness could affect the parents memory of traumatic events, as previous studies report that some psychopathology including schizophrenia predicts less accurate memory of trauma, whereas depression increases the memory of trauma due to rumination about the events (Goodman et al., 2019). Furthermore, children's recall of trauma has been shown to be affected by a variety of factors including parental support regarding the trauma. Lower support predicts memory errors as the child are less likely to disclose the trauma or have learned not to talk about it (Goodman et al., 2019).

Number of types of trauma

Our findings that children at FHR-SZ and FHR-BP had a higher prevalence of number of types of trauma exposures are in keeping with a previous study of children of parents with bipolar disorder (Duffy et al., 2007) and a study reporting higher prevalence of multiple trauma in adolescents with parental psychotic pathology (Wigman et al., 2012). In keeping with previous evidence, it is likely that parents with severe mental illness are both creating an increased risk for adverse environment along with risk for mental illness. Additionally, a pre-existing vulnerability within the child could also evoke increased prevalence of trauma (Fisher et al., 2014).

In addition, both children at FHR-SZ and FHR-BP had a higher lifetime prevalence of three or more types of trauma. This is in line with previous a previous study reporting a dose-response effect where the risk of psychotic symptoms increased with the number of types of trauma exposures, and exposure

to 3 or more types of trauma between age 0 and 17 years are associated with a five-fold increased risk for psychotic symptoms (Croft et al., 2019).

Interpersonal trauma

The findings that both FHR-groups from age 0 to 11 years, had an increased risk for interpersonal trauma compared with PBCs are of importance since individuals who have experienced any interpersonal trauma during childhood are at increased risk for developing psychotic symptoms, schizophrenia, and bipolar disorder during adulthood (Arseneault et al., 2011; Cutajar et al., 2010; Gibson et al., 2016; Leverich et al., 2002; Mauritz et al., 2013; Varese et al., 2012).

Of note, in our study, only children at FHR-SZ and FHR-BP reported having experienced sexual abuse and both FHR-groups had a higher prevalence of physical abuse compared with PBCs. This is in keeping with other studies finding that children with parental history of schizophrenia, bipolar disorder, and psychotic symptoms have a higher prevalence of sexual abuse and physical abuse compared with controls (Fisher et al., 2014; Walsh et al., 2002). Of note, these studies assessed childhood trauma retrospectively in late teen-years or during adulthood (17–65 years) impeding direct comparisons to our age range between 0 and 11 years.

Our results showed that both FHR-groups had a higher prevalence of experiencing domestic violence, parents fighting, throwing things, or threatening each other, compared with PBCs. In keeping with this, previous studies of individuals diagnosed with psychosis, found an association between experiencing domestic violence in childhood and adolescence (age 0–15 years) and an increased risk of developing psychosis, depression, and other psychopathology (Croft et al., 2019; Jaffee et al., 2002; Kelleher et al., 2008; Lepistö et al., 2011). Furthermore, the level of conflicts are higher in families dealing with parental illness (Johnson et al., 2006; Rutter & Quinton, 1984) and a study of witnessing domestic violence among adolescents showed, that families with unstable and difficult situations at home have increased risk of domestic violence (Lepistö et al., 2011). Furthermore, mental illness may impact parental capability and responsiveness to the child due to for example, ruminations or delusions (Reupert & Maybery, 2016). In line with this and our own previous findings regarding adequacy of the home environment (Gantriis et al., 2019), children in FHR-families will not only genetically be at risk of mental illness but are also at risk of being exposed to an unstable environment, creating an accumulated risk for these children. Thus, being at familial risk to schizophrenia or bipolar disorder constitutes a complex interplay between genetic and environmental risk as parents are both passing on genes and providing a more adverse environment (Fisher et al., 2014; Quidé et al., 2020; Reupert & Maybery, 2016).

Moreover, a bidirectional relationship should also be considered. Childhood trauma has been evidenced to predict psychotic experiences or psychosis but also vice versa (Kelleher et al., 2013; Lecei et al., 2019). Additionally, evidence suggests a non-causal relationship where pre-existing vulnerabilities increases the risk for exposure to any trauma and victimization due to the gene-environment correlation (Lecei et al., 2019; Reupert & Maybery, 2016; Varese et al., 2012).

Age periods of risk

In our study, age 0–7 years had the highest risk of interpersonal trauma among the FHR-groups compared with age 7–11 years. A longitudinal twin study found an increased relative risk for psychotic symptoms at age 12 if a child were exposed to maltreatment before age 7 compared with age 7–12 years (Arseneault et al., 2011). These findings are important as some studies find the first years of life particularly critical regarding exposure to trauma, as it increases the risk for neural, behavioural, and mental consequences later in life and enhance vulnerability for later development of psychopathology (Jaffee et al., 2002; Lepistö et al., 2011; Nelson & Gabard-Durnam, 2020). Other studies report that adolescence is the specific age period of risk, as the hypothalamic-pituitary-axis will have increased activity

during that period of age, compared with other age groups, if exposed to interpersonal trauma (Croft et al., 2019; Lupien et al., 2009).

Mechanisms of risk

Several studies have proposed explanations of the mechanisms of risk between exposure to childhood trauma and later development of psychotic experiences or psychosis. Biological models show that childhood trauma can invoke stress-induced neurodevelopmental changes as dysregulation of the hypothalamic pituitary adrenal axis and chronically elevated stress hormones to cause structural changes in the brain causing increased risk for later psychopathology (Aas et al., 2019; Croft et al., 2019; Kelleher et al., 2008; McKay et al., 2020; Morelli et al., 2019; Popovic et al., 2019; Quidé et al., 2020; Walker et al., 2004). Furthermore, adult victims of childhood physical and sexual abuse display persistent sensation of pituitary–adrenal and autonomic stress response. (Heim et al., 2000; Kelleher et al., 2008; McKay et al., 2020) Additionally, it has been shown that early life trauma can affect brain development including brain regions involved in cognitive functions. This can lead to deficits in working memory, which may also be a risk factor for later development of psychopathology (Majer et al., 2010).

Cognitive theories suggest that childhood trauma including domestic violence, sexual abuse, and physical abuse may have a negative impact the individual's cognitive schema. Childhood abuse and victimization may cause the individual to perceive the world or other people as dangerous and threatening and in the end leading to paranoid ideations and increased vulnerability for developing psychosis (Arseneault et al., 2011; Kelleher et al., 2008; Mayo et al., 2017; McKay et al., 2020; Wigman et al., 2012).

Non-interpersonal trauma

The findings regarding no significant difference between the three groups in prevalence of lifetime non-interpersonal trauma are, although not directly comparable, in line with a previous study examining the relationship between types of childhood trauma and development of psychotic symptoms in a sample of first-episode psychosis (Haahr et al., 2018). However, studies concerning associations between non-interpersonal trauma and later development of psychosis are inconsistent (Arseneault et al., 2011; Galletly et al., 2011; Gibson et al., 2016; Haahr et al., 2018; Stain et al., 2014). Our findings regarding any non-interpersonal trauma could suggest that non-interpersonal trauma is more prevalent across the three groups of investigation and independent of familial high risk status compared with interpersonal trauma, which are more frequent in high risk families.

Compared with other items regarding non-interpersonal traumatic events, we found a high response rate for the item reporting **'**confrontation with traumatic news', for example someone in your close family, such as grandparents, who had died or was seriously ill. A sensitivity analysis leaving that item out, did not change any results, but made the risk of experiencing any trauma even higher in the FHR-groups. This could be interpreted as loss of grandparents or severe somatic illness in the close family are a more universal trauma and to a lesser degree dependent on parental mental illness, compared with other kinds of trauma.

Strengths and limitations

The study has several strengths including the longitudinal, prospective design, assessing childhood trauma with multiple assessments during childhood, using both the child and parent reported data, reducing the risk of inaccuracy in memory recall. Another strength is the large sample size and narrow age range of our cohort. Furthermore, childhood trauma was assessed with a standardized, validated semi-structured clinical interview conducted by trained clinicians blinded to high risk status and prior

data concerning the child. Finally, to our knowledge this is the first study to assess childhood trauma among children at FHR-SZ and thus the first to include both children at FHR-SZ and FHR-BP compared with PBCs.

This study also has some limitations. Firstly, K-SADS-PL PTSD-section is not as extensive as other childhood trauma measures. Any childhood trauma and any interpersonal trauma were estimated with a binary measure, reporting the presence or absence of any trauma or any interpersonal trauma. Thus, we were not able to determine whether exposure to interpersonal trauma were related to an individual close to the child or not, where a close exposure to interpersonal trauma predicts are more severe outcome compared with not close (Haahr et al., 2018; Stain et al., 2014). Furthermore, it was not possible to calculate OR on item level for each type of trauma exposure due to lack of power. Evaluation of repeated episodes, frequency, duration, and severity of a certain type of trauma was not possible, and a score of number of types of trauma exposure represents the score of number of different types of trauma not total number of traumatic events experienced. Although parent and child interviews were conducted separately, studies have shown that children due to loyalty to their parents may underreport parental maltreatment and that parents generally reports less maltreatment than their children (Koenders et al., 2020). Using the K-SADS-PL PTSD-section, we were not able to include parental psychopathology as childhood trauma. Finally, other parental disorders besides schizophrenia or bipolar disorder may affect the prevalence of trauma exposure. Future studies could examine the effect of any parental mental illness on exposure of childhood trauma.

CONCLUSIONS

Children at familial high risk of schizophrenia or bipolar disorder have an elevated risk of exposure to childhood trauma including increased number of trauma types and interpersonal trauma. These findings suggest that not only are these children genetically at risk, but they are also at additional environmental risk for later development of severe mental illness. Trauma exposure seems to be stable across childhood, which emphasizes the need for early detection to protect these children from exposure to trauma and to develop intervention strategies before potential onset of mental illness.

More studies of trauma exposure among children at familial high risk as well as follow-up throughout adulthood are of importance to explore correlation of trauma exposure and onset of mental illness in children at both genetically and environmental risk for severe mental illness. Furthermore, future studies within this cohort should elucidate whether interpersonal trauma predicts mental illness including PTSD and stress- and adjustment disorder more than non-interpersonal trauma exposure.

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CONFLICT OF INTEREST

All authors declare no conflict of interest.

AUTHOR CONTRIBUTION

Julie Marie Brandt: Formal analysis; Investigation; Methodology; Validation; Visualization; Writing – original draft; Writing – review & editing. **Nicoline Hemager:** Investigation; Methodology; Project administration; Supervision; Validation; Visualization. **Maja Gregersen:** Investigation; Methodology; Validation; Visualization. **Anne Søndergaard:** Investigation; Validation; Visualization. **Mette Falkenberg Krantz:** Investigation; Validation; Visualization. **Jessica**

Ohland: Data curation; Software; Validation. **Martin Wilms:** Investigation; Validation. **Sinnika Birkehøj Rohd:** Investigation; Validation. **Carsten Hjorthøj:** Formal analysis; Methodology. **Lotte Veddum:** Investigation; Validation; Visualization. **Christina Bruun Knudsen:** Investigation; Validation; Visualization. **Anna Krogh Andreassen:** Investigation; Validation; Visualization. **Aja Greve:** Investigation; Project administration; Validation; Visualization. **Katrine Søborg Spang:** Investigation; Validation; Visualization. **Camilla Austa Christiani:** Investigation; Validation; Visualization. **Ditte Ellersgaard:** Investigation; Validation; Visualization. **Birgitte Klee Burton:** Investigation; Validation; Visualization. **Ditte Lou Gantriis:** Investigation; Validation; Visualization. **Vibeke Bliksted:** Project administration; Supervision; Validation. **Ole Mors:** Conceptualization; Funding acquisition; Project administration; Resources; Supervision; Validation. **Kerstin Jessica Plessen:** Conceptualization; Funding acquisition; Project administration; Supervision. **Jens Richardt Møllegaard Jepsen:** Conceptualization; Funding acquisition; Investigation; Project administration; Supervision. **Merete Nordentoft:** Conceptualization; Funding acquisition; Methodology; Project administration; Resources; Supervision; Visualization. **Anne Amalie Elgaard Thorup:** Conceptualization; Funding acquisition; Investigation; Methodology; Project administration; Supervision; Validation; Visualization.

DATA AVAILABILITY STATEMENT

According to GDPR legislation, individual-level data cannot be shared, but researchers may be granted access to corporate with our project upon application and approval.

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REFERENCES

Aas, M., Pizzagalli, D. A., Laskemoen, J. F., Reponen, E. J., Ueland, T., Melle, I., Agartz, I., Steen, N. E., & Andreassen, O. A. (2019). Elevated hair cortisol is associated with childhood maltreatment and cognitive impairment in schizophrenia and in bipolar disorders. *Schizophrenia Research*, *213*, 65–71. https://doi.org/10.1016/j.schres.2019.01.011

Arseneault, L., Cannon, M., Fisher, H. L., Polanczyk, G., Moffitt, T. E., & Caspi, A. (2011). Childhood trauma and children's emerging psychotic symptoms: A genetically sensitive longitudinal cohort study. *American Journal of Psychiatry*, *168*(1), 65–72. https://doi.org/10.1176/appi.ajp.2010.10040567

Belsky, J. (2013). Differential susceptibility to environmental influences. *International Journal of Child Care and Education Policy*, *7*(2), 15–31. https://doi.org/10.1007/2288-6729-7-2-15

Belsky, J., & Pluess, M. (2009). Beyond diathesis stress: Differential susceptibility to environmental influences. *Psychological Bulletin*, *135*(6), 885–908. https://doi.org/10.1037/a0017376

Croft, J., Heron, J., Teufel, C., Cannon, M., Wolke, D., Thompson, A., Houtepen, L., & Zammit, S. (2019). Association of trauma type, age of exposure, and frequency in childhood and adolescence with psychotic experiences in early adulthood. *JAMA Psychiatry*, *76*(1), 79–86. https://doi.org/10.1001/jamapsychiatry.2018.3155

Cutajar, M. C., Mullen, P. E., Ogloff, J. R. P., Thomas, S. D., Wells, D. L., & Spataro, J. (2010). Schizophrenia and other psychotic disorders in a cohort of sexually abused children. *Archives of General Psychiatry*, *67*(11), 1114–1119. https://doi.org/10.1001/archgenpsychiatry.2010.147

Duffy, A., Alda, M., Trinneer, A., Demidenko, N., Grof, P., & Goodyer, I. M. (2007). Temperament, life events, and psychopathology among the offspring of bipolar parents. *European Child and Adolescent Psychiatry*, *16*(4), 222–228. https://doi.org/10.1007/s00787-006-0592-x

Ellersgaard, D., Plessen, K. J., Jepsen, J. R., Spang, K. S., Hemager, N., Burton, B. K., Jerlang Christiani, C., Gregersen, M., Søndergaard, A., Uddin, M. J., Poulsen, G., Greve, A., Gantriis, D., Mors, O., Nordentoft, M., & Elgaard Thorup, A. A. (2018). 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*, *17*(2), 210–219. https://doi.org/10.1002/wps.20527

Fisher, H. L., Jones, P. B., Fearon, P., Craig, T. K., Dazzan, P., Morgan, K., Hutchinson, G., Doody, G. A., McGuffin, P., Leff, J., Murray, R. M., & Morgan, C. (2010). The varying impact of type, timing and frequency of exposure to childhood adversity on its association with adult psychotic disorder. *Psychological Medicine*, *40*(12), 1967–1978. https://doi.org/10.1017/S0033291710000231

Fisher, H. L., McGuffin, P., Boydell, J., Fearon, P., Craig, T. K., Dazzan, P., Morgan, K., Doody, G. A., Jones, P. B., Leff, J., Murray, R. M., & Morgan, C. (2014). Interplay between childhood physical abuse and familial risk in the onset of psychotic disorders. *Schizophrenia Bulletin*, *40*(6), 1443–1451. https://doi.org/10.1093/schbul/sbt201

Galletly, C., Van Hooff, M., & McFarlane, A. (2011). Psychotic symptoms in young adults exposed to childhood trauma—A 20year follow-up study. *Schizophrenia Research*, *127*(1-3), 76–82. https://doi.org/10.1016/j.schres.2010.12.010

Gantriis, D., Thorup, A., Harder, S., Greve, A., Henriksen, T., Zahle, K. et al. (2019) Home visits in the Danish High Risk and Resilience Study – VIA 7 : assessment of the home environment of 508 7-year-old children born to parents diagnosed with schizophrenia or bipolar disorder. 1–9.

Gibson, L. E., Alloy, L. B., & Ellman, L. M. (2016). Trauma and the psychosis spectrum: A review of symptom specificity and explanatory mechanisms. *Clinical Psychology Review*, *49*, 92–105. https://doi.org/10.1016/j.cpr.2016.08.003

Goldstein, B. I., Shamseddeen, W., Axelson, D. A., Kalas, C., Monk, K., Brent, D. A., Kupfer, D. J., & Birmaher, B. (2010). Clinical, demographic, and familial correlates of bipolar spectrum disorders among offspring of parents with bipolar disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*, *49*(4), 388–396. https://doi.org/10.1016/j.jaac.2010.01.009

Goodman, G. S., Quas, J. A., Goldfarb, D., Gonzalves, L., & Gonzalez, A. (2019). Trauma and long-term memory for childhood events: Impact matters. *Child Development Perspectives*, *13*(1), 3–9. https://doi.org/10.1111/cdep.12307

Gregersen, M., Søndergaard, A., Brandt, J. M., Ellersgaard, D., Birkehøj Rohd, S., Hjorthøj, C., Ohland, J., Krantz, M. F., Wilms, M., Andreassen, A. K., Knudsen, C. B. Veddum, L., Greve, A., Bliksted, V., Mors, O., Clemmensen, L., Møllegaard Jepsen, J. R., Nordentoft, M., Hemager, N., & Thorup, A. A. E. (2021). 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. *Journal of Child Psychology and Psychiatry*. https://doi.org/10.1111/jcpp.13548

Haahr, U. H., Larsen, T. K., Simonsen, E., Rund, B. R., Joa, I., Rossberg, J. I., Johannessen, J. O., Langeveld, J., Evensen, J., Trauelsen, A. M. H., Vaglum, P., Opjordsmoen, S., Hegelstad, W. V., Friis, S., McGlashan, T., & Melle, I. (2018). Relation between premorbid adjustment, duration of untreated psychosis and close interpersonal trauma in first-episode psychosis. *Early Interv Psychiatry*, *12*(3), 316–323. https://doi.org/10.1111/eip.12315

Hameed, M. A., & Lewis, A. J. (2016). Offspring of parents with Schizophrenia: A systematic review of developmental features across childhood. *Harvard Review of Psychiatry*, *24*(2), 104–117. https://doi.org/10.1097/HRP.0000000000000076

Heim, C., Jeffrey Newport, D., Heit, S., Graham, Y. P., Wilcox, M., Bonsall, R. et al. (2000). Pituitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. *JAMA*, *284*(5), 592–597. https://doi.org/10.1001/jama.284.5.592

Hosman, C. M. H., van Doesum, K. T. M., & van Santvoort, F. (2009). Prevention of emotional problems and psychiatric risks in children of parents with a mental illness in the Netherlands: I. The scientific basis to a comprehensive approach. *Australian e-Journal for the Advancement of Mental Health*, *8*(3), 250–263. https://doi.org/10.5172/jamh.8.3.250

Jaffee, S. R., Moffitt, T. E., Caspi, A., Taylor, A., & Arseneault, L. (2002). Influence of adult domestic violence on children's internalizing and externalizing problems: An Environmentally informative twin study. *Journal of the American Academy of Child & Adolescent Psychiatry*, *41*(9), 1095–1103. https://doi.org/10.1097/00004583-200209000-00010

Johnson, J. G., Cohen, P., Chen, H., Kasen, S., & Brook, J. S. (2006). Parenting behaviors associated with risk for offspring personality disorder during adulthood. *Archives of General Psychiatry*, *63*(5), 579–587. https://doi.org/10.1001/archpsyc.63.5.579

Kaufman, J., Birmaher, B., Brent, D., Rao, U., Flynn, C., Moreci, P., Williamson, D. & Ryan, N. (1997). Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): Initial Reliability and Validity Data. *Journal of the American Academy of Child & Adolescent Psychiatry*, *36*(7), 980–988. https://doi.org/10.1097/00004583-199707000-00021

Kelleher, I., Harley, M., Lynch, F., Arseneault, L., Fitzpatrick, C., & Cannon, M. (2008). Associations between childhood trauma, bullying and psychotic symptoms among a school-based adolescent sample. *British Journal of Psychiatry*, *193*(5), 378–382. https://doi.org/10.1192/bjp.bp.108.049536

Kelleher, I., Keeley, H., Corcoran, P., Ramsay, H., Wasserman, C., Carli, V., Sarchiapone, M., Hoven, C., Wasserman, D., & Cannon, M. (2013). Childhood trauma and psychosis in a prospective cohort study: Cause, effect, and directionality. *American Journal of Psychiatry*, *170*(7), 734–741. https://doi.org/10.1176/appi.ajp.2012.12091169

Kline, E., Millman, Z. B., Denenny, D., Wilson, C., Thompson, E., Demro, C., Connors, K., Bussell, K., Reeves, G., & Schiffman, J. (2016). Trauma and psychosis symptoms in a sample of help-seeking youth. *Schizophrenia Research*, *175*(1-3), 174–179. https://doi.org/10.1016/j.schres.2016.04.006

Koenders, M. A., Mesman, E., Giltay, E. J., Elzinga, B. M., & Hillegers, M. H. J. (2020). Traumatic experiences, family functioning, and mood disorder development in bipolar offspring. *British Journal of Clinical Psychology*, *59*(3), 277–289. https://doi.org/10.1111/bjc.12246

Lecei, A., Decoster, J., De Hert, M., Derom, C., Jacobs, N., Menne-Lothmann, C., van Os, J., Thiery, E., Rutten, B. P. F., Wichers, M., & van Winkel, R. (2019). Evidence that the association of childhood trauma with psychosis and related psychopathology is not explained by gene-environment correlation: A monozygotic twin differences approach. *Schizophrenia Research*, *205*, 58–62. https://doi.org/10.1016/j.schres.2018.05.025

Lepistö, S., Luukkaala, T., & Paavilainen, E. (2011). Witnessing and experiencing domestic violence: A descriptive study of adolescents. *Scandinavian Journal of Caring Sciences*, *25*(1), 70–80. https://doi.org/10.1111/j.1471-6712.2010.00792.x

Leverich, G. S., McElroy, S. L., Suppes, T., Keck, P. E., Denicoff, K. D., Nolen, W. A., Altshuler, L. L., Rush, A. J., Kupka, R., Frye, M. A., Autio, K. A., & Post, R. M. (2002). Early physical and sexual abuse associated with an adverse course of bipolar illness. *Biological Psychiatry*, *51*(4), 288–297. https://doi.org/10.1016/S0006-3223(01)01239-2

Lupien, S. J., McEwen, B. S., Gunnar, M. R., & Heim, C. (2009). Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nature Reviews Neuroscience*, *10*(6), 434–445. https://doi.org/10.1038/nrn2639

Majer, M., Nater, U. M., Lin, J. M. S., Capuron, L., & Reeves, W. C. (2010). Association of childhood trauma with cognitive function in healthy adults: A pilot study. *BMC Neurology*, *10*(61), 1–10. https://doi.org/10.1186/1471-2377-10-61

Mauritz, M. W., Goossens, P. J. J., Draijer, N., & van Achterberg, T. (2013). Prevalence of interpersonal trauma exposure and trauma-related disorders in severe mental illness. *European Journal of Psychotraumatology*, *4*(1), 1–16. https://doi.org/10.3402/ejpt.v4i0.19985

Mayo, D., Corey, S., Kelly, L. H., Yohannes, S., Youngquist, A. L., Stuart, B. K., Niendam, T. A., & Loewy, R. L. (2017). The role of trauma and stressful life events among individuals at clinical high risk for psychosis: A review. *Frontiers in Psychiatry*, *8*(55), 1–17. https://doi.org/10.3389/fpsyt.2017.00055

McKay, M. T., Cannon, M., Chambers, D., Conroy, R. M., Coughlan, H., Dodd, P. et al. (2020). Childhood trauma and adult mental disorder: A systematic review and meta-analysis of longitudinal cohort studies. *Acta Psychiatrica Scandinavica*, *2020*, 1–17.

Morelli, N., Fogler, J., Tembulkar, S., Graber, K., Lincoln, S. H., Bosquet Enlow, M., Gonzalez-Heydrich, J. & D'Angelo, E. J. (2019). Potentially traumatic events in youth with and at clinical high risk for psychosis. *Early Intervention in Psychiatry*, *13*(4), 805–809. https://doi.org/10.1111/eip.12565

Mors, O., Perto, G. P., & Mortensen, P. B. (2011). The Danish psychiatric central research register. *Scandinavian Journal of Public Health*, *39*(7 Suppl), 54–57. https://doi.org/10.1177/1403494810395825

Nelson, C. A., & Gabard-Durnam, L. J. (2020). Early adversity and critical periods: Neurodevelopmental consequences of violating the expectable environment. *Trends in Neurosciences*, *43*(3), 133–143. https://doi.org/10.1016/j.tins.2020.01.002

Okkels, N., Trabjerg, B., Arendt, M., & Pedersen, C. B. (2017). Traumatic stress disorders and risk of subsequent schizophrenia spectrum disorder or bipolar disorder: A nationwide cohort study. *Schizophrenia Bulletin*, *43*(1), 180–186. https://doi.org/10.1093/schbul/sbw082

Pedersen, C. B., Gøtzsche, H., & Møller, J. O. M. P. (2006). The Danish civil registration system: A cohort of eight million persons. *Danish Medical Bulletin*, *53*(4), 441–449.

Pedrini, L., Ferrari, C., Lanfredi, M., Bellani, M., Porcelli, S., Caletti, E., Sala, M., Rossetti, M. G., Piccin, S., Dusi, N., Balestrieri, M., Perlini, C., Lazzaretti, M., Mandolini, G. M., Pigoni, A., Boscutti, A., Bonivento, C., Serretti, A., Rossi, R., & Brambilla, P. (2021). The association of childhood trauma, lifetime stressful events and general psychopathological symptoms in euthymic bipolar patients and healthy subjects. *Journal of Affective Disorders*, *289*, 66–73. https://doi.org/10.1016/j.jad.2021.04.014

Popovic, D., Schmitt, A., Kaurani, L., Senner, F., Papiol, S., Malchow, B., Fischer, A., Schulze, T. G., Koutsouleris, N., & Falkai, P. (2019). Childhood trauma in Schizophrenia: Current findings and research perspectives. *Frontiers in Neuroscience*, *13*, 1–14. https://doi.org/10.3389/fnins.2019.00274

Quidé, Y., Tozzi, L., Corcoran, M., Cannon, D. M., & Dauvermann, M. R. (2020). The impact of childhood trauma on developing bipolar disorder: Current understanding and ensuring continued progress. *Neuropsychiatric Disease and Treatment*, *16*, 3095–3115.

Rasic, D., Hajek, T., Alda, M., & Uher, R. (2014). Risk of mental illness in offspring of parents with schizophrenia, bipolar disorder, and major depressive disorder: A meta-analysis of family high-risk studies. *Schizophrenia Bulletin*, *40*(1), 28–38. https://doi.org/10.1093/schbul/sbt114

Read, J., Van Os, J., Morrison, A. P., & Ross, C. A. (2005). Childhood trauma, psychosis and schizophrenia: A literature review with theoretical and clinical implications. *Acta Psychiatrica Scandinavica*, *112*(5), 330–350. https://doi.org/10.1111/j.1600-0447.2005.00634.x

Reupert, A., & Maybery, D. (2016). What do we know about families where parents have a mental illness? A Systematic Review. *Child & Youth Services*, *37*(2), 98–111. https://doi.org/10.1080/0145935X.2016.1104037

Rutter, M., & Quinton, D. (1984). Parental psychiatric disorder: Effects on children. *Psychological Medicine*, *14*(4), 853–880. https://doi.org/10.1017/S0033291700019838

Sandstrom, A., Sahiti, Q., Pavlova, B., & Uher, R. (2019). Offspring of parents with schizophrenia, bipolar disorder, and depression: a review of familial high-risk and molecular genetics studies. *Psychiatric Genetics*, *29*(5), 160–169. https://doi.org/10.1097/YPG.0000000000000240

Schreuder, M. M., Vinkers, C. H., Mesman, E., Claes, S., Nolen, W. A., & Hillegers, M. H. J. (2016). Childhood trauma and HPA axis functionality in offspring of bipolar parents. *Psychoneuroendocrinology*, *74*, 316–323. https://doi.org/10.1016/j.psyneuen.2016.09.017

Stain, H. J., Brønnick, K., Hegelstad, W. T. V., Joa, I., Johannessen, J. O., Langeveld, J., Mawn, L., & Larsen, T. K. (2014). Impact of interpersonal trauma on the social functioning of adults with first-episode psychosis. *Schizophrenia Bulletin*, *40*(6), 1491–1498. https://doi.org/10.1093/schbul/sbt166

Thorup, A. A. E., Hemager, N., Søndergaard, A., & Gregersen, M. (2018). 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 A. *Frontiers in Psychiatry 9*, 1–16.

Thorup, A. A. E., Jepsen, J. R., Ellersgaard, D. V., Burton, B. K., Christiani, C. J., Hemager, N., Skjærbæk, M., Ranning, A., Spang, K. S., Gantriis, D. L., Greve, A. N., Zahle, K. K., Mors, O., Plessen, K. J., & Nordentoft, M. (2015). The Danish High Risk and Resilience Study – VIA 7 - a cohort study of 520 7-year-old children born of parents diagnosed with either schizophrenia, bipolar disorder or neither of these two mental disorders. *BMC Psychiatry*, *15*(1), 1–15. https://doi.org/10.1186/s12888-015-0616-5

Trotta, A., Murray, R. M., & Fisher, H. L. (2015). The impact of childhood adversity on the persistence of psychotic symptoms: A systematic review and meta-analysis. *Psychological Medicine*, *45*(12), 2481–2498. https://doi.org/10.1017/S0033291715000574

Varese, F., Smeets, F., Drukker, M., Lieverse, R., Lataster, T., Viechtbauer, W., Read, J., van Os, J., & Bentall, R. P. (2012). Childhood adversities increase the risk of psychosis: A meta-analysis of patient-control, prospective-and cross-sectional cohort studies. *Schizophrenia Bulletin*, *38*(4), 661–671. https://doi.org/10.1093/schbul/sbs050

Walker, E., Kestler, L., Bollini, A., & Hochman, K. M. (2004). Schizophrenia: Etiology and course. *Annual Review of Psychology*, *55*, 401–430. https://doi.org/10.1146/annurev.psych.55.090902.141950

Walsh, C., MacMillan, H., & Jamieson, E. (2002). The relationship between parental psychiatric disorder and child physical and sexual abuse: Findings from the Ontario health supplement. *Child Abuse & Neglect*, *26*(1), 11–22. https://doi.org/10.1016/S0145-2134(01)00308-8

Watson, S., Gallagher, P., Dougall, D., Porter, R., Moncrieff, J., Ferrier, I. N. & Young, A. H. (2014). Childhood trauma in bipolar disorder. *Australian and New Zealand Journal of Psychiatry*, *48*(6), 564–570. https://doi.org/10.1177/0004867413516681

Wigman, J. T. W., van Winkel, R., Ormel, J., Verhulst, F. C., van Os, J., & Vollebergh, W. A. M. (2012). Early trauma and familial risk in the development of the extended psychosis phenotype in adolescence. *Acta Psychiatrica Scand*, *126*(4), 266–273. https://doi.org/10.1111/j.1600-0447.2012.01857.x

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