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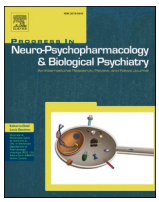

Hair cortisol concentrations and perceived stress in 7-year-old children at familial high-risk of schizophrenia or bipolar disorder

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ABSTRACT

Background: Dysregulation of the HPA-axis, perceived stress and interpersonal trauma are associated with an elevated risk for schizophrenia and bipolar disorder. Being at familial high-risk of these two mental disorders also constitutes an increased risk. In this study, we aimed to investigate hair cortisol concentrations and perceived stress among 7-year-old children at familial high-risk of schizophrenia (FHR-SZ), bipolar disorder (FHR-BP), and population-based controls (controls).

Methods: A total of 515 children (mean age 7.8, SD 0.2) from baseline assessment of the Danish High Risk and Resilience Study – VIA 7 participated in this study. Hair cortisol concentrations were analyzed among 322 children (FHR-SZ; $N = 111$, FHR-BP; $N = 82$, controls; $N = 129$). Perceived stress was assessed with the Daily Life Stressor Scale including 512 children (FHR-SZ; $N = 195$, FHR-BP; $N = 118$, controls; $N = 199$). Interpersonal trauma was measured with face-to-face interviews.

Results: Seven-year-old children at FHR-SZ or FHR-BP did not have a higher level of hair cortisol concentrations compared with controls (FHR-SZ: mean: 5.10, 95%CI 3.69–6.52; FHR-BP: mean: 5.01, 95%CI 3.27–6.72; controls: mean: 4.51, 95%CI 3.61–5.40; $p = 0.77$). Self-reported perceived stress was higher among children at FHR-SZ and FHR-BP compared with controls (FHR-SZ: mean: 12.09, 95%CI 10.99–13.19; FHR-BP: mean: 10.69, 95% CI 9.38–11.99; controls: mean: 8.90, 95%CI 8.13–9.68; $p < 0.001$). There was no significant association between hair cortisol concentrations and perceived stress ($p = 0.84$). Exploratory analyses revealed that interpersonal trauma exposure was neither associated with elevated hair cortisol nor perceived stress.

Conclusions: Children at FHR-SZ and FHR-BP did not exhibit higher levels of hair cortisol concentrations at age 7, while both FHR-groups had higher level of self-reported perceived stress compared with controls. Early attention to stress in children at FHR is crucial and these vulnerabilities should be targeted in future interventions studies.

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1. Introduction

Stress is an important factor in the etiology of severe mental illness including schizophrenia and bipolar disorder (Aas et al., 2019; De Barrera et al., 2019; Schreuder et al., 2016; Söder et al., 2019; Streit et al., 2016; Walker et al., 2008). Studies of adults with schizophrenia and bipolar disorder report higher levels of stress in individuals with these illnesses compared with healthy controls (Coello et al., 2019; Streit et al., 2016), and environmental stressors from daily life challenges to trauma contributes to impaired tolerance towards stress and increases the risk for onset and relapse of bipolar disorder and psychosis spectrum disorders (Cullen et al., 2014a; Fisher et al., 2014; Howes et al., 2017; Streit et al., 2016). In childhood, exposure to stress, and especially prolonged stress, is associated with an increased risk of mental health consequences (Fuchs et al., 2018; Vanaelst et al., 2012a).

The neural diathesis-stress model proposes that along with environmental factors, biological vulnerability contributes to an increased risk for later development of mental illness (Cullen et al., 2014a; Quidé et al., 2020; Schreuder et al., 2016; Walker et al., 2008). Together with the assumption that having a parent with severe mental illness can cause elevated levels of stress exposure during childhood (Ellenbogen et al., 2010; Schreuder et al., 2016), this means that children of parents with schizophrenia or bipolar disorder will be at both genetically and environmentally increased risk of developing mental illness.

Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and its end product cortisol is a preferred biomarker in the measurement of biological stress and is associated with both schizophrenia and bipolar disorder (Coello et al., 2019; Streit et al., 2016). Cortisol can be measured through serum, saliva, urine or hair (De Barrera et al., 2019; Simmons et al., 2016; Vanaelst et al., 2012a). Where serum, saliva and urine cortisol primarily measure acute responses that can vary with a variety of factors including food intake, sleep and acute stress (Coello et al., 2019; Stalder and Kirschbaum, 2012), hair cortisol is an increasingly used marker that provides a reliable, long-term cortisol measure. Furthermore, assessment of hair cortisol includes a rapid, easy and a non-invasive sampling procedure where cortisol concentration is unaffected by sampling procedure (De Barrera et al., 2019; Coello et al., 2019; Fuchs et al., 2018; Gray et al., 2018; Stalder et al., 2017; Stalder and Kirschbaum, 2012). To date, the majority of studies on hair cortisol concentrations are derived from adult samples, and even though studies of hair cortisol concentrations in children are emerging, they are still limited (Fuchs et al., 2018; Gray et al., 2018; Noppe et al., 2014; Stalder et al., 2017; Vanaelst et al., 2012b).

Further, while there is increasing evidence of HPA axis hyperactivation and elevated hair cortisol concentrations among adults with schizophrenia or bipolar disorder (Coello et al., 2019; Söder et al., 2019; Streit et al., 2016), studies of hair cortisol among children at familial risk for these two disorders, while still in childhood, are lacking. Studies of other types of cortisol measures are sparse and with heterogenous results. One study of individuals at familial risk of psychosis (age range 18–65 years) did not find higher hair cortisol concentrations in at risk individuals, compared with controls (Söder et al., 2019). Another study of children with first degree relatives with schizophrenia reported lower salivary cortisol compared with low risk children (age range 11–14 years) (Cullen et al., 2014b). In a longitudinal study, children of parents with bipolar disorder displayed elevated levels of daytime salivary cortisol with three assessments from age 16 to 20 years (Ellenbogen et al., 2006, 2010; Ostiguy et al., 2011) whereas another study of children (mean age 28, age range 24–32) with parents with bipolar disorder, found no differences in diurnal salivary cortisol compared with controls (Schreuder et al., 2016).

Along with cortisol measurements, questionnaires measuring perceived stress have been shown to be a valuable stress indicator (De Barrera et al., 2019; Vanaelst et al., 2012a). Findings among FHR-samples, individuals at clinical risk for psychosis and individuals with schizophrenia and bipolar disorder all show increased levels of perceived stress (Cullen et al., 2014a; DeVylder et al., 2013; Streit et al., 2016). Of note, despite both hair cortisol and questionnaires being validated measures of stress, findings of an association between these two types of measures are inconsistent. Some studies report a correlation between biological and perceived stress whereas others do not (De Barrera et al., 2019; Rietschel et al., 2016; Stalder et al., 2017).

Childhood trauma has been associated with persisting consequences for the HPA-axis activity, but with observations of both hyper- and hypoactivity (De Bellis and Zisk, 2014; Schreuder et al., 2016). Among adults with schizophrenia and bipolar disorder there is evidence for increased hair cortisol concentrations if exposed to childhood trauma (Aas et al., 2019; Staufenbiel et al., 2014). However, studies examining if childhood trauma differentially affects salivary or hair cortisol concentrations in adult offspring at familial risk of psychosis or bipolar disorder compared with controls are limited and have inconsistent findings (Schreuder et al., 2016; Söder et al., 2019). Furthermore, a recent study reported that only the most severe stressors such as child abuse were predictive of increased hair cortisol concentrations (Söder et al., 2019). Moreover, interpersonal trauma exposure, trauma with intention to harm such as sexual abuse, physical abuse, and domestic violence, have been associated with the a higher risk of psychopathology compared with accidental trauma (Croft et al., 2019; Gibson et al., 2016).

Investigating biological as well as perceived stress among children at familial risk of schizophrenia or bipolar disorder can provide an insight into possible pathways towards illness onset. However, no other studies have examined hair cortisol concentrations and perceived stress during early childhood in children at familial risk for developing schizophrenia or bipolar disorder.

The aims of this study were to 1) Examine hair cortisol concentrations among children at familial high-risk of schizophrenia or bipolar disorder compared with controls. 2) Investigate level of perceived stress in children at familial high-risk of schizophrenia or bipolar disorder compared with controls. 3) Examine associations between concentrations of hair cortisol and level of perceived stress. And 4) for exploratory analyses, examine if exposure to interpersonal trauma during age 0–7 years was associated with increased hair cortisol concentration and levels of perceived stress at age 7 among children with familial high-risk of schizophrenia, bipolar disorder, and controls.

2. Materials and methods

The current study is a cross-sectional study with baseline data from the ongoing, longitudinal, population-based study The Danish High Risk and Resilience Study – VIA7 (hereafter the VIA7 study). The original cohort consists of 522 7-year-old children born to familial high-risk of schizophrenia spectrum disorder ($N = 202$; ICD-10 codes: F20, F22 and F25, or ICD- 8 codes 295, 297, 298.29, 298.39, 298.89 and 298.99), bipolar disorder ($N = 120$; ICD-10 codes: F30 and F31, or ICD-8 codes 296.19 and 296.39) or population-based controls ($N = 200$). The cohort is examined at face-to-face follow-ups every fourth year throughout childhood with baseline assessment at age 7.

2.1. Participants

Inclusion criteria were children at 7 years of age with at least one parent with a register-based diagnosis of schizophrenia spectrum disorder (FHR-SZ) or bipolar disorder (FHR-BP), and population-based controls (hereafter controls). Children in the control group were children born to parents with neither of these two disorders. In case one parent had a register diagnosis of schizophrenia and the other parent had a register diagnosis of bipolar disorder, the child was allocated to the FHR-SZ group due to the ICD-10 diagnostic hierarchy. All children and parents had to be born and living in Denmark. Controls were matched to children at FHR-SZ on sex, municipality, and age. Children at FHR-BP were an unmatched sample, but comparable to the two other

groups on sex and age at inclusion. Baseline assessment took place from January 1, 2013, to January 31, 2016. Children in the study could have mental disorders or medical conditions prior to participation of the study. The study design and participants are described in detail elsewhere (Thorup et al., 2015).

2.2. Procedures

The study was approved by the Danish Data Protection Agency. The Danish Committee on Health Research Ethics evaluated the VIA7 study and deemed formal approval unnecessary due to the observational nature of the study. Hair samples were collected as a part of the Gene-Environment Study Protocol who obtained formal approval (00466 PSV-2009-0). Written and informed consent was obtained from all parents or other legal guardians of the child and all children provided informed assent prior to assessment.

2.3. Measures

2.3.1. Hair cortisol concentrations

Hair samples at the size of half a pencil (approximately 10 mg hair) were collected from or as close as possible to the vertex posterior region of the scalp, where growth rates are most consistent (Pragst and Balikova, 2006; Stalder and Kirschbaum, 2012). The samples were carefully cut with scissors as close to the scalp as possible by trained assessors that were either psychologists, medical doctors, or research nurses. The scalp-near ends of the samples were marked with cotton-yarn, placed in aluminum foil, and stored in a dark and dry biobank at room temperature, until analyses were undertaken.

Analyses were conducted at the Kirschbaum Laboratory, Dresden (Stalder and Kirschbaum, 2012). Hair segments were cut to a length of up to 3 cm measured from the scalp-end of the sample, representing a period of up to 3 months prior to sampling, based on a growth rate of approximately 1 cm/month (Stalder and Kirschbaum, 2012; Wennig, 2000). Three-hundred-and-one samples had a length of 3 cm. Twenty-one samples had a length between 1 cm to 2.5 cm. The weight for all samples were 7.5 mg after preparation for analyses. All samples were included in the analyses. Cortisol was extracted from the hair as described by Davenport et al. (2006) (Davenport et al., 2006). In brief, the hair was initially placed in 10 ml glass containers and washed in 2.5 ml isopropanol. The tubes were gently rotated for 3 min and afterwards decanted. The wash was repeated twice and afterwards samples dried for 12 h. For steroid extraction, hair segments were added to a 2 ml tube with 1800 μl methanol and stored for 18 h at room temperature. Samples were then spun in a microcentrifuge at 10.000 rpm for 2 min. Afterwards 1 ml of clear supernatant was transferred to a new 2 ml tube. The alcohol was evaporated at 50 degrees Celsius under constant steam of nitrogen. When completely dry, the samples were reconstituted with 150 μl double-distilled water. Fifty μl was used for cortisol determination using commercially available immunoassay with chemiluminescence detection (CLIA, IBL-Hamborg, Germany). Inter- and intra-assay variabilities were below 8%.

Laboratory personnel performing analyses were blinded towards high-risk status of the samples.

2.3.2. Perceived stress

Perceived stress was assessed using a shortened version of the self-report Daily Life Stressor Scale (hereafter DLSS) (Kearney, 1993). DLSS is a measure to assess everyday stressful events during the preceding week in individuals age 7–17 years. Out of 30 items in the original version, 14 items were selected following pilot testing. These items were translated into Danish and back translated into English. The shortened version was approved by the author behind the instrument (through personal communication). Each item represents a potentially stressful event in everyday life of the child (see online appendix S1) and items are scored on a five-point Likert scale from 0 to 4, ranging from (0) "not at all", (1) "a little", (2) "some", (3) "a lot" and to (4) "very much". A higher score represents a higher level of perceived stress and total score in the shortened version ranges from 0 to 54.

Due to the young age of the children, the items were read aloud to the children by trained assessors. All assessors were blinded to familial high-risk status of the child.

2.3.3. Other measures

Interpersonal trauma was measured with the PTSD section from the clinical interview Kiddie Schedule for Affective Disorders and Schizophrenia – Present and Lifetime Version (K-SADS-PL) (Kaufman et al., 1997). First the child, and then the primary caregiver was interviewed separately by the same assessor. They were interviewed about trauma exposure during early childhood, age 0–7 years. Exposure to interpersonal trauma (victim of a violent act, physical abuse, sexual abuse, and domestic violence) was rated as present or absent. Methods are described in detail elsewhere (Brandt et al., 2022). The Child Behavior Checklist (CBCL) (Achenbach and LA, 2001) was used to assess problem behavior, with a higher score indicating more problem behavior (range 0–226). The Children's Global Assessment Scale (C-GAS) (Shaffer et al., 1983) was used to assess the child's current level of functioning where a higher score represents higher level of functioning (range 1–100).

2.4. Statistical analyses

Background characteristics were analyzed using chi square and one-way ANOVA as appropriate.

Crosstabulations were used to calculate frequencies and percentages for level of hair cortisol concentrations and DLSS total scores. Linear trend of covariance (ANCOVA) was used to analyze mean and mean differences in hair cortisol concentration and DLSS total score depending on FHR-group. Analyses were adjusted for sex of the child.

To assess internal consistency of responses in DLSS, Cronbach's alpha was calculated and accepted on the condition of $\alpha \geq 0.70$.

Associations between DLSS total score and hair cortisol concentrations were calculated with simple linear regression. To test for interaction, the interaction term FHR-group x DLSS total score was added to the model.

For exploratory analyses, simple linear regression was used to calculate associations between any interpersonal trauma and level of hair cortisol concentration and DLSS total score, respectively. These analyses were checked for interaction by adding interaction term FHR-group x any interpersonal trauma to the models. If non-significant, the interaction term was removed from the model. Significant unadjusted analyses were adjusted for FHR-status of the child.

Level of statistical significance was set to <0.05. All analyses were performed using IBM SPSS, version 25.

3. Results

3.1. Sample characteristics

In this study 515 children provided hair samples or filled in DLSS. Initially 403 children provided hair samples for analyses, however due to technical problems in the laboratory analyzing the samples, 75 random samples had to be excluded. Five samples had to be excluded as there was not enough material for analysis. One sample was excluded by the laboratory due to risk of contamination. Thus, for analyses of hair cortisol concentrations, 322 children (FHR-SZ; $N = 111$, FHR-BP; $N = 82$, controls; $N = 129$) children provided data at age 7, equivalent with 61.7% of children from the original cohort ($N = 522$). Out of the 322 children, one child at FHR-SZ was double high-risk (FHR-SZ/SZ). Five hundred and twelve children (FHR-SZ; $N = 195$, FHR-BP; $N = 118$, controls; $N = 199$) participated in DLSS (98.1% of the total cohort). Out of the 512, eight children at FHR-SZ were at double high-risk (FHR-SZ/SZ, $N = 7$; FHR-SZ/BP, $N = 1$). Three children participated in hair

samples but not DLSS and 193 children participated in DLSS but not hair samples (Table 1).

Children participating in hair samples or DLSS did not differ regarding age of inclusion or sex (Table 1). Within the sample providing hair for analyses, there were no significant differences between the three groups on age of inclusion (mean age 7.8 SD 0.20, range 7.01–8.41, $p = 0.20$) or sex. The same accounted for the sample participating in DLSS (mean age 7.8 SD 0.21, range 6.91–8.41, $p = 0.08$).

3.2. Drop-out analyses

Analyses revealed skewed drop-out of children participating in hair samples and those who did not regarding FHR-group ($X^2(2) = 6.791$, $p = 0.03$). There was no significant difference in sex ($X^2(1) = 0.096$, $p = 0.76$), problem behavior ($F(1.492) = 0.152$, $p = 0.70$) or level of functioning ($F(1.512) = 2.690$, $p = 0.10$) of those participating in hair samples and those who did not. Children participating in DLSS did not differ significantly from the total cohort regarding FHR-group ($X^2(2) = 4.754$, $p = 0.09$), sex ($X^2(1) = 0.166$, $p = 0.68$) or problem behavior ($F(1.492) = 0.095$, $p = 0.76$). Children not participating in DLSS ($N = 5$) had significantly lower level of functioning compared with children participating in DLSS ($N = 509$) ($F(1.512) = 5.136$, $p = 0.02$).

3.3. Hair cortisol concentrations in children at familial high-risk

Observed means of hair cortisol concentrations were 5.10 (95% CI 3.69–6.52) pg/mg hair in children at FHR-SZ, 5.01 (95% CI 3.27–6.72) pg/mg hair in children at FHR-BP, and 4.51 (95% CI 3.61–5.40) pg/mg hair in controls. Hair cortisol concentrations did not differ significantly across the three groups ($p = 0.49$) (Fig. 1a, Table S1). Adjusting analyses for sex did not alter the results ($p = 0.15$, Table S2).

3.4. Perceived stress in children at familial high-risk

The items in DLSS showed good internal consistency (Cronbach's alpha = 0.762).

Children at FHR-SZ had significantly higher mean scores of perceived stress (observed mean: 12.09, 95% CI 3.69–6.52, <0.001; mean diff: 3.19, 95% CI 1.83–4.54, $p < 0.001$) compared with controls (observed mean: 8.90, 95% CI 8.13–9.68; mean diff: 1.78, 95% CI 0.22–3.34). Children at FHR-BP were at an intermediate level and likewise reported a significantly higher level of perceived stress (observed mean: 10.69, 95% CI 9.38–11.99, <0.001) compared with controls. The two high-risk groups did not differ significantly from each other (mean diff: 1.41, 95% CI -0.16 to 2.98, p = 0.08) (Fig. 1b, Table S1). Between-group differences did not change when adjusting for sex ($p = 0.77$, Table S2).

3.5. Associations between hair cortisol concentrations and perceived stress

Higher level of perceived stress was not associated with higher level of cortisol (B = 0.012, 95% CI-0.099 to 0.122, $p = 0.836$) (Fig. 2). No interaction between DLSS total score and FHR-status was found.

3.6. Exploratory analyses of associations between exposure to interpersonal trauma and hair cortisol concentrations and level of perceived stress

Children who had been exposed to interpersonal trauma between age 0–7 years, did not show a higher level of hair cortisol concentration at age 7 years compared with children who had not been exposed to interpersonal trauma during early childhood (B = 1.43, 95% CI -0.61 to 3.47, $p = 0.17$). Interaction between interpersonal trauma and FHR-status was non-significant ($p = 0.36$, Fig. 3a).

Across the sample, children who had been exposed to interpersonal trauma reported higher levels of perceived stress compared with children without interpersonal trauma exposure (B = 2.48, 95% CI 0.87 to 4.08, $p = 0.003$). Adjusting analyses for FHR-status rendered these results to non-significant (B = 1.60, 95% CI -0.04 to 3.24, $p = 0.06$). No interaction between FHR-status and interpersonal trauma on level of perceived stress was found ($p = 0.72$, Fig. 3b).

4. Discussion

Hair cortisol concentrations were not higher in FHR-SZ and FHR-BP compared with controls at age 7. Both children at FHR-SZ and FHR-BP had significantly higher levels of self-reported perceived stress compared with controls. We did not find an association between hair cortisol concentration and perceived stress. Finally, in exploratory analyses, no association between exposure to interpersonal trauma from age 0–7 years and increased level of hair cortisol concentration across the cohort at age 7 years was found. An association between interpersonal trauma and higher level of perceived stress was found across the

Table 1
Sample characteristics of 7-year-old children at FHR-SZ, FHR-BP and controls in the Danish High Risk and Resilience Study – VIA7.

					P-value for pairwise comparisons		
	FHR-SZ	FHR-BP	Controls	*P* value	FHR-SZ vs. Controls	FHR-BP vs. Controls	FHR-SZ vs. FHR-BP
Children, N[c]	198	118	199	–	–	–	–
Female, N (%)	93 (47.0%)	55 (46.6%)	92 (46.2%)	0.99[a]	–	–	–
Age at inclusion, years, mean (SD)	7.8 (0.2)	7.9 (0.2)	7.8 (0.2)	0.08[b]	–	–	–
CBCL[d] total score, mean (SD)[e]	27.3 (21.1)	23.4 (19.7)	17.0 (14.7)	**<0.001**[b]	**<0.001**	**0.004**	0.08
C-GAS[f] total score, mean (SD)[g]	68.1 (15.5)	73.6 (14.9)	77.7 (13.5)	**<0.001**[b]	**<0.001**	**0.02**	**0.002**
Any interpersonal trauma, age 0–7 years[h], N (%)[i,*]	53 (29.9%)	24 (20.3%)	10 (5.1%)	**<0.001**[a]	**<0.001**	**<0.001**	0.19

Abbreviations: FHR-SZ, children at familial high risk of schizophrenia spectrum disorders; FHR-BP, children at familial high risk of bipolar disorder. CBCL: Child Behavior Checklist; C-GAS, Children's Global Assessment Scale.

[a] Chi square test.

[b] One way ANOVA test with post hoc Least Significant Difference.

[c] Children participating in hair samples or DLSS. For hair samples 322 children participated and 512 children participated in DLSS. Three children participated in hair samples but not DLSS, and 193 children participated in DLSS but not hair samples.

[d] CBCL total score range: 0–226. Higher score indicates more problem behavior. Range of total score in this cohort: 0–103.

[e] Includes 190 children at FHR-SZ, 111 children at FHR-BP and 191 controls.

[f] C-GAS score, range 1–100. Higher score indicates higher level of function. Range in this cohort: 35–100.

[g] Includes 197 children at FHR-SZ, 118 children at FHR-BP and 197 controls.

[h] Measured with Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present Lifetime Version - PTSD section.

[i] Includes 197 children at FHR-SZ, 118 children at FHR-BP and 195 controls.

[*] Brandt et al., 2022

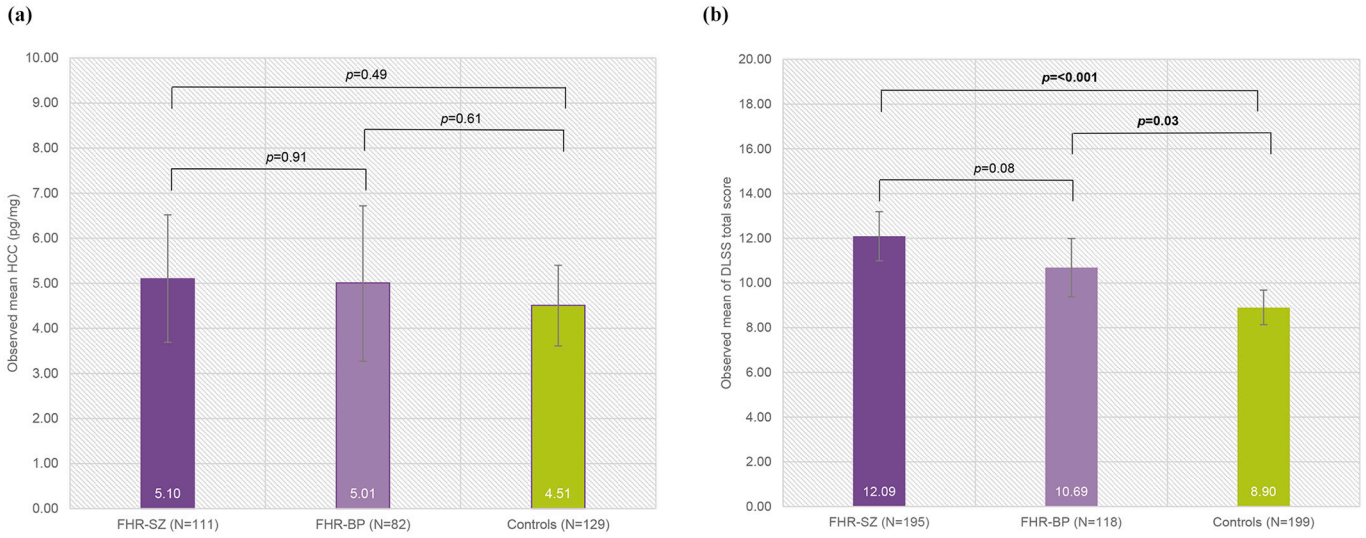

Fig. 1. a. Observed mean of hair cortisol concentrations (HCC) in 7-year-old children at FHR-SZ, FHR-BP and controls in The Danish High Risk and Resilience Study – VIA7. b. Observed mean of perceived stress (DLSS total score) in 7-year-old children at FHR-SZ, FHR-BP and controls in The Danish High Risk and Resilience Study – VIA7.
Abbreviations: FHR-SZ, children at familial high risk of schizophrenia spectrum disorders; FHR-BP, children at familial high risk of bipolar disorder.
Children participating in hair samples (N=322)
Children participating in assessment with Daily Life Stressor Scale, DLSS ($N = 512$)
95% CI represented by error bars
Significant p-values (<0.05) in bold.

sample. These differences were attenuated when adjusting for FHR-group.

Our findings indicating no differences in hair cortisol concentrations between children at FHR-SZ and FHR-BP compared with controls are in keeping with a study of hair cortisol among first-degree relatives of individuals with psychosis (age range 18–65 years) (Söder et al., 2019) and a study of offspring (age range 24–32 years) of parents with bipolar disorder and healthy controls measuring daytime salivary cortisol (Schreuder et al., 2016). Contrary to this, a longitudinal study reported elevated level of daytime salivary cortisol in children at familial high-risk of bipolar disorder compared with controls in late childhood and early adulthood (age 16 (Ellenbogen et al., 2006), age 18 (Ellenbogen et al., 2010) and 20 years (Ostiguy et al., 2011)). Similarly, a study of individuals at clinical high-risk of schizophrenia (age range 12–35 years) (Walker et al., 2013) showed elevated levels of salivary cortisol. In our study, all children were in early childhood and within the same age range (age 7), thus the alterations in results could potentially be due to age differences between the samples, as there is evidence of hair cortisol concentrations decreasing with age from birth to age 9 (Dettenborn et al., 2012; Karlén et al., 2013; Noppe et al., 2014) and afterwards increasing throughout adolescence and into the early adulthood years (Walker et al., 2013). Of note, our range of hair cortisol concentrations across the sample corresponded to that of a previous study validating reference intervals for hair cortisol concentrations among healthy children between age 6–7 years (Noppe et al., 2014). Another possible explanation for deviating results could be methodological differences in measurement of cortisol (saliva and hair samples) as previous studies comparing measurement methods are conflicting (Manenschijn et al., 2012; Stalder and Kirschbaum, 2012; Vanaelst et al., 2012b).

Taken together, further research is warranted to determine the value of cortisol in hair in children at FHR-SZ and FHR-BP. This includes disentangling whether environmental factors to a larger extent contribute to elevated cortisol levels compared with genetic liability for severe mental illness. In keeping with previous studies including a recent review of hair cortisol in children, hair cortisol may be affected by a variety of factors such as developmental stages of the child, individual insight, affect and emotions, and environmental factors (Bolhuis et al., 2019; Gray et al., 2018; Neumann et al., 2017). Future research is needed before hair cortisol can be used as a valid biomarker of chronic stress in children (Gray et al., 2018). Lastly, children's level of long-term stress may be influenced by a variety of factors besides parental illness, including social support as a relevant confounder. Children experiencing social support may feel less stressed compared with children lacking or experiencing less parental social support (Goodman et al., 2019; Stalder et al., 2017).

In accordance with a study of adolescents (age range 9–12 years) with a family history of psychosis (Cullen et al., 2014a) and a study of adult patients with schizophrenia and bipolar disorder (Streit et al., 2016), we found that children at FHR-SZ and FHR-BP expressed elevated levels of perceived stress compared with controls. A previous study reported that if children at clinical high-risk of schizophrenia and healthy controls (age range 12–30 years) were confronted with equivalent stress exposures, at risk children had a lower self-reported stress tolerance compared with controls (DeVylder et al., 2013). Exploratory analyses within the present study did not find an association between interpersonal trauma and higher levels of perceived stress, when taking FHR-status into account. Thus, it could be hypothesized that other environmental stressors besides trauma, such as living with a parent with severe mental illness, could contribute to the children's level of perceived stress. This is in line with previous findings from the current cohort reporting that children at FHR-SZ and FHR-BP were more prone to live in an inadequate home environment (Gantriis et al., 2019).

Our findings that elevated hair cortisol concentrations were not associated with increased levels of self-reported perceived stress are similar to those in a population-based study (Gerber et al., 2013), a review (Staufenbiel et al., 2013), and a study of adults with schizophrenia, bipolar disorder and controls (Streit et al., 2016). Divergence in results could potentially be caused by the discrepancy in sample sizes participating in hair analyses and DLSS in this study. As more children at FHR did not participate in hair samples compared with controls, one could speculate, that the results could potentially be affected by lower heterogeneity in the sample participating in analyses of hair cortisol concentrations than the sample participating in DLSS. Additionally, one could hypothesize that alterations could be due to inter- and

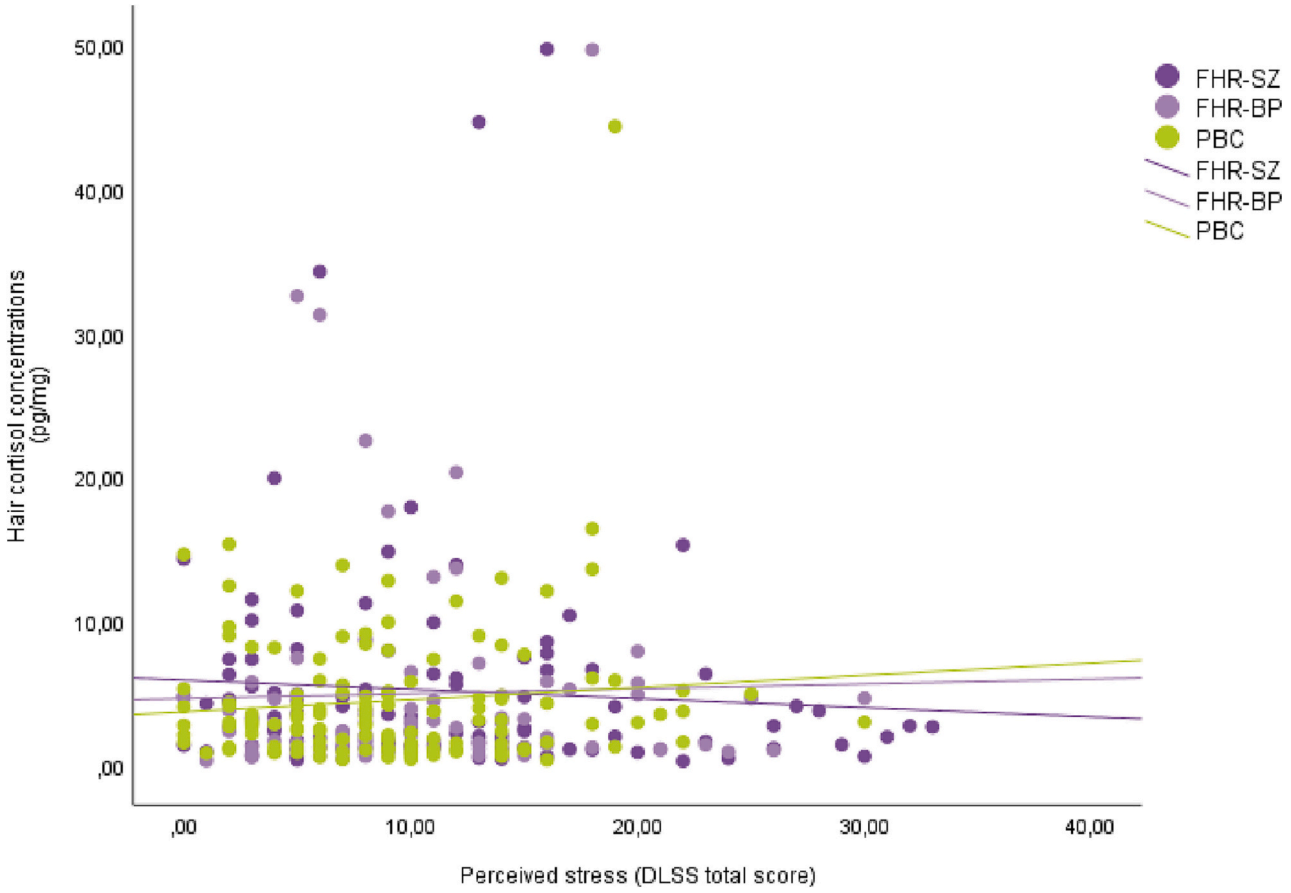

Fig. 2. Associations between hair cortisol concentrations and perceived stress (DLSS total score) in children at FHR-SZ, FHR-BP and controls in The Danish High Risk and Resilience Study – VIA 7.
Abbreviations: FHR-SZ, children at familial high risk of schizophrenia spectrum disorders; FHR-BP, children at familial high risk of bipolar disorder.
Children participating in both hair samples and assessment with Daily Life Stressor Scale, DLSS (Total $N = 319$; FHR-SZ: $N = 108$; FHR-BP: $N = 82$; controls: $N = 129$).
B = 0.012 (95% CI: −0.099 to 0.122) $p = 0.836$.
FHR-SZ: B = 5.93 (95% CI: 3.33 to 8.52).
FHR-BP: B = 4.45 (95% CI: 1.32 to 7.98).
Controls: B = 3.73 (95% CI: 2.07 to 5.38).
Interaction with familial high-risk was non-significant ($p = 0.25$).

intraindividual differences in response to stressors regarding both the type of stressor and how the individual facing it responds to it (Vanaelst et al., 2012b). It could also be due to differences in the dynamics in biological vs. psychological stress systems with the endocrine stress response lagging behind the psychological response, where individuals can report perceived psychological stress without producing measurable biological stress (Milam et al., 2014; Vanaelst et al., 2012a; Vanaelst et al., 2012b). Consequently, levels of perceived stress could potentially not be high enough to impact cortisol levels in hair. The lack of association between hair cortisol concentration and perceived stress could also be attributable the measurements of stress with questionnaires and cortisol partially reflect different information including periods of time. While DLSS measures perceived daily life stress during the last week (Kearney, 1993), hair cortisol samples comprises a long-term cortisol representing up to the preceding three months (Vanaelst et al., 2012b). The latter has been evidenced to be affected by more severe types of stressors than daily life stress, such as bullying, migration, low socio-economic status and childhood interpersonal trauma (Söder et al., 2019).

Across the sample, we did not find an association between exposure to interpersonal trauma between age 0–7 years and elevated level of hair cortisol concentrations age 7. This is in keeping with some general population studies of childhood trauma and hair cortisol concentrations in children and adolescents (Boeckel et al., 2017; Milam et al., 2014) but in contrast with others (Danese and Baldwin, 2017; Gray et al., 2018; Karlén et al., 2015; Simmons et al., 2016) including a study of adults at familial risk of psychosis reporting interpersonal trauma to be associated with increase in hair cortisol concentrations irrespective of risk status (Söder et al., 2019). Furthermore, opposing with a previous high-risk study measuring salivary cortisol concentrations in offspring at familial high-risk of bipolar disorder (age range 24–32 years) (Schreuder et al., 2016) we did not find that the FHR-groups evidenced higher levels of hair cortisol if exposed to childhood trauma compared with controls, as no interaction effect was found. Contrary, in adult samples, individuals with bipolar disorder or schizophrenia had elevated level of hair cortisol concentrations following childhood trauma exposure compared with controls (Aas et al., 2019; Staufenbiel et al., 2014). It could be hypothesized that our findings could be attributable to a delayed response in cortisol following trauma, due to the young age of the children in our cohort (Vanaelst et al., 2012b). One could also speculate, that the findings could be influenced by a potential recall bias, as previous studies have shown that severe mental illness, including schizophrenia, affects interpretation and memory of traumatic events (Goodman et al., 2019).

Additionally, even though we did not find significant associations of lower levels of cortisol in children exposed to trauma, our findings could

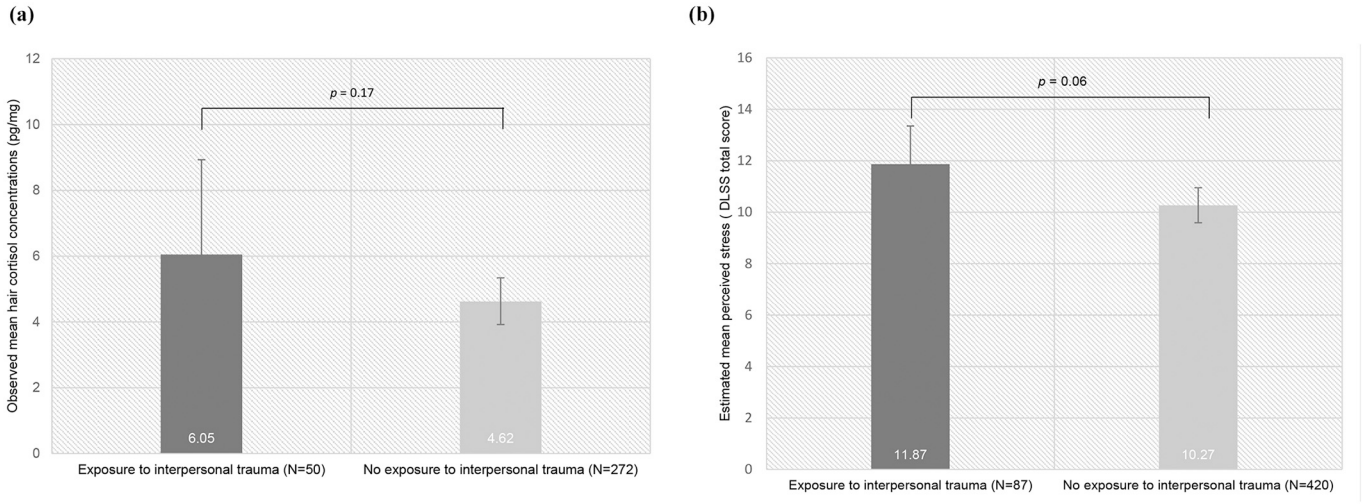

Fig. 3. a. Associations between exposure to interpersonal trauma and hair cortisol concentrations in 7-year-old children at FHR-SZ, FHR-BP and controls in The Danish High Risk and Resilience Study - VIA7. b. Associations between exposure to interpersonal trauma and level of self-reported perceived stress in 7-year-old children at FHR-SZ, FHR-BP and controls in The Danish High Risk and Resilience Study - VIA7.
Abbreviations: FHR-SZ, children at familial high risk of schizophrenia spectrum disorders; FHR-BP, children at familial high risk of bipolar disorder. Interpersonal trauma: victim of a violent crime, witness to domestic violence, physical abuse, sexual abuse.
95% CI represented by error bars.
B=1.43 (95% CI -0.61 to 3.47) p=0.17
Interaction with familial high-risk was non-significant (p=0.36).
Analyses adjusted for FHR-status of the child.
B = 1.60 (95% CI -0.04 to 3.24) $p = 0.06$.
Interaction with familial high-risk was non-significant ($p = 0.72$).

potentially support the notion of hypo-activity of the HPA axis and reduction in hair cortisol concentration if exposed to neglect or severe childhood trauma in early childhood (De Bellis and Zisk, 2014; Schalinski et al., 2019; Steudte-Schmiedgen et al., 2016; White et al., 2018). Yet, it is noteworthy that results in studies of hair cortisol concentrations following trauma exposure in children, adolescents as well as adults are mixed. Furthermore, studies of hair cortisol concentrations following childhood trauma in children at FHR-SZ and FHR-BP are lacking. Lastly, the HPA axis may be more vulnerable to adversity during specific developmental periods (Gray et al., 2018; Schreuder et al., 2016), thus longitudinal studies related to time of exposure and children of various ages are warranted.

4.1. Strengths and limitations

A strength to this study is the study design with a large, nationwide, register-based sample of both children of FHR-SZ, FHR-BP, and controls. Further, a strength is that both assessment of hair cortisol concentrations and self-reported perceived stress were included in early childhood and all within the same narrow age band (age 7) which increases the reliability of between group differences in children at FHR. Additionally, the children's level of perceived stress was assessed through self-report read aloud to the children by trained assessors. Lastly, to our knowledge, this is the first study to assess hair cortisol concentrations among children at FHR-SZ, and the first to assess hair cortisol concentrations among children at FHR-BP as young as age 7.

Some limitations should also be taken into account. As a result of technical problems in the laboratory, some children had to be excluded. Thus, the sample for hair cortisol analyses was smaller compared with the sample participating in DLSS. Furthermore, despite the fact that hair samples were excluded completely at random, drop out analyses revealed skewed drop-out of the FHR-groups. Consequently, this could indicate less heterogeneity in the sample participating in analyses of hair cortisol, compared with the sample participating in DLSS. No adjustments for potential confounding variables such as frequency of hair wash or hair treatment (dyeing or bleaching of hair) were conducted in this study, as a recent systematic review of hair cortisol concentrations in children concluded these did not have an effect on hair cortisol concentrations (Gray et al., 2018). Furthermore, in this study, a decision regarding no adjustments for steroid containing medication was made, as there is conflicting evidence regarding the effect of steroid use (topical as well as inhaled) on hair cortisol concentrations (Gray et al., 2018; Stalder and Kirschbaum, 2012). Thus, future studies may investigate this role on hair cortisol in children.

Additionally, DLSS only queried the prior week, whereas hair samples covered up to the preceding three months. However, it is possible that the preceding two weeks may not have been covered depending on growth rate and how close to the scalp the hair sample was cut. Thus, hair cortisol concentrations could potentially not include the same period of time as indexed in the questionnaire indicating a potential measurement bias. A limitation is also that level of perceived stress was not examined through a multi-informant approach including both the primary caregiver and the child's response. Exposure to interpersonal trauma was reported as a binary exposure reflecting presence or non-presence of interpersonal trauma. The instrument did not allow for determining severity, recurrence, or duration of trauma exposure. Moreover, we were not able to distinguish whether interpersonal trauma was involving someone close or not close to the child. Lastly, a limitation to this study is, that two sibling pairs participated in hair samples and nine sibling pairs participated in the DLSS.

5. Conclusions

The present study found that 7-year-old children at FHR-SZ or FHR-BP did not have a higher level of hair cortisol concentrations compared with populations-based controls. Both groups of children at familial high-risk had higher levels of self-reported perceived stress as early as age 7. Increased levels of perceived stress as early as age 7 emphasizes the need for early attention towards children at familial risk of severe mental illness to prevent potential development of mental illness.

Future studies, including within this cohort, should examine the effect of age on hair cortisol concentrations in the FHR-groups and how stress influences mental health among children at FHR-SZ or FHR-BP. Lastly, future studies within this cohort could investigate potential associations between chronic stressors such as rearing home environment and hair cortisol in children at FHR-SZ, FHR-BP, and controls.

Ethical statement

The study was approved by the Danish Data Protection Agency. The Danish Committee on Health Research Ethics evaluated the VIA7 study and deemed formal approval unnecessary due to the observational nature of the study. Hair samples were legally collected as a part of the Gene-Environment Study Protocol who obtained formal approval (00466 PSV-2009-0). Written and informed consent was obtained from all parents or other legal guardians of the child and all children were orally informed prior to assessment.

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CRediT authorship contribution statement

Julie Marie Brandt: Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Nicoline Hemager:** Validation, Investigation, Writing – review & editing, Supervision. **Ditte Ellersgaard:** Validation, Investigation, Writing – review & editing. **Maja Gregersen:** Validation, Investigation, Writing – review & editing. **Anne Søndergaard:** Validation, Investigation, Writing – review & editing. **Jessica Ohland:** Data curation, Writing – review & editing. **Katrine Søborg Spang:** Validation, Investigation, Writing – review & editing. **Camilla Christiani:** Validation, Investigation, Writing – review & editing. **Birgitte Klee Burton:** Validation, Investigation, Writing – review & editing. **Aja Greve:** Validation, Investigation, Writing – review & editing. **Carsten Hjorthøj:** Data curation, Writing – review & editing. **Ole Mors:** Conceptualization, Methodology, Resources, Writing – review & editing, Supervision, Funding acquisition. **Kerstin Jessica Plessen:** Conceptualization, Methodology, Resources, Writing – review & editing, Supervision. **Jens Richardt Møllegaard Jepsen:** Conceptualization, Methodology, Investigation, Resources, Supervision. **Merete Nordentoft:** Conceptualization, Methodology, Resources, Writing – review & editing, Supervision, Project administration, Funding acquisition. **Anne Amalie Elgaard Thorup:** Conceptualization, Methodology, Investigation, Resources, Writing – review & editing, Supervision, Project administration.

Declaration of Competing Interest

All authors declare no conflict of interest.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pnpbp.2023.110750.

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