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Association between early risk factors and level of functioning at age seven in children at familial risk for schizophrenia or bipolar disorder - The Danish High Risk and Resilience Study VIA 7

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Abstract

Background: Facing multiple risk factors, relative to single risk factor exposure early in life can have great implications for negative child development.
Objective: We aim to examine whether the prevalence of early risk factors is higher among children with familial high risk for schizophrenia or bipolar disorder compared to controls. Further, to investigate the association between number of early risk factors and level of functioning at age seven, and whether this possible association is different in children with familial high risk compared to controls.
Method: The Danish High Risk and Resilience Study VIA 7 is a population-based cohort study of children of parents diagnosed with schizophrenia (N = 202), bipolar disorder (N = 120) and controls (N = 200). We conducted a semi-structured anamnestic interview with the child's primary caregiver to assess early risk factors from pregnancy to age four. We used the Children's Global Assessment Scale to measure level of functioning at age seven.
Results: 13 out of 17 risk factors were more prevalent in children at familial high risk for schizophrenia and 7 out of 17 risk factors were more prevalent in children at familial high risk for bipolar disorder compared to controls. Level of functioning decreased 2.7 (95% CI, 2.2; 3.3)-points per risk factor, but the association was not significantly different across the three groups ($p = 0.09$).
Conclusions: Our results showed that children at age seven with familial high risk for schizophrenia or bipolar disorder experience a greater number of early risk factors. A higher number of early risk factors were associated with lower level of functioning at age seven. However, the association is not different for children with familial high risk or controls.

Keywords: risk factors; cumulative risk; familial high risk; schizophrenia; bipolar disorder

Introduction

The concept of risk can broadly be defined as any biological or environmental exposure that increases the likelihood of negative or undesirable developmental outcomes (1-3). Fetal life and the first years of life are sensitive periods that can be associated with later developmental vulnerability (4, 5). Risk factors early in life can potentially affect brain

structure and the functioning of the brain, thus affect child development and the risk for psychopathology later in life (4-7).

The impact of risks begins prenatally, since the fetal brain can be influenced by risk factors such as unplanned pregnancy (8-10), unwanted pregnancy (11, 12) or maternal substance use, including medication use (13, 14), cigarette smoking (15-18), alcohol use (19-21) and drug abuse (22). Moreover, prenatal exposure to maternal stress can potentially affect the fetal brain development (6, 23-25) and thus play a role in the development of adverse physical and mental health outcomes in offspring.

Postnatal, the first 3 years of life is a critical period for brain growth and development, with the potential to impact later health-related quality of life (26). Risk factors during early childhood include child-parent separation (27, 28), regulatory problems, i.e. problems of feeding, sleeping and excessive crying (29, 30), atypical sensory responses, e.g. hypo- or hypersensitivity (31), stimulation seeking behavior (32), poor attachment patterns (33-35) as well as stressful life events and trauma in early childhood for the primary caregiver (36, 37) or the child themselves (6, 38-40).

Risk factors often occur in combination, not in isolation (41). One approach to examine the impact of multiple risk factors and how risk factors operate conjointly to influence child development is the cumulative risk approach. In this approach risk factors are defined dichotomously, with lesser significance on the particular risk factor or the particular cluster of risk factors. Instead, the number of risk factors are summed across different dichotomous risk factors (2). The assumption is that the number of risk factors, rather than an individual or singular risk factor, account for developmental delays or problems (3, 42). The support for cumulative risk approaches is demonstrated in findings where multiple, relative to single, risk exposures have worse developmental consequences (1), and in the finding, that children are often faced with a constellation of risk factors rather than an isolated instance (2).

Children at familial risk for severe mental illness are vulnerable due to their genetic predisposition and their increased likelihood of growing up with environmental exposures (43). In the Danish High Risk and Resilience Study – VIA 7 (hereafter the VIA 7 study) children with familial high risk for schizophrenia or bipolar disorder had an elevated prevalence of psychiatric diagnoses and dimensional psychopathology as well as a lower level of functioning compared to controls (44). Further, both familial high-risk (FHR) groups displayed deficits regard to processing speed of visual attention (45), and reported more bullying victimization (46).

Children with familial high risk for schizophrenia (FHR-SZ) reported lower quality of life and self-esteem, (46), showed impaired motor functioning (47), deficits in receptive and pragmatic language, social responsiveness and adaptive social functioning (48), and widespread neurocognitive impairment (49, 50). Further, children with FHR-SZ, and to a lesser extent children with familial high risk for bipolar disorder (FHR-BP), were at increased risk of growing up in a home environment with an insufficient level of stimulation and support (51). These findings underline that children born to parents with schizophrenia or bipolar disorder display early signs of vulnerability or developmental impairments.

The objective of this study was to investigate the association between the number of early risk factors during fetal life and the first years of life and level of functioning at age seven. First, we aimed to examine whether the prevalence of early risk factors is higher among children with familial high risk for schizophrenia or bipolar disorder compared to children of parents without these disorders. Second, we aimed to examine whether the potential association between the number of early risk factors during fetal life and the first years of life and level of functioning is different in children with familial high risk for schizophrenia or bipolar disorder compared to children from control families.

Methods

This study is part of the VIA 7 study, a nationwide familial high-risk study of 522 7-year-old children, born to parents diagnosed with schizophrenia spectrum disorder, bipolar affective disorder or population-based controls with neither of these two disorders (PBC). The VIA 7 study design has been described in detail elsewhere (52).

Participants

The participating families were identified through the Danish Civil Registration System (53) and the Danish Psychiatric Central Research Register (54). The children had at least one parent diagnosed with schizophrenia spectrum psychosis (FHR-SZ, n = 202), defined as schizophrenia, delusional disorder or schizoaffective disorder (ICD 10-codes: F20, F22, F25 or ICD 8-codes: 295, 297, 298.29, 298.39, 298.89, 298.99), bipolar disorder (FHR-BP, n = 120) (ICD 10-codes: F30, F31 or ICD 8-codes: 296.19, 296.39), or none of the above (PBC, n = 200). The children from the control group were matched to FHR-SZ children on municipality, sex and age. We included FHR-BP children as a non-matched group, but the group was comparable to the other groups with respect to age and gender. Index parents were defined as the affected parent (i.e., the parent with a diagnosis in the registers) or the matched PBC

parent, and non-index parents were defined as the other biological parent without a diagnosis of schizophrenia or bipolar disorder in the registers. The sex of the index parent in the schizophrenia group defined the sex of the index parent in the PBC group.

Procedures

Data collection took place in Denmark from January 1, 2013, through January 31, 2016. The project was approved by the Danish Data Protection Agency (2012-58-0004). The study procedures were aligned with the guidelines of the National Committee for Health Research Ethics, although formal ethical approval was not required due to the observational nature of the study. This study was not preregistered.

The families were assessed by psychologists, medical doctors, and/or nurses, who were all trained, certified and supervised in all instruments. The assessor who examined the child was blinded to the illness status of the parent.

Measures

To assess early risk factors during fetal life and the first years of the child's life, information was obtained by an extensive semi-structured anamnestic face-to-face interview with the adult appointed as the primary caregiver. The primary caregiver was defined as the adult that spent the most time with and knew the child best at the time of the data collection, i.e. when the child was seven years old. The anamnestic interview consisted of a range of questions covering different topics such as socio-demography, pregnancy, the child's first years of life and current conditions. A professor in child and adolescence psychiatry and a specialist in child neuropsychology developed the anamnestic interview. The interview was developed to cover important milestones in child development as well as early signs of aberrant development. Data about pregnancy and the first years of life was usually obtained from the biological mother, also when she was not appointed as the primary caregiver.

Table 1 contains description of the 17 variables identified as early risk factors from the anamnestic interview. Importantly, in this study we use the term *risk factor* to describe any early risk exposures and risk markers that increase the likelihood of adverse developmental outcomes.

The child's current level of functioning was assessed using the Children's Global Assessment Scale (CGAS, (55)) as part of the psychopathological interview Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime Version (K-SADS-PL, (56)). CGAS was rated for the previous month, and level of functioning was determined on a scale from 1 to 100,

the lower the score, the poorer level of functioning. The training and interrater reliability of the K-SADS-PL in the VIA 7 study was moderate to good and has been described in detail elsewhere (44).

Statistical analysis

Demographic and clinical characteristics of the three groups (FHR-SZ, FHR-BP and PBC) were assessed using one-way analysis of variance (ANOVA) or Pearson's chi-squared test of independence as appropriate. The prevalence of an early risk factor in the three groups were assessed using Pearson's chi-squared test of independence or Wilcoxon (Mann-Whitney) rank-sum test as appropriate. Fischer's exact test was used when sample sizes were small (N < 5 in a cell).

The risk variables were dichotomized to indicate the presence or absence of a risk, with 0 reflecting that the risk factor was not present and 1 reflecting that the risk factor was present (e.g., mother did not smoke during pregnancy = 0; mother smoked during pregnancy = 1). In case of a continuous variable where objective categorical definitions of risk were not available, the presence of a risk was defined as the lowest or top 10% of the sample (which was the case with questions concerning well-being in relation to comfort, eating and sleeping). Since only few children displayed more than nine risk factors, 10 and more risk factors were collapsed to 9+ for the risk index.

To inspect the observed raw data, we made a figure with mean CGAS-scores for each possible number of risk factors in the three groups (see supplementary figure). To explore the relationship between the child's CGAS-score and number of risk factors, a number of different statistical models were fitted to the data (a piecewise-linear spline model with a knot in four risk factors, a multiple linear regression model with an interaction term between risk factor index and group). We found that a multiple linear regression model with the child's CGAS-score as a dependent variable, and early risk factor index and group (FHR-SZ, FHR-BP and PBC) as predictors was the best fit for our data (Figure 1).

All analyses were performed using Stata 16 statistical software, and a significance level of 5% was applied. To avoid overcorrection, we did not adjust for psychopathology given its intrinsic association with high-risk status.

Availability of data and material

Access to the datasets and analysis code used in this study may be granted by the VIA PIs upon reasonable request.

TABLE 1. Definitions and ratings of risk factors from the anamnestic interview with the primary caregiver

Variable	Definition	Rating
Risk factors during pregnancy		
Unwanted pregnancy	The pregnancy was not wanted	Yes No
Unplanned pregnancy	The pregnancy was not planned	Yes No
Medication intake by biological mother during pregnancy	Biological mother took regular medicine during the pregnancy	Yes No
Cigarette smoking by biological mother during pregnancy	Biological mother smoked cigarettes during pregnancy	Yes No
Alcohol consumption by biological mother during pregnancy	Biological mother drank alcohol during pregnancy	Yes, once weekly Yes, sometimes No
Drug use by biological mother during pregnancy	Biological mother took drugs during pregnancy	Yes No
Stressful life events for biological mother during pregnancy	Stressful life events for biological mother during pregnancy (for instance critical illness or death in the family, financial problems, unstable housing conditions)*	0-3 stressful life events
Risk factors during the child's first years of life		
Spent the most time with the child during the first years of life (0-3 years old)	Person that the child spent the most time with during the first three years of life	Biological parent Other
Stressful life events for primary caregiver during the child's first years of life (0-3 years old)	Stressful life events for the primary caregiver during the child's first years of life (0-3 years) (for instance psychosocially, death in the family, disease)*	0-3 stressful life events
Stressful life events for the child during the child's first years of life (0-3 years old)	Stressful life events for the child during the child's first years of life (0-3 years) (for instance psychosocially, death in the family, disease)*	0-3 stressful life events
Comforting (0-12 months old)	Scale from 1 to 7, with 1 indicating that the child was happy, easy to comfort and pleased most of the time, and 7 indicating that the child was difficult to comfort and displeased most of the time	1-7
Eating (0-12 months old)	Scale from 1 to 7, with 1 indicating no problems with eating, and 7 indicating a lot of trouble with eating and keeping weight	1-7
Sleeping (0-12 months old)	Scale from 1 to 7, with 1 indicating no problems with sleeping, and being rested and happy after sleep, and 7 indicating sleeping unrestful and interruptedly most of the time, often being tired and not well rested	1-7
Hypersensitivity (0-48 months old)	The child responds very strongly to stimuli, is particularly sensitive and overreact to what he/she experiences, and displays avoidant behaviour. The child easily becomes anxious, starts to cry or freezes at certain stimuli. The child responds with discomfort to e.g. touching, loud noises, strong light or an unknown smell or taste	Yes No
Hyposensitivity (0-48 months old)	The child doesn't respond to stimuli (i.e. what is happening around them), even though he/she doesn't seem sad or anxious. The child clearly doesn't respond as much as other children to e.g. noises, smell, taste, touch	Yes No
Stimulation seeking (0-48 months old)	The child displays stimulus-seeking behaviour to a degree where he/she accidentally destroys things or does something, that is potentially self-harming	Yes No
Attachment behaviour (9-24 months old)	The child displays poor attachment behaviour meaning that the child doesn't seek a parent or another familiar adult if he/she gets upset, scared or frightened	Yes No

Note. *Parental severe mental illness were excluded as a stressful life event

Results

Demographic characteristics of the cohort are presented in Table 2. The 522 children from the three groups did not differ significantly regarding sex. Regarding age, children at FHR-SZ did not differ significantly from PBC or FHR-BP, however children at FHR-BP were slightly older than the PBC children (p = 0.035). Compared with the PBC children, the FHR-SZ and FHR-BP children displayed a significantly lower mean CGAS score.

TABLE 2. Demographic and clinical characteristics of children, index parents and non-index parents from families with parental schizophrenia, parental bipolar disorder and families without schizophrenia or bipolar disorder

	FHR-SZ	FHR-BP	PBC	P-value	P-value Pairwise comparisons FHR-SZ vs. PBC	FHR-BP vs. PBC	FHR-BP vs. FHR-SZ
Children, N	202	120	200	-	-	-	-
Female, N (%)	93 (46.04)	56 (46.67)	93 (46.50)	0.993[b]	-	-	-
Age at inclusion, mean (SD)	7.84 (0.22)	7.86 (0.20)	7.81 (0.20)	0.097[c]	-	-	-
CGAS[a], N, mean (SD)	199, 68.07 (15.40)	118, 73.55 (14.91)	197, 77.71 (13.47)	**<0.001[c]**	**<0.001[c]**	**0.015[c]**	**0.001[c]**
Index parents, N	200	116	204	-	-	-	-
Female, N (%)	111 (55.50)	64 (55.17)	115 (56.37)	0.974[b]	-	-	-
Age at child's birth, mean (SD)	30.20 (6.14)	33.12 (7.03)	32.83 (4.78)	**<0.001[c]**	**<0.001[c]**	0.670[c]	**<0.001[c]**
Employed or studying, N (%)	93 (49.73)	61 (55.96)	185 (92.04)	**<0.001[b]**	**<0.001[b]**	**<0.001[b]**	0.301[b]
Education, N	178	109	197				
Primary/lower secondary, N (%)	54 (30.34)	10 (9.17)	8 (4.06)				
Upper secondary, vocational short cycle tertiary, N (%)	76 (42.70)	45 (41.28)	95 (48.22)	**<0.001[b]**	**<0.001[b]**	0.142[b]	**<0.001[b]**
Bachelor degree, equivalent or higher, N (%)	48 (26.97)	54 (49.54)	94 (47.72)				
Non-index parents, N	186	114	192	-	-	-	-
Female, N (%)	82 (44.09)	51 (44.74)	83 (43.23)	0.966[b]	-	-	-
Age at child's birth, mean (SD)	30.92 (6.37)	33.10 (5.39)	32.97 (4.28)	**<0.001[c]**	**<0.001[c]**	0.814[c]	**0.001[c]**
Employed or studying, N (%)	133 (75.14)	93 (85.32)	179 (95.21)	**<0.001[b]**	**<0.001[b]**	**0.003[b]**	**0.040[b]**
Education, N	176	106	187				
Primary/lower secondary, N (%)	31 (17.61)	5 (4.72)	10 (5.35)				
Upper secondary, vocational short cycle tertiary, N (%)	86 (48.86)	44 (41.51)	89 (47.59)	**<0.001[b]**	**<0.001[b]**	0.543[b]	**<0.001[b]**
Bachelor degree, equivalent or higher, N (%)	59 (33.52)	57 (53.77)	88 (47.06)				

Notes. FHR-SZ = familial high risk for schizophrenia; FHR-BP = familial high risk for bipolar disorder; PBC = population based controls; Index parent = the affected biological parent or the matched control; Non-index parent = the other biological parent; [a]CGAS = Children's Global Assessment Scale. Ranges from 1-100, with higher scores indicating better functioning; [b]Chi-square test of independency in contingency table; [c]One-way ANOVA

TABLE 3. Pairwise comparisons of early risk factors during pregnancy and the child's first years of life in children with familial high risk for schizophrenia, children at familial high risk for bipolar disorder and children of parents without these disorders

Early risk factor	FHR-SZ	FHR-BP	PBC	P-value	FHR-SZ vs. PBC	FHR-BP vs. PBC	FHR-SZ vs. FHR-BP
						P-value Pairwise comparisons	
	N (%)	N (%)	N (%)	-	-	-	-
Risk factors during pregnancy							
Unwanted pregnancy							
- Yes	21 (10.77)	7 (5.93)	2 (1.02)	<0.001[a]	<0.001[a]	0.011[a]	0.146[a]
- No	174 (89.23)	111 (94.07)	195 (98.98)				
Unplanned pregnancy							
- Yes	81 (41.12)	27 (22.88)	28 (14.14)	<0.001[a]	<0.001[a]	0.047[a]	0.001[a]
- No	116 (58.88)	91 (77.12)	170 (85.86)				
Medication intake by biological mother during pregnancy							
- Yes	51 (26.02)	24 (20.51)	19 (9.64)	<0.001[a]	<0.001[a]	0.007[a]	0.269[a]
- No	145 (73.98)	93 (79.49)	178 (90.36)				
Cigarette smoking by biological mother during pregnancy							
- Yes	79 (40.93)	27 (23.48)	21 (10.71)	<0.001[a]	<0.001[a]	0.003[a]	0.002[a]
- No	114 (59.07)	88 (76.52)	175 (89.29)				
Alcohol consumption by biological mother during pregnancy							
- Yes, once weekly	9(4.66)	4 (3.39)	4 (2.05)				
- Yes, sometimes	46 (23.83)	37 (31.36)	57 (29.23)	0.377[b]	-	-	-
- No	138 (71.50)	77 (65.25)	134 (68.72)				
Drug use by biological mother during pregnancy							
- Yes	8 (3.98)	1 (0.85)	0 (0.00)	0.004[b]	0.007[b]	0.372[b]	0.162[b]
- No	193 (96.02)	117 (99.15)	199 (100.00)				
Stressful life events for biological mother during pregnancy[e]							
- None	55 (31.25)	34 (31.19)	87 (47.54)				
- One	56 (31.82)	37 (33.94)	66 (36.07)	<0.001[a]	<0.001[a]	<0.001[a]	0.968[a]
- Two	34 (19.32)	21 (19.27)	23(12.57)				
- Three	31(17.61)	17 (15.60)	7 (3.83)				
Risk markers during the child's first years of life							
Spent the most time with the child during the first years of life (0-3 years old)							
- Biological parent	190 (95.96)	117 (100.00)	195 (100.00)	0.001[b]	0.007[b]	NA	0.028[b]
- Other	8 (4.04)	0 (0.00)	0 (0.00)				
Stressful life events for primary caregiver during the child's first years of life (0-3 years old)[e]							
- None	34 (16.83)	22 (18.33)	87 (43.50)				
- One	52 (25.74)	22 (18.33)	58 (29.00)	<0.001[a]	<0.001[a]	<0.001[a]	0.438[a]
- Two	54 (26.73)	32 (26.67)	38 (19.00)				
- Three	62 (30.69)	44 (36.67)	17 (8.50)				
Stressful life events for the child during the child's first years of life (0-3 years old)[e]							
- None	57 (28.22)	43 (35.83)	117 (58.50)				
- One	60 (29.70)	28 (23.33)	58 (29.00)	<0.001[a]	<0.001[a]	<0.001[a]	0.159[a]
- Two	45 (22.28)	33 (27.50)	16 (8.00)				
- Three	40 (19.80)	16 (13.33)	9 (4.50)				
Comforting (0-12 months old)[f]							
- Median (IQI)	2 (1;3)[c]	2 (1;2)[c]	1 (1;2)[c]	0.180[d]	-	-	-

Eating (0-12 months old)[f]								
-	Median (IQI)	1 (1;3)[c]	1 (1;2)[c]	1 (1;2)[2]	0.139[d]	-	-	-
Sleeping (0-12 months old)[f]								
-	Median (IQI)	2 (1;3)[c]	2 (1;3)[c]	1 (1;3)[c]	0.388[d]	-	-	-
Hypersensitivity (0-48 months old)								
-	Yes	41 (20.60)	25 (21.19)	29 (14.65)	0.212[a]	-	-	-
-	No	158 (79.40)	93 (78.81)	169 (85.35)				
Hyposensitivity (0-48 months old)								
-	Yes	12 (6.06)	2 (1.69)	4 (2.02)	0.062[b]	-	-	-
-	No	186 (93.94)	116 (98.31)	194 (97.98)				
Stimulation seeking (0-48 months old)								
-	Yes	45 (22.73)	20 (17.09)	24 (12.18)	**0.022**[a]	**0.006**[a]	0.225[a]	0.233[a]
-	No	153 (77.27)	97 (82.91)	173 (87.82)				
Attachment behavior (9-24 months old)								
-	Yes	49 (25.00)	19 (16.38)	32 (16.24)	0.055[a]	-	-	-
-	No	147 (75.00)	97 (83.62)	165 (83.76)				
Mean cumulative risk								
-	Number of risk factors	4.78 (2.34)[g]	4.03 (2.15)[g]	2.83 (1.74)[g]	**<0.001**[h]	**<0.001**[h]	**<0.001**[h]	**0.006**[h]

Notes. FHR-SZ = familial high risk for schizophrenia; FHR-BP = familial high risk for bipolar disorder; PBC = population based controls; NA = not available.
[a]Pearson chi2; [b]Fisher's exact; [c]IQI = Interquartile Interval; [d]Wilcoxon (Mann-Whitney) rank-sum, Kruskal-Wallis; [e]Possible to mention up to three stressful life events; [f]Variable rated on a scale from 1 to 7, with 1 indicating no problems in the area, and 7 indicating substantial problems in the area; [g]Standard deviation; [h]Oneway anova

Compared with controls, the FHR-SZ group was characterized by a higher frequency of unwanted ($p < 0.001$) and unplanned pregnancies ($p < 0.001$), as well as a higher frequency of mothers had taken medication ($p < 0.001$), smoked cigarettes ($P < 0.001$) or taken drugs ($p = 0.007$) during pregnancy. Furthermore, a higher number of stressful life events was reported for the biological mother during pregnancy in this group compared with controls ($p < 0.001$).

The FHR-BP group had a higher frequency of unwanted ($p = 0.011$) and unplanned pregnancies ($p = 0.047$) compared with controls. During pregnancy a higher frequency of the mothers with FHR-BP took medication ($p = 0.007$) or smoked cigarettes ($p = 0.003$) and had a higher frequency of reported stressful life events ($p < 0.001$). When comparing the two high-risk groups, there were significantly more unplanned pregnancies in the FHR-SZ group ($p = 0.001$), and a higher frequency of mothers in the FHR-SZ group who smoked cigarettes during pregnancy ($p = 0.002$).

During the first years of the child's life a larger proportion of the FHR-SZ children, compared with controls, spent most time with someone else than a biological parent ($p = 0.007$). Moreover, a larger proportion of the FHR-SZ children compared with controls was reported to have problems during the first year of life regarding comforting ($p = 0.049$) and eating ($p = 0.031$). During the first two years of life, a relatively larger proportion of the FHR-SZ children were reported to have problems concerning attachment behavior ($p = 0.032$), and during the first four years of life concerning extensive stimulation seeking behavior ($p = 0.006$) compared with controls. Finally, during the child's first years of life, a higher frequency of stressful life events for both the primary caregiver ($p < 0.001$) and the child ($p < 0.001$) was reported in the FHR-SZ group compared with controls. Similarly, the FHR-BP children had a higher frequency of stressful life events both for the primary caregiver ($p < 0.001$) and the child ($p < 0.001$) compared with controls during the first years of life. When comparing the two familial high risk groups a higher proportion of the FHR-SZ children spent more time with someone else than a biological parent during the first years of life ($p = 0.028$).

A multiple linear regression model was used to describe the association between a child's daily functioning measured as CGAS-score at age seven and the number of early risk factors, $F(3, 510) = 46.19$, $p = <0.001$ and R^2 accounted for 21.37% of the explained variability in the child's CGAS-score at age seven. Average difference in CGAS-score was -9.64 (-6.78:-12.50) for FHR-SZ children compared

with children from the control group and -4.15 (-0.94:-7.37) for FHR-BP compared with controls.

On average the child's CGAS-score at age seven decreased 2.7 (95% CI 2.2; 3.3)-points per risk factor the child had experienced during fetal life and/or the first years of life (Figure 1). This decrease did not differ significantly between the three groups as no significant risk factor by group interaction was observed ($p = 0.09$).
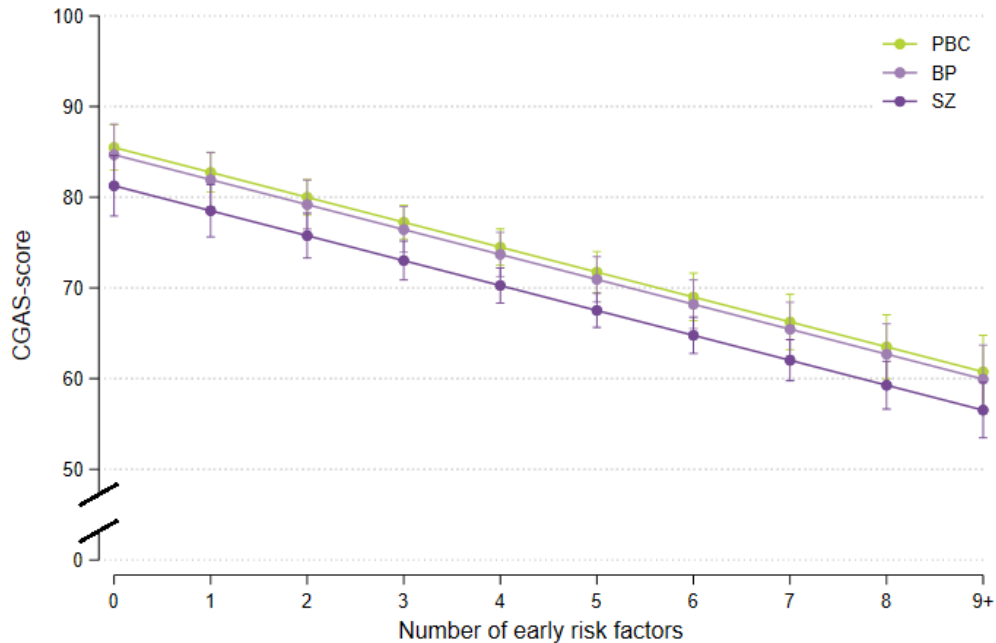

FIGURE 1: Linear regression model of the association between number of early risk factors and CGAS-score in children with familial high risk for schizophrenia, children with familial high risk for bipolar disorder and children of parents without these disorders

Discussion

In this large population-based cohort study, we found, that children from families with parental schizophrenia or bipolar disorder are exposed to a higher number of early risk factors, both during fetal life and in the first years of life compared with control children.

In both familial high-risk groups, pregnancies were more often unwanted and unplanned, the biological mothers more often took medication and smoked cigarettes during pregnancy, and a higher number of stressful life events was reported during pregnancy. In the FHR-SZ group a higher number of biological mothers also reported drug use during pregnancy.

During the first years of life, children at FHR-SZ were more often facing risk factors. They spent more time with someone else than a biological parent, and had more problems related to comforting, eating, attachment and extensive stimulation seeking. Both children and primary caregivers from the two high-

risk groups had experienced more stressful life events compared to controls.

Furthermore, we found a linear relationship between number of early risk factors and level of functioning at age seven, so as the number of risk factors increased the level of functioning decreased, indicating that the number of early risk factors are associated with a child's level of functioning at age seven. This association was not different between groups, which imply that the effect of each risk factor is the same irrespective of familial risk. However, compared with controls, the children in the familial high-risk groups displayed a significantly lower level of functioning and were facing more early risk factors indicating that familial high risk is a vulnerability marker. Importantly, the association between early risk factors and children's level of functioning at age 7 is not necessarily a causal influence and could be due to familial confounding effects. Thus, our study can point to associations but we cannot point to causal inference due to the observational design (57).

Other studies have used quasi-experimental design or the sibling-comparison approach, which has the advances that it is possible to account for all selection factors that make the siblings similar including the genetic and environmental factors that are shared by siblings (58-61).

Our results are in line with studies that emphasize a linear model of cumulative risk, i.e., the more risks present, the worse the child outcome (42, 62). Other studies have suggested that a dramatic increase in problem behavior outcome occurs after a certain number of risk factors, with risk factors potentiating each other leading to a synergistic effect (42, 63, 64). In particular, studies have found that the experience of three to four risk factors is associated with a drastic increase in child adjustment problems (64-66). In our study, we did not find a specific threshold, where the association between a certain number of early risk factors and level of functioning at age seven became significantly stronger. In other words, there was not a certain number of early risk factors beyond which the level of functioning decreased dramatically; neither did we find an exponential effect. As suggested by Appleyard et al. (42) this indicates that there does not seem to be a 'point of no return' where interventions for children and families are superfluous. Reduction of any risk factor matters and with the right support, a lot of the risk factor exposure can be avoided.

Our findings are important as they reveal that on a group level, children born to a parent diagnosed with schizophrenia or bipolar disorder already in fetal life and the first years of life are exposed to a higher number of risk factors, potentially affecting the development and later functioning, hence playing a role in developing severe mental illness. Our findings contribute to the understanding that early interventions already in pre-pregnancy, throughout birth, infancy and early childhood for families with parental schizophrenia or bipolar disorder would be beneficial for development of high-risk children (26, 67). Targeting the parents in these groups with enhanced and specialized prenatal care and social support, hopefully, could reduce prenatal risks; hence positively influence the developmental course of the offspring (68).

Strengths and limitations
This study has several strengths. The VIA 7 study used national registers to recruit families, which contributes to a representative and large nationwide cohort. Further, the children included in the study were within narrow age range making it possible to compare their current level of functioning at the same age. We used a very thorough anamnestic interview with information on many different risk factors relevant for child development. Finally, all assessors of the children were blinded to the risk status in the families.

However, some limitations need to be addressed. The first two limitations mentioned concern the risk of recall bias. Interview-based data will always be predominantly subjective and depend on, whether the primary caregiver would assess something as problematic or not. Secondly, all information was obtained when the child was seven years old and therefore it is a risk that the primary caregiver remembered inaccurately or merely had forgotten. A recent study found very small magnitudes for maternal psychopathology biasing reports on child behavior problems, suggesting that parents are valid informants irrespective of potential current symptoms (69) indicating that the primary caregivers in all three groups constitute as equally valid informants. However, one could also argue that the lower the functioning of the child, the higher the probability that the parent would remember. This could potentially lead to ratings of more risk factors in children from families with parental schizophrenia. Another limitation is the dichotomization of risk variables, which is a common challenge in the area of cumulative risks (1, 42, 70). The summing of risk factors into a count, with a risk/no risk dichotomy, weights all risks equally and does not account for variations in timing or the duration of a given risk factor, nor does it take in to account the severity, contribution or patterns of the different risk factors. The dichotomization was a necessary approach in order to be able to count the number of risk factors. Finally, in this study we have not distinguished between external factors affecting the child (e.g., maternal smoking), and more internal risk factors that could be an expression of the child's behavior (e.g., extensive stimulation seeking behavior) since the purpose of this study was a total count of all identified early risk factors from the anamnestic interview, giving equal weight to all risk factors.

Conclusions
In conclusion, children with familial high risk for schizophrenia or bipolar disorder experience a greater number of early risk factors compared to controls. We found a linear association between number of early risk factors and level of functioning at age seven. The more risk factors a child is facing in fetal life and the first years of life, the lower the level of functioning at age seven. Furthermore, the association between number of risk factors and the child's level of functioning did not differ between children at risk for schizophrenia or bipolar disorder or control children.

Clinical significance

Our findings emphasize the need for specialized, non-stigmatizing and flexible perinatal support and early parent and family intervention, in order to reduce risk exposures and thereby improve positive offspring development and potentially prevent transition to mental illness.

Conflict of interests

The authors report no conflicts of interests.

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