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Is the Association Between Parents' Mental Illness and Child Psychopathology Mediated via Home Environment and Caregiver's Psychosocial Functioning? A Mediation Analysis of the Danish High Risk and Resilience Study—VIA7, a Population-Based Cohort Study

Md Jamal Uddin*[,1,2,3,4,5], Claus Thorn Ekstrøm[4], Nicoline Hemager[1,2,3], Camilla A. J. Christiani[1,2,3], Maja Gregersen[1,2,3], Ditte Vestbjerg Ellersgaard[1,3], Katrine Søborg Spang[1,3,6], Aja Greve[3,7,8], Ditte Lou Gantriis[3,7,8], Birgitte Klee Burton[1,2,6], Anne Søndergaard[1,2,6], Ron Nudel[3,9], Preben Bo Mortensen[3,10], Marianne Giørtz Pedersen[3,10,11], Carsten Bøcker Pedersen[3,10], Yunpeng Wang[3,12], Thomas Werge[3,9], Jonas Bybjerg-Grauholm[3,13], Kerstin J. von Plessen[3,5,14], Vibeke Bliksted[3,7,8], Ole Mors[3,7,8], Anne A. E. Thorup[1,2,3,6], and Merete Nordentoft[1,2,3]

[1]CORE - Copenhagen Research Centre for Mental Health, Mental Health Center Copenhagen, Capital Region of Denmark, Copenhagen University Hospital, Copenhagen, Denmark; [2]Department of Public Health, University of Copenhagen, Copenhagen, Denmark; [3]The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Aarhus, Denmark; [4]Section of Biostatistics, Department of Public Health, University of Copenhagen, Copenhagen, Denmark; [5]Department of Statistics, Shahjalal University of Science and Technology, Sylhet, Bangladesh; [6]Research Unit, Child and Adolescent Mental Health Center, University of Copenhagen, Copenhagen, Denmark; [7]The Psychosis Research Unit, Aarhus University Hospital, Aarhus, Denmark; [8]Faculty of Health and Medical Services, University of Aarhus, Aarhus, Denmark; [9]Institute of Biological Psychiatry, Mental Health Centre Sct. Hans, Mental Health Services Copenhagen, Roskilde, Denmark; [10]Department of Economics and Business Economics, National Center for Register-Based Research, Aarhus University, Aarhus, Denmark; [11]Centre for Integrated Register-Based Research, CIRRAU, Aarhus University, Aarhus, Denmark; [12]Department of Psychology, Lifespan Changes in Brain and Cognition (LCBC), University of Oslo, Oslo, Norway; [13]Department for Congenital Disorders, Center for Neonatal Screening, Statens Serum Institut, Copenhagen, Denmark; [14]Division of Child and Adolescent Psychiatry, Department of Psychiatry, Lausanne University Hospital, Lausanne, Switzerland

*To whom correspondence should be addressed; CORE - Copenhagen Research Centre for Mental Health, Capital Region of Denmark, Copenhagen University Hospital, Forskningsenheden, Kildegårdsvej 28 (Opgang 15, 4. sal), 2900 Hellerup, Denmark; tel: +4538647453, fax: (+45) 38 64 75 04; e-mails: md.jamal.uddin@regionh.dk, jamal-sta@sust.edu

We aimed to investigate to which degree the home environment and/or primary caregivers' level of functioning mediate the association between parental mental illness (eg, schizophrenia) and child psychopathology. We used data from the nationwide Danish High Risk and Resilience Study—VIA7. The study sample comprised 522 seven-year-old children. The main outcome was the child psychopathology, assessed with the Child Behavior Checklist (CBCL). The exposure variable had 3 categories: children at familial high risk of schizophrenia spectrum psychosis (FHR-SZ), bipolar disorder (FHR-BP), and population-based controls. Mediators were quality of the Home Observation for Measurement of the Environment (HOME) and primary caregiver's Personal and Social Performance Scale (primary caregiver functioning). Primary caregiver's IQ and polygenic risk scores (PRS) for the educational attainment of the children were considered as covariates. We found a significant indirect adjusted effect of FHR status vs controls on CBCL total scores (FHR-SZ = 5.34, 95% confidence interval [CI]: 3.50–7.47 and FHR-BP = 4.54, 95% CI: 2.65–6.68), through primary caregiver functioning and HOME. Both mediators combined explained 53% and 64% variation of the total effects of FHR-SZ and FHR-BP, respectively. Adjusting for the PRS in the mediation models only resulted in minor changes in the FHR effects on the CBCL. We conclude that the HOME and the primary caregiver functioning are important mediating factors for child psychopathology, especially in children born with familial risk for severe mental illness. This knowledge may represent a window of opportunity for the development of preventive strategies (eg, intervention to improve primary caregiver functioning and home environment).

Key words: parental mental illness/familial high risk/child psychopathology/home environment/primary caregiver's psychosocial functioning

Introduction

Children at familial high risk of schizophrenia spectrum psychosis (FHR-SZ) or bipolar disorder (FHR-BP) are exposed to more environmental risk factors (eg, traumatic life events, lack of parental support) compared with children whose parents do not have a severe mental illness.[1,2] These children are likely to develop early signs of psychopathology[3–5] and neurocognitive deficits.[5–7] Previous studies have shown that children's neurocognition, social development, and academic functioning[8,9] are related to factors in their home environments,[8,9] primary caregiver's psychosocial functioning,[10,11] and to their genetic composition.[12]

The association between child psychopathology and parental mental illness[3,5] might be partly explained by factors like the home environments,[13] or primary caregiver's level of functioning, which could be part of a causal pathway and may act as mediators.[14]

Several previous studies have tried to disentangle and quantify genetic and environmental risk factors contributing to children's level of psychopathology.[12,15] However, the potential of using data from familial high-risk (FHR) children, including mediation analyses, has only been explored in a few studies,[16] and mediation analysis would be an important alternative to general statistical models (eg, linear regression) to obtain valid inference.[17] For example, Burt et al.[17] hypothesized that parenting and family environmental factors mediated the association between maternal depressive symptoms and offspring psychopathology in late adolescence. The authors showed the importance of mediation analysis in the FHR study. By using mediation analyses, we aimed to explore the underlying mechanism by which one variable (FHR status) influences another variable (child's psychopathology) through mediator variables (home environments and primary caregiver's level of functioning)[18] (figure 1). Here, a mediating variable is an intermediate variable on the causal pathway between exposure and the outcome.[19]

We hypothesized that the association between parent's mental illness and child psychopathology is partly mediated by the home environment and/or primary caregiver's level of functioning.

Methods

Participants

We used data from the nationwide Danish High Risk and Resilience Study—VIA7. The VIA7 study was conducted in Denmark from January 1, 2013 to January 31, 2016. A more detailed description of the study design can be found elsewhere.[5,20,21] We included 202 children of parents diagnosed with FHR-SZ, 120 children of parents diagnosed with FHR-BP, and 200 population-based

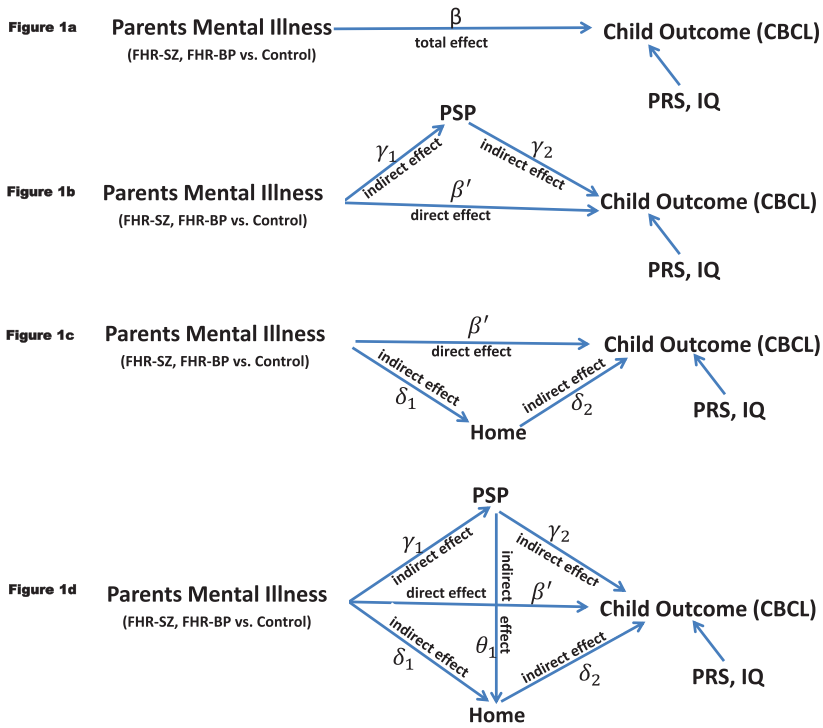

Fig. 1. Directed acyclic graph (DAG) for illustrating the research questions and the analytical models with different effects (total, direct, and indirect). *Note:* CBCL, child behavior checklist school-age version; Controls, population-based controls; FHR-BP, children with familial high risk for bipolar disorder; FHR-SZ, children with familial high risk for schizophrenia spectrum psychosis; Home, home environments; IQ, IQ of primary caregiver; PRS, polygenic risk scores for educational attainment of the children; PSP, primary caregiver's personal and social functioning (primary caregiver functioning).

controls, all identified through Danish registers.[22,23] An index parent could have more than 1 child who turned 7 years old during the data collection period, 16 pairs of siblings were included. All families were contacted by mail and by telephone and transportation was arranged for them if needed. All families completed a very comprehensive test battery including information on both parents and the child. The child was assessed with both interviews, tests and questionnaire in various domains (psychopathology, neurocognition, social behavior and development, family environment, etc.). The primary caregivers were almost always in a stable condition and thus able to provide reliable information. The data collection lasted approximately 3 days and all families received a verbal feedback. We explained the detailed sample selection in supplementary figure S1. Population-based control children had parents who had never been diagnosed with any of the abovementioned mental illnesses and were matched with the FHR-SZ children on age, sex, and municipality.

The Danish Data Protection Agency approved the VIA7 study and written consent was obtained from all adult participants and the legal guardian of the child. The VIA7 study followed the guidelines from The Danish National Committee on Health Research Ethics.

Procedures

A group of trained mental health professionals (doctors, psychologists, nurses) were involved in the entire data collection procedure. Some assessments were conducted at participants' homes. Child assessors were blinded to the FHR status.

Measures

Exposure Variable. The exposure variable had 3 categories: FHR-SZ, FHR-BP, and controls.

Outcome Variable. Child psychopathology was assessed with the Child Behavior Checklist (CBCL) school-age version,[24] a questionnaire completed by the primary caregiver based on their impression of the child's behavior within the previous month. The CBCL contains 118 items related to various kinds of behavioral problems. Each item was rated on a Likert scale from 0 (not true) to 2 (very true or often true). The CBCL total score is the sum of all items and was used as the primary outcome. Moreover, 2 broadband subscales, the CBCL Internalizing (eg, anxiety, depression, and social withdrawal) and the CBCL Externalizing (eg, aggression and impulsivity), were used as secondary outcomes.[5] Higher CBCL scores indicate higher levels of behavioral and/or emotional problems.[5]

Mediator Variables. We used 2 mediator variables: the children's home environment and the primary caregiver's level of functioning. In each family, a primary caregiver for the child was identified to be the main informant about the child. Primary caregiver was the biological or nonbiological caregiver who spent the most time with the child. That means the adult, who is taking care of the child on a regular basis and who is registered with the same official address as the child, is invited to give information (ie, interviews and questionnaires) about the child's actual well-being and behavior ("primary caregiver"). This is often but not always one of the biological parents. The other biological parent and in some cases the new partner of the primary caregiver were also invited to participate if they had been living with the child for at least the last year.[20] The child's home environment was assessed with The Middle Childhood—Home Observation for Measurement of the Environment (HOME) Inventory interview,[25] a semi-structured interview that takes place in the home with the child and the primary caregiver both being present. It captures information about the level of stimulation and support provided in the child's home. The interview is based both on dialogue with the child and the primary caregiver and on observations made by the interviewer. It consists of 59 binary items related to the following topics: responsivity, encouragement of maturity, emotional climate, learning materials and opportunities, enrichment, family companionship, family integration, and physical environment.[10,17] The primary caregiver's current level of functioning was assessed with the Personal and Social Performance Scale (primary caregiver functioning).[26] The primary caregiver functioning is a 100-point rating scale based on a semi-structured interview. There are 4 main assessment sections: (a) socially useful activities including work and study; (b) personal and social relationships; (c) self-care; and (d) disturbing and aggressive behaviors. The higher the value of primary caregiver functioning scores the better the functioning.

Covariates.. Apart from age and sex of the children, we also considered the primary caregiver's estimated level of intelligence quotient (IQ),[27] assessed with the Reynolds Intellectual Screening Test (RIST) derived from the Reynolds Intellectual Assessment Scale (RIAS).[28]

Polygenic Risk Scores (PRS)

The majority of the sample underwent genotyping. PRS for schizophrenia, bipolar disorder, and educational attainment were computed for available children and parents. Detailed information can be found in the online supplements.

Statistical Analyses

We considered 2 mediators: the primary caregiver functioning score and HOME score. We assumed the mediator's primary caregiver functioning to influence the HOME. That means a serial/sequence multiple

mediation model (model 6, Andrew F. Hayes[29,30]) is required to explain the simultaneous mediation effects of both mediators on the CBCL. Hence, we analyzed data using different linear models including independent and serial mediation models. We assumed no confounding between FHR and CBCL, FHR and primary caregiver functioning/Home, and primary caregiver functioning/Home and CBCL.[31]

The analytical models are illustrated in figure 1. Our primary goal was to estimate the percentage of the total effects of the FHR-SZ and FHR-BP vs control on the CBCL total score that was explained by the primary caregiver functioning and/or HOME. We obtained 3 types of effects from a mediation model: total, direct and indirect effects in which the total effect can be decomposed into the natural direct and indirect effects marginally.[32] The total and direct effects of FHR-SZ and FHR-BP on the CBCL are β (figure 1a) and β' (figure 1b-d) respectively. The indirect effects can be estimated via primary caregiver functioning or/and HOME. Hence, the indirect effect through only primary caregiver functioning was $\gamma_1\gamma_2$ (figure 1b) through only HOME $\delta_1\delta_2$ (figure 1c); through primary caregiver functioning and HOME (serial mediation) it was $\gamma_1\gamma_2 + \delta_1\delta_2 + \gamma_1\theta_1\delta_2$ (figure 1d). All models were adjusted for the estimated IQ of the primary caregiver. Since neither sex nor children's age had any significant impact on the CBCL of our study, in the analytical models, we did not adjust them. To check the sensitivity of our results, we divided the CBCL total scores into 2 broadband subscales, externalizing and internalizing scores, and repeated the same analyses. Additionally, as children with neurodevelopmental disorders (ie, current diagnoses of any attention-deficit hyperactivity disorder [ADHD] and/or autism spectrum disorders [ASD]) may have a bidirectional effect on HOME, we excluded them (supplementary figure S2) and repeated the same analyses.

To control for genetic contribution to the association between FHR status and the child's psychopathology, a separate mediation analysis was performed using the available data on PRS for schizophrenia, bipolar disorder of children and parents, and PRS for the children's educational attainment. In that case, we assessed the association between FHR status and the CBCL scores by adjusting the standardized PRS. As the educational attainment, PRS of the children is a proxy for the child IQ[33,34] and as the two were also correlated (r = 0.15, P = .002), we did not adjust for child IQ in mediation models.

In all mediation models, the indirect effects, including percentile-based bootstrap confidence intervals (CI), were estimated using bootstrapping with 5000 re-samples. All analyses were performed using PROCESSv3.1 macro by Andrew F. Hayes[29] in SPSS 25. We used 2 types of mediation models, a simple mediation model in which only one mediator, including a covariate, is considered at a time (model 4)[19,29] and a serial multiple mediation model in which 2 mediators are considered simultaneously (model 6).[29,30]

Results

Demographic and Clinical Characteristics

Table 1 shows the distribution of participants' characteristics across the 3 exposure groups. We had information on the CBCL for 494 children (95%; 192 FHR-SZ children, 111 FHR-BP children, and 191 control). Moreover, the PRS for educational attainment, schizophrenia and bipolar disorder was calculated for 402 children (77%) (supplementary figure S1). We found that FHR-SZ and FHR-BP children had a mean CBCL = 27.20 (SD = 21.05) and 23.41 (SD = 19.71), respectively, which were higher than the control [17.01 (SD = 14.72)] (table 1 and figure 2). Similarly, the mean HOME score for FHR-SZ children [44.97 (SD = 6.41)] was lower than for the control group [49.03 (SD = 4.35)]. We observed a significant negative marginal correlation between CBCL total and HOME, r = −0.36 [95% CI: −0.43, −0.29], CBCL and primary caregiver functioning, r = −0.29 [CI: −0.37, −0.21], and CBCL and IQ, r = −0.14 [CI: −0.22, −0.06]. We noticed a moderate positive correlation between the 2 mediators, primary caregiver functioning and Home, r = 0.43 [CI: 0.35, 0.50], P < .01 (supplementary table S3).

Mediation Analyses (Total, Direct, and Indirect Effects of FHR on the CBCL Total Score)

Mediation analyses showed that the total effects of FHR-BP and FHR-SZ as compared to the control on the CBCL total scores were 6.47 [CI: 2.11, 10.83] (P = .004) and 10.41 [CI: 6.66, 14.16] (P < .0001), respectively (table 2).

When considering primary caregiver functioning as the only mediator and adjusting for the primary caregiver's IQ, the percentage of the total effects explained by the primary caregiver functioning was 51% for FHR-BP and 32% for FHR-SZ, respectively. Similarly, the percentage of the total effects explained by another mediator (ie, only HOME) was 40% and 39%, respectively (figure 3b).

When considering both mediators, ie, primary caregiver functioning and HOME, simultaneously (figure 1d) including the IQ of the primary caregiver as the covariate, there was a significant indirect effect of parent's mental illness, FHR-BP = 4.54 [CI: 2.65, 6.68], FHR-SZ = 5.34 [CI: 3.50, 7.47], on the CBCL total through primary caregiver functioning and HOME (table 2). Here both mediators explained 64% and 53% variation of the total effects of FHR-BP and FHR-SZ, respectively (figure 3b). Note that the mediator(s) explained more of the variation in the FHR-BP group than the FHR-SZ group.

Table 1. Distribution of Participants Characteristics Across the Exposure Groups

Covariates	*N*	FHR-SZ	FHR-BP	Controls	*P* value	Pairwise Comparisons		
						FHR-SZ vs Controls	FHR-BP vs Controls	FHR-BP vs FHR-SZ
Children	522	202	120	200				
Female, *N* (%)	242	93 (46.0)	56 (46.7)	93 (45.5)	.993	0.926	0.977	0.913
Age at inclusion, years, mean (SD)	522	7.84 (0.22)	7.86 (0.20)	7.81 (0.20)	.097	0.532	0.106	1.00
CBCL: total score (sum of all items)	494	27.20 (21.05)	23.41 (19.71)	17.01 (14.72)	<.001	<0.001	0.012	0.26
CBCL externalizing score	495	7.78 (7.43)	6.17 (6.68)	4.08 (4.72)	<.001	<0.001	0.018	0.10
CBCL internalizing score	495	6.57 (5.88)	6.60 (6.83)	4.84 (4.47)	.004	0.008	0.027	1.00
Home status								
Living with both biological parents, *N* (%)	300	74 (39.6)	61 (55.0)	165 (85.1)	<.001	<0.001	<0.001	0.010
Living out of home, *N* (%)	12	—	—	—	—	—	—	—
Living with index parent, *N* (%)	378	115 (61.2)	79 (71.2)	184 (94.9)	<.001	<0.001	<0.001	0.090
Living with a single parent, *N* (%)	125	70 (37.4)	34 (30.6)	21 (10.8)	<.001	<0.001	<0.001	0.234
HOME total score, mean (SD)	508	44.97 (6.41)	46.70 (4.68)	49.03 (4.35)	<.001	<0.001	<0.001	0.017
Primary caregiver's level of functioning (PSP), mean (SD)	511	73.19 (14.10)	74.47 (14.12)	84.42 (9.11)	<.0001	<0.001	<0.001	1.00
Primary caregiver's estimated IQ[a], mean (SD)	513	102.34 (8.73)	105.15 (8.09)	103.89 (7.93)	.012	0.186	0.576	0.011
Education of index parents	482							
Primary/lower secondary, *N* (%)	72	54 (30.5)	10 (9.3)	8 (4.1)	<.0001	<0.0001	0.930	<0.0001
Upper secondary, vocational, short-cycle tertiary, *N* (%)	214	75 (42.4)	44 (40.7)	95 (48.2)				
Bachelor's degree, equivalent or higher, *N* (%)	196	48 (27.1)	54 (50.0)	94 (47.7)				
PRS for educational attainment of the children, mean (SD)	402	−0.14 (1.00)	0.16 (0.98)	0.03 (1.00)	.07	0.41	0.99	0.07
PRS for schizophrenia of the children, mean (SD)	402	0.04 (0.95)	0.18 (1.01)	−0.15 (1.02)	.03	0.27	0.04	0.93
PRS for bipolar disorder of the children, mean (SD)	402	0.09 (0.91)	0.07 (1.05)	−0.12 (1.04)	.13	0.20	0.37	1.00

Note: The *P* value threshold for PRS was selected based on R^2 values.
[a]Reynolds Intellectual Screening Test (RIST); for continuous variable, the *P* values (Bonferroni corrected) based on 1-way ANOVA and for binary/categorical variables, the *P* value based on chi-square test.
CBCL, child behavior checklist school-age version; Controls, population-based controls; FHR-BP, children with familial high risk for bipolar disorder; FHR-SZ, children with familial high risk for schizophrenia spectrum psychosis; Home, home environments; IQ, IQ of primary caregiver; PRS, polygenic risk scores (standardized scores) for educational attainment of the children (*P* value threshold .0001), for schizophrenia of the children (*P* value threshold .000001), for bipolar disorder of the children (*P* value threshold .90); PSP, psychosocial functioning.

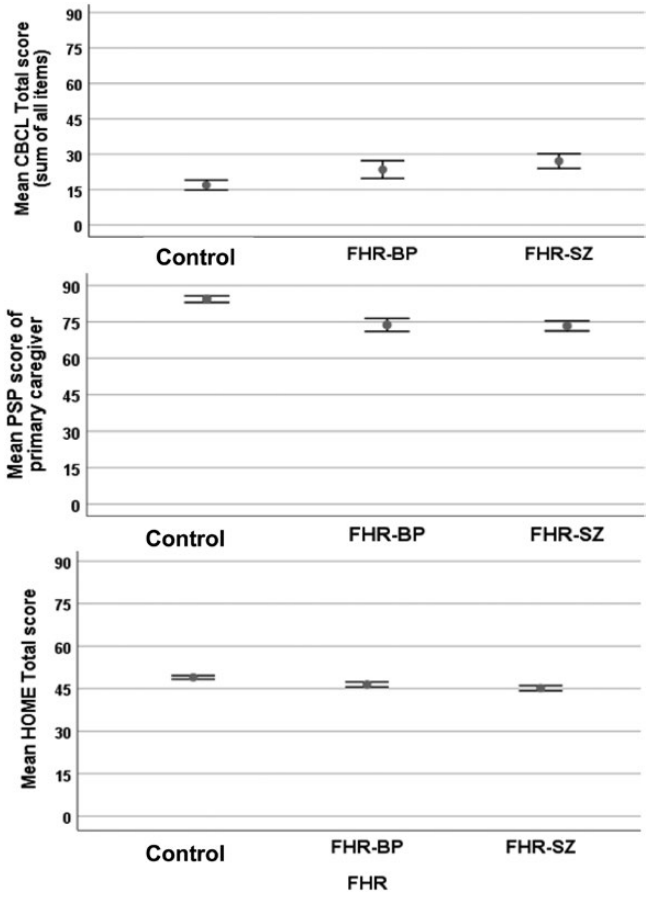

Fig. 2. Mean CBCL total scores (left), personal and level of functioning scale (primary caregiver functioning) of the primary caregiver (middle), and home environment scores (right) including 95% confidence interval for 3 exposure groups. *Note:* CBCL, child behavior checklist school-age version; Controls, population-based controls; FHR-BP, children with familial high risk for bipolar disorder; FHR-SZ, children with familial high risk for schizophrenia spectrum psychosis; Home, home environments; PSP, primary caregiver's personal and social functioning (primary caregiver functioning).

Sensitivity Analyses

Supplementary tables S1 and S2 show the estimates of the total effects, direct effects, indirect effects, and proportion mediated of the effect of FHR-BP vs control and FHR-SZ vs control on the CBCL externalizing and internalizing score. For CBCL externalizing scores, both mediators explained 51% and 38% variation in the FHR-BP group and FHR-SZ group, respectively (figure 3d and supplementary table S1). Similarly, for CBCL internalizing scores, both mediators explained 57% and 63% variation in the FHR-BP group and FHR-SZ group, respectively (figure 3f, supplementary table S2). Furthermore, supplementary table S5 shows the total effects, direct effects, indirect effects, and proportion mediated (supplementary figure S3) of the effect of FHR-BP and FHR-SZ on the CBCL total for the children without ADHD and ASD. The results appear to be consistent with the primary analyses except for a slight increase in the percentage of variation explained by the mediators mostly for the FHR-SZ group.

Analysis Only for Subjects With PRS Data

The effect of PRS for the education of children on the CBCL was statistically significant in all models without mediators (supplementary table S4). We observed only small changes in the estimates after adjusting the PRS for children's educational attainment, implying that the PRS has a small impact on the CBCL. (table 2). For example, for the CBCL total with both mediators, before and after adjustment for the PRS, the total effects of FHR-SZ was 10.22 [CI: 6.05, 14.40] and 9.65 [CI: 5.50, 13.80], respectively (table 2). The association between other PRS, such as schizophrenia and bipolar disorder of child and parent, and CBCL was not statistically significant and therefore, we did not consider them in the mediation models (data not shown).

Discussion

In this study, our main goal was to investigate how much of the association between parental mental illness and children's psychopathology was mediated through the level of the daily functioning of the primary caregiver and/or the child's home environment. We found that the parent's mental illness was strongly associated with the child's psychopathology even after adjustment for the primary caregiver's IQ and the educational attainment PRS of the child. Moreover, our mediation analyses showed that parental mental illness was significantly, indirectly (via mediation through the level of functioning and home environment) associated with the child's psychopathology. Both mediators together accounted for 53% and 64% of the variation of the total effects of FHR-SZ and FHR-BP, respectively. This confirms that the home environment and the primary caregiver's level of functioning are strong mediators and thus potential risk factors for the mental health of the children.

As we also observed in previous studies,[5,10,27] there was a clear difference between exposure groups. Furthermore, after adjustment for the genetic composition of the children, eg, educational attainment PRS, we only found a small change in the effect estimates of the FHR status, meaning that the PRS explained only a small proportion of the total variance in the child's psychopathology. Also, the direct effect of the FHR-BP on the child's psychopathology was statistically insignificant.

Putting these findings in a perspective of developmental psychopathology is very meaningful. Developmental psychopathology is the understanding that many small steps and contributions may lead to a mental disorder later and that many pathways can lead to the same illness. Also, a more dimensional and hierarchical approach is now

Table 2. Estimates of the Total Effects, Direct Effects, Indirect Effects, and Proportion Mediated of the Effect of FHR-BP vs Controls and FHR-SZ vs Controls on the CBCL Total

Exposure Category	Total Effect	Direct Effect	Indirect Effect	% of Variation Accounted by the Mediator[c]
Mediator: Primary caregiver functioning (*corresponds to* figure 1b)				
Crude model (n = 489)				
FHR-BP[b]	6.47 [2.11, 10.83]	2.92 [−1.55, 7.40]	3.55 [1.98, 5.41]	55%
FHR-SZ[b]	10.41 [6.66, 14.16]	6.69 [2.76, 10.63]	3.72 [2.15, 5.47]	36%
Model adjusted with caregiver IQ[a] (n = 489)				
FHR-BP	6.96 [2.73, 11.19]	3.58 [−0.68, 7.84]	3.38, [1.75, 5.32]	51%
FHR-SZ	10.23 [6.61, 13.84]	7.00 [3.27, 10.72]	3.23, [1.69, 4.99]	32%
Analysis using subjects that have available PRS data for child educational attainment (n = 387)				
FHR-BP	5.56 [0.79, 10.34]	2.69 [−2.22, 7.61]	2.87 [1.34, 4.59]	52%
FHR-SZ	10.06 [5.85, 14.27]	7.07 [2.66, 11.48]	2.99 [1.46, 4.73]	30%
Model adjusted with PRS for the educational attainment of child[a] (n = 387)				
FHR-BP	5.85 [1.18, 10.52]	3.13 [−1.57, 7.84]	2.72 [1.18, 4.45]	46%
FHR-SZ	9.49 [5.36, 13.63]	6.73 [2.41, 11.06]	2.76 [1.25, 4.42]	29%
Model adjusted with IQ of caregiver and PRS for the educational attainment of child[a] (n = 386)				
FHR-BP	6.38 [1.74, 11.02]	3.83 [−0.90, 8.57]	2.55 [0.97, 4.29]	40%
FHR-SZ	9.43 [5.37, 13.49]	7.06 [2.76, 13.49]	2.37 [0.95, 3.96]	25%
Mediator: Home environment (*corresponds to* figure 1c)				
Crude model (n = 485)				
FHR-BP	6.50 [2.15, 10.85]	3.70 [−0.51, 7.92]	2.79 [1.52, 4.27]	43%
FHR-SZ	9.96 [6.22, 13.69]	5.71 [1.97, 9.46]	4.24 [2.83, 5.82]	43%
Model adjusted with primary caregiver IQ[a] (n = 485)				
FHR-BP	7.00 [2.74, 11.27]	4.19 [0.03, 8.34]	2.82, [1.55, 4.35]	40%
FHR-SZ	9.91 [6.29, 13.53]	6.05 [2.52, 9.57]	3.47, [2.53, 5.41]	39%
Analysis using subjects that have available PRS data for child educational attainment[a] (n = 387)				
FHR-BP	5.46 [0.69, 10.24]	2.95 [−1.69, 7.59]	2.51 [1.20, 4.10]	46%
FHR-SZ	10.05 [5.84, 14.26]	5.98 [1.74, 10.22]	4.07 [2.61, 5.70]	40%
Model adjusted with PRS for the educational attainment of child[a] (n = 387)				
FHR-BP	5.79 [1.12, 10.46]	3.34 [−1.19, 7.87]	2.45 [1.17, 3.99]	42%
FHR-SZ	9.51 [5.8, 13.63]	5.70 [1.57, 9.83]	3.81 [2.44, 5.32]	40%
Model adjusted with IQ of caregiver and PRS for the educational attainment of child[a] (n = 386)				
FHR-BP	6.37 [1.73, 11.02]	3.86 [−0.70, 8.43]	2.51 [1.26, 4.02]	39%
FHR-SZ	9.47 [5.42, 13.53]	6.04 [1.92, 10.15]	3.44 [2.06, 4.95]	36%
Mediator: Primary caregiver functioning and home environment (*corresponds to* figure 1d)				
Crude model (n = 484)				
FHR-BP	6.58 [2.30, 10.86]	2.10 [−2.04, 6.23]	4.46 [2.71, 6.56]	68%
FHR-SZ	10.18 [6.46, 13.89]	4.37 [0.75, 7.99]	5.78 [3.97, 7.86]	57%

Table 2. Continued

Exposure Category	Total Effect	Direct Effect	Indirect Effect	% of Variation Accounted by the Mediator[c]
Model adjusted with primary caregiver IQ[a] (n = 483)				
FHR-BP	7.07 [1.81, 11.34]	2.52 [−1.68, 6.72]	4.54 [2.65, 6.68]	64%
FHR-SZ	10.05 [5.42, 13.68]	4.68 [1.02, 8.34]	5.34 [3.50, 7.47]	53%
Analysis using subjects that have available PRS data for child educational attainment (n = 382)				
FHR-BP	5.56 [0.80, 10.31]	1.92 [−2.70, 6.54]	3.63 [1.87, 5.57]	65%
FHR-SZ	10.22 [6.05, 14.40]	5.19 [0.94, 9.43]	5.02 [3.27, 6.90]	49%
Model adjusted with PRS for the educational attainment of child[a] (n = 382)				
FHR-BP	5.85 [1.17, 10.52]	2.34 [−2.24, 6.93]	3.51 [1.75, 5.42]	60%
FHR-SZ	9.65 [5.50, 13.80]	4.96 [0.75, 9.18]	4.67 [2.93, 6.50]	48%
Model adjusted with IQ of caregiver and PRS for the educational attainment of child (n = 382)				
FHR-BP	6.43 [1.78, 11.07]	2.86 [−1.81, 7.52]	3.59 [1.81, 5.56]	55%
FHR-SZ	9.63 [5.55, 13.70]	5.34 [1.09, 9.59]	4.28 [2.57, 6.34]	44%

Note:
[a]Primary caregiver IQ and polygenic risk scores (PRS) of child education (P value threshold .0001) are significantly associated with the Child Behavior Checklist (CBCL) school-age version total.
[b]Bootstrap estimate and 95% percentile bootstrap confidence interval with 5000 bootstrap samples.
[c]Percentage of variation accounted by the mediator = (estimate indirect effect/estimate total effect) × 100.
CBCL: child behavior checklist school-age version; Controls, population-based controls; FHR-BP: children with familial high risk for bipolar disorder; FHR-SZ: children with familial high risk for schizophrenia spectrum psychosis; Home: home environments; primary caregiver functioning; IQ: IQ of primary caregiver; PRS: polygenic risk scores for educational attainment of the children.

dominating, focusing on a single general factor for psychopathology, the *p*-factor, that forms the basis for an individual's risk of later mental illness.[35,36] This model implies that early signs of risk of mental illnesses are subtle, transdiagnostic, and unspecific.[35,36] The CBCL scores are in this perspective a more relevant outcome than a diagnosis because internalizing and externalizing symptoms may progress to many kinds of problems later on—or they may diminish or even disappear. And environmental factors are thought to be of significant major importance when these trajectories are determined.[37]

Being a parent is a demanding task and having a mental illness can make the task very difficult, especially if combined with cognitive difficulties, side effects of medication, sleeping problems, or paranoid thoughts about others. These problems are expected to influence the relationship with the child, the learning environment provided for the child, the ability to understand the child's perspective and needs, and the time, energy, and resources that can be devoted to parenting. Therefore, everyday functioning measured by primary caregiver functioning captures issues that are important for an adult's functioning but also aspects relevant for parenting; eg, independent housekeeping, booking appointments for general practitioner (GP) when needed, managing one's own finances and interacting with other people. Problems in these areas of life may very likely also influence the daily living of the child with increased risk of adverse life events, neglect, or poorer quality of stimulation and support, although the parent is doing what is possible. This is also why recommendations in the field of FHR point at interventions that support and improve the parent's functioning and parenting skills because that will lead to better living conditions for the child.[38]

Since the HOME score is based on direct observations and interviews and the instrument is well validated,[25] we believe that these data are highly reliable and of high quality. Also, from the perspective of developmental psychopathology, the level of stimulation and support provided in the home environment is of utmost importance for a child's developmental pathway.[39,40] The way parents handle a child's emerging mental problems like episodes with anxiety or problems with temper outbursts or anger is thought to be important for how such problems may develop later on.[41] This is in line with our results showing that both primary caregiver level of functioning and home environment mediate the effect of FHR status on psychopathology in the offspring.

Our findings suggest the need for intervention programs for the families who had lower home environment scores or lower psychosocial functioning of the primary

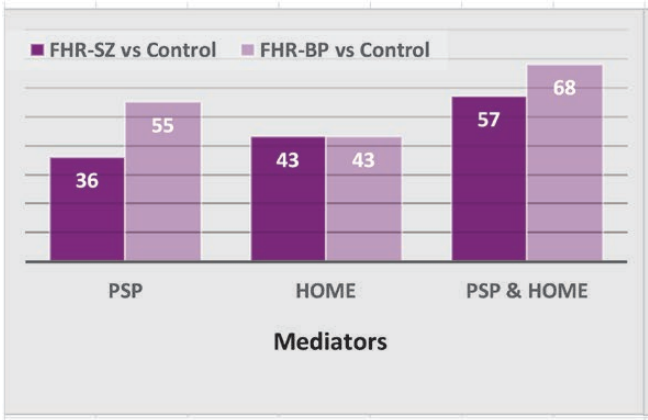

Figure 3a: Percentage of the total effect of the FHR-SZ and FHR-BP on the **CBCL Total score** explained by the mediators

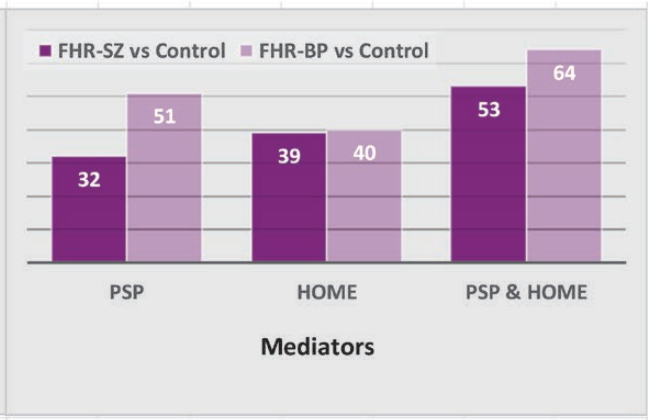

Figure 3b: Percentage of the total effect of the FHR-SZ and FHR-BP on the **CBCL Total score** explained by the mediators when IQ of the caregiver adjusted in the model

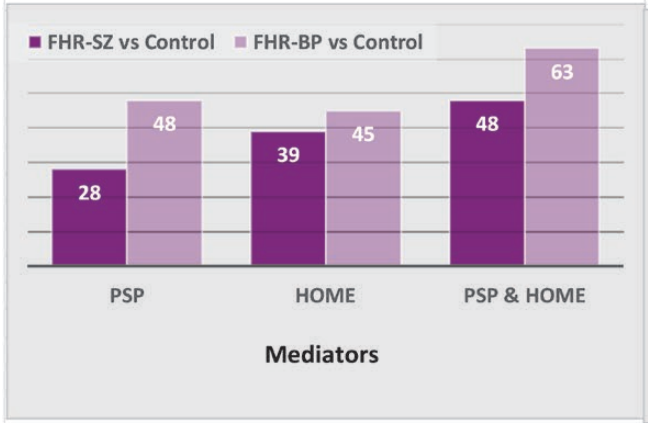

Figure 3c: Percentage of the total effect of the FHR-SZ and FHR-BP on the **CBCL externalizing score** explained by the mediators

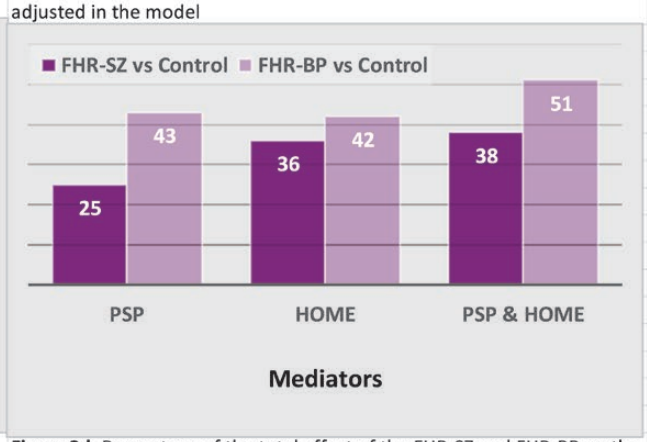

Figure 3d: Percentage of the total effect of the FHR-SZ and FHR-BP on the **CBCL externalizing score** explained by the mediators when IQ of the caregiver adjusted in the model

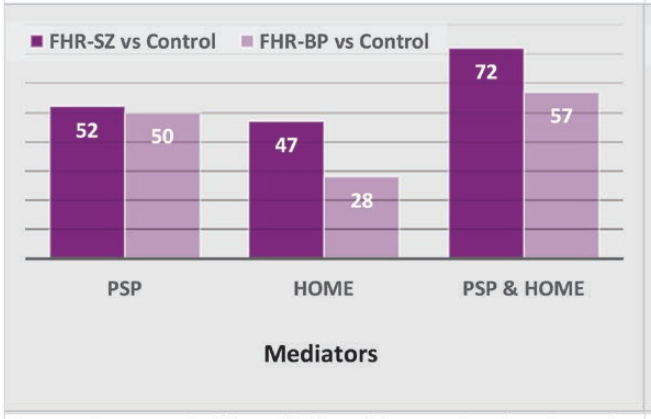

Figure 3e: Percentage of the total effect of the FHR-SZ and FHR-BP on the **CBCL internalizing score** explained by the mediators

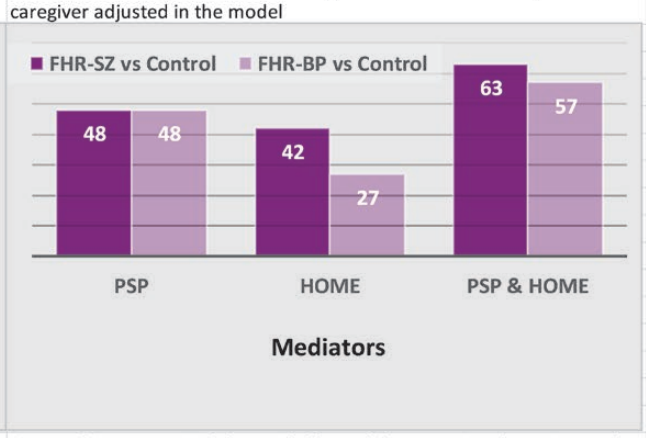

Figure 3f: Percentage of the total effect of the FHR-SZ and FHR-BP on the **CBCL internalizing score** explained by the mediators when IQ of the caregiver adjusted in the model

Fig. 3. Summary results for all mediation models with and without adjustment of the covariates (ie, primary caregiver IQ). *Note:* CBCL, child behavior checklist school-age version; Controls, population-based controls; FHR-BP, children with familial high risk for bipolar disorder; FHR-SZ, children with familial high risk for schizophrenia spectrum psychosis; Home, home environments; IQ, IQ of primary caregiver; PRS, polygenic risk scores for educational attainment of the children; PSP, primary caregiver's personal and social functioning (primary caregiver functioning).

caregiver. Parental training and family intervention could be a way to improve parental skills and the overall home environment if offered by the child management system.

Strengths and Limitations

Our study has several strengths; first, it has a large sample extracted from Danish national registers; second, to our

knowledge, this is the first FHR study applying mediation analysis that will help to set future interventions; third, we have direct measurements of the home environment, obtained through home visits with an interview of the child and with primary caregiver; fourth, only 3% of families declined the home interview; fifth, few items like neurodevelopmental symptoms in CBCL total score may be unrelated to the primary caregiver functioning/Home; finally, to understand the actual effect of Home/primary caregiver functioning on the association between FHR status and childhood psychopathology, we also analyzed our data using CBCL internalizing and externalizing scores and the results seem consistent with the main analyses.

There are also some limitations of our study: first, primary caregiver functioning and HOME are point estimates; thus, the primary caregiver functioning and the child's home environment could have historically been different and still have an impact on current psychopathology; second, the impact of mediation can be changed over time, so, further studies should be conducted using longitudinal data when such data become available[42]; third, because of parents' separation, many children lived with 2 homes. However, we only included the home information in which the child spent most of the time. Fourth, although we have data for parental substance use, the data were only for the last 12 months and we did not use this variable in our analysis. Fifth, Denmark is a high-income country with a tax-financed, universally available welfare system. As a result, the study's recommendations may only be directly transferable to such countries. Finally, when we did the sensitivity analysis excluding ADHD and/or ASD children, we get higher estimates. Thus, the main results are potentially conservative regarding the effects of the mediators.

Conclusion

The home environment and the primary caregiver's level of functioning are important mediating factors for the child's level of psychopathology, especially in children who are born with familial risk for severe mental illness. This may represent a window of opportunity for developing preventive strategies (eg, supporting parental functioning and thereby improving home environment) in the future.

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Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin Open* online.

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