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 – VIA 7, a population-based cohort study

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Abstract

We aimed to investigate to which degree the home environment and/or primary caregivers’ level of functioning mediate the association between parental mental illness (e.g. schizophrenia) and child psychopathology. We used data from the nationwide Danish High Risk and Resilience Study–VIA7. The study sample comprised of 522 7-year-old children. The main outcome was the child psychopathology, assessed with the Child Behaviour Checklist (CBCL). The exposure variable had three 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 environment (HOME), and primary caregiver’s Personal and Social Performance Scale (primary caregiver functioning). Primary caregiver’s IQ and Polygenic Risk Score (PRS) for the educational attainment of the children were considered as covariates. We found a significant indirect adjusted effect of FHR status versus controls on CBCL total scores, (FHR-SZ =5.34, 95% confidence interval (CI): 3.50 to 7.47 and FHR-BP =4.54, 95% CI: 2.65 to 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 (e.g. intervention to improve primary caregiver functioning and home environment).

Keywords: 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 or bipolar disorder are exposed to more environmental risk factors (e.g. traumatic life events, lack of parental support) compared to children whose parents do not have a severe mental illness. These children are likely to develop early signs of psychopathology and neurocognitive deficits. Previous studies have shown that children’s neurocognition, social development, and academic functioning are related to factors in their home environments, primary caregiver’s psychosocial functioning, and to their genetic composition.

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

Several previous studies have tried to disentangle and quantify genetic and environmental risk factors contributing to children’s level of psychopathology. However, the potential of using data from familial high-risk (FHR) children, including mediation analyses, has only been explored in a few studies, and mediation analysis would be an important alternative to general statistical models (e.g. linear regression) to obtain valid inference. For example, Burt et al. 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.

With 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) (Figure 1).

Here, a mediating variable is an intermediate variable on the causal pathway between exposure and the outcome.
We hypothesised 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.

2. 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 schizophrenia (FHR-SZ), 120 children of parents diagnosed with bipolar disorder (FHR-BP) and 200 population-based controls, all identified through Danish registers\(^22,23\). An index parent could have more than one child who turned 7 year 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 behaviour 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 three days and all families received a verbal feedback. We explained the detailed sample selection in Figure S1 (online supplements). Population-based control children had parents who had never been diagnosed with any of the above-mentioned 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 VIA 7 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 procedures. Some assessments were conducted at participants’ homes. Child assessors were blinded to the FHR status.

**Measures**

*Exposure variable:* The exposure variable had three categories: FHR-SZ, FHR-BP, and controls.

*Outcome variable:* Child psychopathology assessed with the Child Behaviour Checklist school-age version (CBCL)\(^{24}\), a questionnaire completed by the primary caregiver based on their impression of the child’s behaviour within the previous month. The CBCL contains 118 items related to various kinds of behavioural problems. Each item was rated on a Likert scale from zero (not true) to two (very true or often true). The CBCL total score is the sum of all items and was used as the primary outcome. Moreover, two broad-band subscales, the CBCL Internalizing (e.g. anxiety, depression and social withdrawal) and the CBCL Externalizing (e.g. aggression and impulsivity) scales, were used as secondary outcomes\(^5\). Higher CBCL scores indicate higher levels of behavioural and/or emotional problems\(^5\).
Mediator variables: We used two 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 non-biological 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 (i.e., 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. The child’s home environment was assessed with The Middle Childhood – Home Observation for Measurement of the Environment (HOME) Inventory interview, 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. The primary caregiver’s current level of functioning was assessed with the Personal and Social Performance Scale (primary caregiver functioning). The primary caregiver functioning is a 100-point rating scale based on a semi-structured interview. There are four main assessment sections: a) socially useful activities including work and study; b) personal and social relationships; c) self-care; and d) disturbing and aggressive behaviours. The higher the value of primary caregiver functioning score the better the functioning.
Covariates: Apart from age and sex of the children, we also considered the primary caregiver’s estimated level of intelligence (IQ)\textsuperscript{27}, assessed with the Reynolds Intellectual Screening Test (RIST) derived from the Reynolds Intellectual Assessment Scale (RIAS)\textsuperscript{28}.

**Polygenic risk scores**

The majority of the sample underwent genotyping. Polygenic risk scores (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 two mediators: the primary caregiver functioning score and HOME score. We assumed the mediator primary caregiver functioning to influence the HOME. That means a serial/sequence multiple mediation model (model 6, Andrew F. Hayes\textsuperscript{29,30}) is required to explain the simultaneous mediation effects of both mediators on the CBCL. Hence, we analysed 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\textsuperscript{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 three 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\textsuperscript{32}. The total and direct effects of FHR-SZ and FHR-B on the CBCL are $\beta$ (Figure 1) and $\beta'$ (Figure 1a-c), 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 1a), through only HOME $\delta_1\delta_2$ (Figure 1b); 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 1c). 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 two broad-band subscales, externalizing and internalizing scores, and repeated the same analyzes. Additionally, as children with neurodevelopmental disorders (i.e. 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 (Figure S2) and repeated the same analyzes.

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 ($r=0.15$, $p=0.002$), we did not adjust for child IQ in mediation models.

In all mediation models, the indirect effects, including percentile-based bootstrap confidence intervals, were estimated using bootstrapping with 5,000 re-samples. All analyses were performed using PROCESSv3.1 macro by Andrew F. Hayes$^{29}$ in SPSS 25. We used two 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 two mediators are considered simultaneously (model 6)$^{29,30}$. 
3. Results:

Demographic and clinical characteristics

Table 1 shows the distribution of participants’ characteristics across the three 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%) (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% confidence interval (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 two mediators, primary caregiver functioning and Home, r=0.43 [CI: 0.35, 0.50], P<0.01 (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 was 6.47 [CI: 2.11, 10.83] (P=0.004), and 10.41 [CI: 6.66, 14.16] (P<0.0001), respectively (Table 2a).

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 (i.e. only HOME) was 40% and 39%, respectively (Figure 3b).

When considering both mediators, i.e. primary caregiver functioning and HOME, simultaneously (Figure 1c), 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 2c). 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 2]

Sensitivity analyses

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 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, Table S2). Furthermore, Table S5 shows the total effects, direct effects, indirect effects, and proportion mediated (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 (Table S4). When including mediators, we noticed only small changes in the estimates after adjusting the PRS for children's educational attainment, which suggests only small effect of PRS 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 2c). 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).

4. 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\textsuperscript{5,10,27}, there was a clear difference between exposure groups. Furthermore, after adjustment for the genetic composition of the children, e.g. 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 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\textsuperscript{35,36}. This model implies that early signs of risk of mental illnesses are subtle, transdiagnostic and unspecific\textsuperscript{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\textsuperscript{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; e.g. independent housekeeping, booking appointments for 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 familial
high-risk 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\textsuperscript{38}.

Since the HOME score is based on direct observations and interviews and the instrument is
well-validated\textsuperscript{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\textsuperscript{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\textsuperscript{41}. This is in line with our results showing that both primary
caregiver level of functioning and home environment mediate the effect of familial high-risk
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 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.

\textit{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 familial high-risk 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 analysed 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; third, because of parents’ separation, many children lived with two 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 was only for 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. Therefore, the recommendations based on the study may only be direct transferrable 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 (e.g. supporting parental functioning and thereby improving home-environment) in the future.
References:

1. Wan MW, Abel KM, Green J. The transmission of risk to children from mothers with schizophrenia: A developmental psychopathology model. *Clin Psychol Rev*. 2008;28(4):613-637. doi:10.1016/j.cpr.2007.09.001

2. DelBello MP, Geller B. Review of studies of child and adolescent offspring of bipolar parents. *Bipolar Disord*. 2001;3(6):325-334. Accessed January 31, 2019. http://www.ncbi.nlm.nih.gov/pubmed/11843782

3. Rasic D, Hajek T, Alda M, Uher R. Risk of Mental Illness in Offspring of Parents With Schizophrenia, Bipolar Disorder, and Major Depressive Disorder: A Meta-Analysis of Family High-Risk Studies. *Schizophr Bull*. 2014;40(1). Accessed January 31, 2019. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3885302/

4. Thorup AAE, Laursen TM, Munk-Olsen T, et al. Incidence of child and adolescent mental disorders in children aged 0-17 with familial high risk for severe mental illness - A Danish register study. *Schizophr Res*. 2018;197:298-304. doi:10.1016/j.schres.2017.11.009

5. Ellersgaard D, Jessica Plessen K, Richardt Jepsen J, et al. Psychopathology in 7-year-old children with familial high risk of developing schizophrenia spectrum psychosis or bipolar disorder - The Danish High Risk and Resilience Study - VIA 7, a population-based cohort study. *World Psychiatry*. 2018;17(2):210-219. doi:10.1002/wps.20527

6. Agnew-Blais J, Seidman LJ. Neurocognition in youth and young adults under age 30 at familial risk for schizophrenia: a quantitative and qualitative review. *Cogn Neuropsychiatry*. 2013;18(1-2):44-82. doi:10.1080/13546805.2012.676309

7. Vos T, Barber RM, Bell B, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: A systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2015;386(9995):743-800. doi:10.1016/S0140-6736(15)60692-4

8. Linver MR, Brooks-Gunn J, Kohen DE. Family processes as pathways from income to young children’s development. *Dev Psychol*. 2002;38(5):719-734. Accessed January 31, 2019. http://www.ncbi.nlm.nih.gov/pubmed/12220050

9. Totsika V, Sylva K. The Home Observation for Measurement of the Environment Revisited. *Child Adolesc Ment Health*. 2004;9(1):25-35. doi:10.1046/j.1475-
10. Gantriis D Lou, Thorup AAE, Harder S, et al. Home visits in the Danish High Risk and Resilience Study – VIA 7 Assessment of the home environment of 508 7-year-old children born to parents diagnosed with schizophrenia or bipolar disorder. *Acta Psychiatr Scand.* 2019;140(2):acps.13057. doi:10.1111/acps.13057

11. World Health Organization. Department of Child and Adolescent Health and Development. *The Importance of Caregiver-Child Interactions for the Survival and Healthy Development of Young Children: A Review.* Dept. of Child and Adolescent Health and Development, World Health Organization; 2004.

12. Jansen PR, Polderman TJCC, Bolhuis K, et al. Polygenic scores for schizophrenia and educational attainment are associated with behavioural problems in early childhood in the general population. *J Child Psychol Psychiatry Allied Discip.* 2018;59(1):39-47. doi:10.1111/jcpp.12759

13. Rubio-Codina M, Attanasio O, Grantham-McGregor S. Mediating pathways in the socio-economic gradient of child development: Evidence from children 6-42 months in Bogota. *Int J Behav Dev.* 2016;40(6):483-491. doi:10.1177/0165025415626515

14. Braungart-Rieker J, Rende RD, Plomin R, DeFries JC, Fulker DW. Genetic mediation of longitudinal associations between family environment and childhood behavior problems. *Dev Psychopathol.* 1995;7(2):233-245. doi:10.1017/S0954579400006477

15. Schulz-Heik RJ, Rhee SH, Silvern LE, et al. The association between conduct problems and maltreatment: testing genetic and environmental mediation. *Behav Genet.* 2010;40(3):338-348. doi:10.1007/s10519-009-9324-6

16. Iacono V, Beaulieu L, Hodgins S, Ellenbogen MA. Parenting practices in middle childhood mediate the relation between growing up with a parent having bipolar disorder and offspring psychopathology from childhood into early adulthood. *Dev Psychopathol.* 2018;30(2):635-649. doi:10.1017/S095457941700116X

17. Burt KB, Van Dulmen MHM, Carlivati J, et al. Mediating links between maternal depression and offspring psychopathology: the importance of independent data. *J Child Psychol Psychiatry.* 2005;46(5):490-499. doi:10.1111/j.1469-7610.2004.00367.x

18. Cohen J, Cohen P, West SG, Aiken LS. *Applied Multiple Regression/Correlation Analysis for the Behavioral Sciences.* Routledge; 2013.
19. Hayes AF. *Introduction to Mediation, Moderation and Conditional Process Analysis*. Vol 53. Second Edi.; 2013. doi:10.5539/ass.v11n9p207

20. Thorup AAE, Jepsen JR, Ellersgaard DV, et al. The Danish High Risk and Resilience Study–VIA 7-a cohort study of 520 7-year-old children born of parents diagnosed with either schizophrenia, bipolar disorder or neither of these two mental disorders. *BMC Psychiatry*. 2015;15(1):233. doi:10.1186/s12888-015-0616-5

21. Hemager N, Plessen KJ, Thorup A, et al. Assessment of neurocognitive functions in 7-year-old children at familial high risk for schizophrenia or bipolar disorder: the Danish high risk and resilience study VIA 7. *JAMA psychiatry*. 2018;75(8):844-852.

22. Pedersen CB, Götzsche H, Møller JO, Mortensen PB. The Danish Civil Registration System. A cohort of eight million persons. *Dan Med Bull*. 2006;53(4):441-449. Accessed September 19, 2019. http://www.ncbi.nlm.nih.gov/pubmed/17150149

23. Mors O, Perto GP, Mortensen PB. The Danish Psychiatric Central Research Register. *Scand J Public Health*. 2011;39(7_suppl):54-57. doi:10.1177/1403494810395825

24. Achenbach TM. *Manual for the Child Behavior Checklist/4-18 and 1991 Profile*. Dept. of Psychiatry, University of Vermont; 1991. Accessed August 13, 2019. https://books.google.dk/books/about/Manual_for_the_Child_Behavior_Checklist.html?id=I5btOwAACAAJ&redir_esc=y

25. Bradley RH, Caldwell BM, Rock SL, Hamrick HM, Harris P. Home Observation for Measurement of the Environment: Development of a Home Inventory for use with families having children 6 to 10 years old. *Contemp Educ Psychol*. 1988;13(1):58-71. doi:10.1016/0361-476X(88)90006-9

26. Morosini PL, Magliano L, Brambilla L, Ugolini S, Pioli R. Development, reliability and acceptability of a new version of the DSM-IV Social and Occupational Functioning Assessment Scale (SOFAS) to assess routine social functioning. *Acta Psychiatr Scand*. 2000;101(4):323-329. Accessed August 6, 2019. http://www.ncbi.nlm.nih.gov/pubmed/10782554

27. Ronfani L, Vecchi Brumatti L, Mariuz M, et al. The Complex Interaction between Home Environment, Socioeconomic Status, Maternal IQ and Early Child Neurocognitive Development: A Multivariate Analysis of Data Collected in a Newborn Cohort Study. Gorlova OY, ed. *PLoS One*. 2015;10(5):e0127052.
28. Cecil R. Reynolds and RWK. RIAS (Reynolds Intellectual Assessment Scales) and the RIST (Reynolds Intellectual Screening Test): Professional Manual. Psychological Assessment Resources.; 2003. https://www.parinc.com/Products/Pkey/364

29. Andrew F. Hayes. The PROCESS macro for SPSS and SAS - PROCESS macro for SPSS and SAS. Published 2018. Accessed January 31, 2019. https://processmacro.org/index.html

30. Hayes AF. Introduction to Mediation, Moderation, and Conditional Process Analysis: A Regression-Based Approach. 2nd ed. (Little TD, ed.). The Guilford Press; 2017. Accessed August 13, 2019. https://www.guilford.com/books/Introduction-to-Mediation-Moderation-and-Conditional-Process-Analysis/Andrew-Hayes/9781462534654

31. VanderWeele T. Explanation in causal inference: methods for mediation and interaction. Published online 2015.

32. Starkopf L, Porsborg M, Thomas A, Gerds A, Torp-Pedersen C, Lange T. Comparison of Five Software Solutions to Mediation Analysis. Accessed August 29, 2019. https://ifsv.sund.ku.dk/biostat/annualreport/images/0/0a/Research_Report_17-01.pdf

33. Piffer D, Kirkegaard EOW. The genetic correlation between educational attainment, intracranial volume and IQ is due to recent polygenic selection on general cognitive ability. Open Behav Genet. Published online April 12, 2014. doi:10.26775/OBG.2014.04.12

34. H.J. S, J.-C. D, E. A, et al. Polygenic Risk Scores, School Achievement, and Risk for Schizophrenia: A Danish Population-Based Study. Biol Psychiatry. 2018;84(9):684-691. doi:http://dx.doi.org/10.1016/j.biopsych.2018.04.012

35. Caspi A, Houts RM, Ambler A, et al. Longitudinal Assessment of Mental Health Disorders and Comorbidities Across 4 Decades Among Participants in the Dunedin Birth Cohort Study. JAMA Netw open. 2020;3(4):e203221. doi:10.1001/jamanetworkopen.2020.3221

36. Murray AL, Eisner M, Ribeaud D. The Development of the General Factor of Psychopathology ‘p Factor’ Through Childhood and Adolescence. J Abnorm Child Psychol. 2016;44(8):1573-1586. doi:10.1007/s10802-016-0132-1
37. Forbes MK, Rapee RM, Krueger RF. Opportunities for the prevention of mental disorders by reducing general psychopathology in early childhood. *Behav Res Ther.* 2019;119:103411. doi:10.1016/j.brat.2019.103411

38. Seidman LJ, Nordentoft M. New targets for prevention of schizophrenia: is it time for interventions in the premorbid phase? *Schizophr Bull.* 2015;41(4):795-800.

39. Rutter M, Sroufe LA. Developmental psychopathology: Concepts and challenges. *Dev Psychopathol.* 2000;12(3):265-296.

40. Beauchaine TP, Constantino JN, Hayden EP. Psychiatry and developmental psychopathology: Unifying themes and future directions. *Compr Psychiatry.* 2018;87:143-152.

41. Leibenluft E, Stoddard J. The developmental psychopathology of irritability. *Dev Psychopathol.* 2013;25(4 0 2):1473.

42. Thorup AAE, Hemager N, Søndergaard A, et al. The Danish High Risk and Resilience Study—VIA 11: Study Protocol for the First Follow-Up of the VIA 7 Cohort—522 Children Born to Parents With Schizophrenia Spectrum Disorders or Bipolar Disorder and Controls Being Re-examined for the First Time at Age 1. *Front psychiatry.* 2018;9:661.
**Figure Legends:**

Figure 1: Directed Acyclic Graph (DAG) for illustrating the research questions and the analytical models with different effects (total, direct and indirect)

Figure 2: Mean CBCL total scores (left), Personal and level of functioning care (primary caregiver functioning) of the primary caregiver (middle) and Home environment scores (right) including 95% confidence interval for three exposure groups.

Figure 3: Summary results for all mediation models with and without adjustment of the covariates (i.e., primary caregiver IQ)

**Table Legends:**

Table 1: Distribution of participants characteristics across the exposure groups.

Table 2: 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 Total.
Figure Legends

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**Abbreviation:** FHR-SZ: children with familial high risk for schizophrenia spectrum psychosis; FHR-BP: children with familial high risk for bipolar disorder; controls – population-based controls; CBCL: child behaviour checklist school-age version; Home: home environments; PSP: Primary caregiver’s personal and social functioning (primary caregiver functioning); IQ: IQ of primary caregiver; PRS: Polygenic risk scores for education attainment of the children.

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Table 1: Distribution of participants characteristics across the exposure groups

| Covariates                                      | N   | FHR-SZ | FHR-BP | Controls | N (%) | P-value | FHR-SZ vs. Controls | FHR-BP vs. Controls | FHR-BP vs. FHR-SZ |
|------------------------------------------------|-----|--------|--------|----------|-------|---------|-------------------|-------------------|------------------|
| Children                                       | 522 | 202    | 120    | 200      |       |         |                   |                   |                  |
| Female, N (%)                                  | 242 | 93     | 56     | 93       | (46.0)| (46.7)  | 0.993             | 0.926             | 0.977            | 0.913            |
| Age at inclusion, years, mean (SD)             | 522 | 7.84   | 7.86   | 7.81     | (0.22)| (0.20)  | 0.097             | 0.532             | 0.106            | 1.00             |
| CBCL: Total score (sum of all items)           | 494 | 27.20  | 23.41  | 17.01    | (21.05)| (19.71) | <0.001            | <0.001            | 0.012            | 0.26             |
| CBCL Externalising score                       | 495 | 7.78   | 6.17   | 4.08     | (7.43)| (6.68)  | <0.001            | <0.001            | 0.018            | 0.10             |
| CBCL Internalising score                       | 495 | 6.57   | 6.60   | 4.84     | (5.88)| (6.83)  | 0.004             | 0.008             | 0.027            | 1.00             |
| Home Status                                    |     |        |        |          |       |         |                   |                   |                  |
| Living with both biological parents, N (%)     | 300 | 74     | 61     | 165      | (39.6)| (55.0)  | <0.001            | <0.001            | <0.001           | 0.010            |
| Living out of home, N (%)                      | 12  | -      | -      | -        |       | -       | -                 | -                 | -                | -                |
| Living with index parent, N (%)                | 378 | 115    | 79     | 184      | (61.2)| (71.2)  | <0.001            | <0.001            | <0.001           | 0.90             |
| Living with a single parent, N (%)             | 125 | 70     | 34     | 21       | (37.4)| (30.6)  | <0.001            | <0.001            | <0.001           | 0.234            |
| HOME total score, mean (SD)                    | 508 | 44.97  | 46.70  | 49.03    | (6.41)| (4.68)  | <0.001            | <0.001            | <0.001           | 0.17             |
| Primary caregiver’s level of functioning (PSP), mean (SD) | 511 | 73.19  | 74.47  | 84.42    | (14.10)| (14.12)| <0.0001           | <0.001            | <0.001           | 1.00             |
| Primary caregiver’s estimated IQ, mean (SD)    | 513 | 102.34 | 105.15 | 103.89   | (8.73)| (8.09)  | 0.012             | 0.186             | 0.576            | 0.011            |
| Education of index Parents                     | 482 |        |        |          |       |         |                   |                   |                  |
| Primary/lower secondary, N (%)                 | 72  | 54     | 10     | 8        | (30.5)| (9.3)   | <0.0001           | <0.0001           | 0.930            | <0.0001          |
| Upper secondary, vocational, short-cycle tertiary, N (%) | 214 | 75     | 44     | 95       | (42.4)| (40.7)  | 95 (48.2)         |                   |                  |
| Bachelor’s degree, equivalent or higher, N (%) | 196 | 48     | 54     | 94       | (27.1)| (50.0)  | 94 (47.7)         |                   |                  |
| PRS for educational attainment of the children, mean (SD) | 402 | -0.14  | 0.16   | 0.03     | (1.00)| (0.98)  | 0.07              | 0.41              | 0.99             | 0.07             |
| PRS for schizophrenia of the children, mean (SD) | 402 | 0.04   | 0.18   | -0.15    | (0.95)| (1.01)  | 0.03              | 0.27              | 0.04             | 0.93             |
| PRS for bipolar disorder of the children, mean (SD) | 402 | 0.09   | 0.07   | -0.12    | (0.91)| (1.05)  | 0.13              | 0.20              | 0.37             | 1.00             |

*Reynolds Intellectual Screening Test (RIST); For continuous variable, the P-values (Bonferroni corrected) based one-way analysis of variance (ANOVA) and for binary/categorical variables, the P-value based on Chi-square test.

Abbreviation: FHR-SZ: children with familial high risk for schizophrenia spectrum psychosis; FHR-BP: children with familial high risk for bipolar disorder; Controls – population-based controls; CBCL: child behaviour checklist school-age version; HOME: home environments; PSP: Psychosocial functioning; IQ: IQ of primary caregiver; PRS: Polygenic risk scores (standardized scores) for education attainment of the children (p-value threshold 0.0001), for schizophrenia of the children (p-value threshold 0.000001), for bipolar disorder of the children (p-value threshold 0.90). The P-value threshold were selected based R-square values.
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.

**Table 2a: Mediator: Primary caregiver functioning (corresponds to the Figure 1a)**

| Exposure Category | Total Effect | Direct Effect | Indirect Effect | % of variation accounted by the mediator | mediator |
|-------------------|-------------|---------------|-----------------|----------------------------------------|----------|
| **Crude model (n=489)** |             |               |                 |                                        |          |
| FHR-BP            | 6.47        | [2.11, 10.83] | [2.55, 10.83]   | 55%                                    |          |
| FHR-SZ            | 10.41       | [2.76, 14.16] | [2.57, 10.54]   | 36%                                    |          |
| **Model adjusted with caregiver IQ* (n=489)** |             |               |                 |                                        |          |
| FHR-BP            | 6.96        | [2.73, 11.19] | [2.76, 10.63]   | 51%                                    |          |
| FHR-SZ            | 10.23       | [6.61, 13.84] | [2.57, 10.72]   | 32%                                    |          |
| **Analysis using subjects that have available PRS data for child educational attainment (n=387)** |             |               |                 |                                        |          |
| FHR-BP            | 5.56        | [1.74, 10.34] | [2.57, 10.54]   | 46%                                    |          |
| FHR-SZ            | 10.06       | [5.85, 14.27] | [2.66, 14.48]   | 30%                                    |          |
| **Model adjusted with PRS for the educational attainment of child* (n=387)** |             |               |                 |                                        |          |
| FHR-BP            | 5.85        | [1.18, 10.52] | [1.18, 4.45]    | 43%                                    |          |
| FHR-SZ            | 9.49        | [3.68, 13.63] | [2.41, 11.06]   | 39%                                    |          |
| **Model adjusted with IQ of caregiver and PRS for the educational attainment of child* (n=386)** |             |               |                 |                                        |          |
| FHR-BP            | 6.38        | [1.74, 11.02] | [0.97, 4.29]    | 40%                                    |          |
| FHR-SZ            | 9.43        | [5.37, 13.49] | [0.95, 3.96]    | 25%                                    |          |

**Table 2b: Mediator: Home Environment (corresponds to the Figure 1b)**

| Exposure Category | Total Effect | Direct Effect | Indirect Effect | % of variation accounted by the mediator | mediator |
|-------------------|-------------|---------------|-----------------|----------------------------------------|----------|
| **Crude model (n=485)** |             |               |                 |                                        |          |
| FHR-BP            | 6.50        | [2.15, 10.85] | [1.52, 4.27]    | 43%                                    |          |
| FHR-SZ            | 9.96        | [6.22, 13.69] | [2.83, 5.82]    | 43%                                    |          |
| **Model adjusted with primary caregiver IQ* (n=485)** |             |               |                 |                                        |          |
| FHR-BP            | 7.00        | [2.74, 11.27] | [1.55, 4.35]    | 40%                                    |          |
| FHR-SZ            | 9.91        | [6.29, 13.53] | [2.53, 5.41]    | 39%                                    |          |
| **Analysis using subjects that have available PRS data for child educational attainment* (n=387)** |             |               |                 |                                        |          |
| FHR-BP            | 5.46        | [0.69, 10.24] | [1.20, 4.10]    | 46%                                    |          |
| FHR-SZ            | 10.05       | [5.84, 14.26] | [2.61, 5.70]    | 40%                                    |          |
| **Model adjusted with PRS for the educational attainment of child* (n=387)** |             |               |                 |                                        |          |
| FHR-BP            | 5.79        | [1.12, 10.46] | [1.17, 3.99]    | 42%                                    |          |
| FHR-SZ            | 9.51        | [5.8, 13.63]  | [2.44, 5.32]    | 40%                                    |          |
| **Model adjusted with IQ of caregiver and PRS for the educational attainment of child* (n=386)** |             |               |                 |                                        |          |
| FHR-BP            | 6.37        | [1.73, 11.02] | [1.26, 4.02]    | 39%                                    |          |
| Exposure Category | Total Effect | Direct Effect | Indirect Effects | % of variation accounted by the mediator |
|-------------------|--------------|---------------|-----------------|-----------------------------------------|
| FRH-BP            | 6.58         | 2.10          | 4.46            | 68%                                     |
|                   | [2.30, 10.86]| [-2.04, 6.23] | [2.71, 6.56]    |                                         |
| FRH-SZ            | 10.18        | 4.37          | 5.78            | 57%                                     |
|                   | [6.46, 13.89]| [0.75, 7.99]  | [3.97, 7.86]    |                                         |

Model adjusted with primary caregiver IQ* (n=483)

| Exposure Category | Total Effect | Direct Effect | Indirect Effects | % of variation accounted by the mediator |
|-------------------|--------------|---------------|-----------------|-----------------------------------------|
| FRH-BP            | 7.07         | 2.52          | 4.54            | 64%                                     |
|                   | [1.81, 11.34]| [-1.68, 6.72] | [2.65, 6.68]    |                                         |
| FRH-SZ            | 10.05        | 4.68          | 5.34            | 53%                                     |
|                   | [5.42, 13.68]| [1.02, 8.34]  | [3.50, 7.47]    |                                         |

Analysis using subjects that have available PRS data for child educational attainment (n=382)

| Exposure Category | Total Effect | Direct Effect | Indirect Effects | % of variation accounted by the mediator |
|-------------------|--------------|---------------|-----------------|-----------------------------------------|
| FRH-BP            | 5.56         | 1.92          | 3.63            | 65%                                     |
|                   | [0.80, 10.31]| [-2.70, 6.54] | [1.87, 5.57]    |                                         |
| FRH-SZ            | 10.22        | 5.19          | 5.02            | 49%                                     |
|                   | [6.05, 14.40]| [0.94, 9.43]  | [3.27, 6.90]    |                                         |

Model adjusted with PRS for the educational attainment of child* (n=382)

| Exposure Category | Total Effect | Direct Effect | Indirect Effects | % of variation accounted by the mediator |
|-------------------|--------------|---------------|-----------------|-----------------------------------------|
| FRH-BP            | 5.85         | 2.34          | 3.51            | 60%                                     |
|                   | [1.17, 10.52]| [-2.24, 6.93] | [1.75, 5.42]    |                                         |
| FRH-SZ            | 9.65         | 4.96          | 4.67            | 48%                                     |
|                   | [5.50, 13.80]| [0.75, 9.18]  | [2.93, 6.50]    |                                         |

Model adjusted with IQ of caregiver and PRS for the educational attainment of child (n=382)

| Exposure Category | Total Effect | Direct Effect | Indirect Effects | % of variation accounted by the mediator |
|-------------------|--------------|---------------|-----------------|-----------------------------------------|
| FRH-BP            | 6.43         | 2.86          | 3.59            | 55%                                     |
|                   | [1.78, 11.07]| [-1.81, 7.52] | [1.81, 5.56]    |                                         |
| FRH-SZ            | 9.63         | 5.34          | 4.28            | 44%                                     |
|                   | [5.55, 13.70]| [1.09, 9.59]  | [2.57, 6.34]    |                                         |

Abbreviation: FHR-SZ: children with familial high risk for schizophrenia spectrum psychosis; FHR-BP: children with familial high risk for bipolar disorder; Controls – population-based controls; CBCL: child behaviour checklist school-age version; Home: home environments; primary caregiver functioning; IQ: IQ of primary caregiver; PRS: Polygenic risk scores for education attainment of the children.

*Primary caregiver IQ and polygenic risk scores (PRS) of child education (p-value threshold 0.0001) are significantly associated with the Child Behaviour Checklist school-age version (CBCL) Total

Y Bootstrap estimate and 95% percentile bootstrap confidence interval with 5,000 bootstrap samples.

§ % of variation accounted by the mediator = (Estimate indirect effect / Estimate total effect) × 100
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