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Accumulation of Disadvantages Across Multiple Domains Amongst Subgroups of Children of Parents With Schizophrenia or Bipolar Disorder: Clustering Data from the Danish High Risk and Resilience Study VIA 7

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Objective: **Children with familial high-risk of schizophrenia (FHR-SZ) or bipolar disorder (FHR-BP) are frequently affected in a range of domains known to be precursors of severe mental illness. No previous studies have gathered known precursors to examine whether they distribute evenly across familial high risk (FHR) children or if they cluster among a smaller group. Since such examination holds the potential to identify high and low risk of severe mental illness groups, we aimed to cluster FHR and control children affected to various degrees.**

Method: **In The Danish High Risk and Resilience Study VIA 7, a clinical cohort study, 514 7-year-old children with FHR-SZ or FHR-BP and matched controls were assessed in domains of motor function, neurocognition, emotional control, behavior, social cognition, self-perception, language, psychotic experiences, and psychopathology, and grouped using cluster analysis. Associations between clusters and parents' level of education, functioning, caregiver status, child's level of stimulation and support in the home, and polygenic risk scores were examined.**

Results: **A total of four groups including one of broadly affected children were identified. The broadly affected group was represented 4–5-fold (18.1%) amongst FHR-SZ children and 2–3-fold (10.2%) amongst FHR-BP children, compared to controls (4.1%) ($P < .001$), and the broadly affected group had lower levels of caregiver functioning ($P < .001$) and stimulation and support at home ($P < .001$).**

Conclusion: **Precursors of severe mental illness distribute unevenly among FHR children; while approximately half are not affected in any domains, the other half are affected to various degrees. Targeted support towards the affected groups is indicated.**

Key words: familial high-risk/schizophrenia/bipolar disorder/cross-domain/distribution

Introduction

Children of parents diagnosed with schizophrenia or bipolar disorder have a 10-fold increased risk of developing a severe mental illness compared to the general population.[1] High-risk studies examining children with familial high-risk of schizophrenia and bipolar disorder have provided considerable knowledge on the possible precursors amongst these children, and a range of domains have been identified to be affected amongst familial high-risk children who later develop a severe mental illness.[2–8] Previous studies regarding children born to parents with schizophrenia, and to a lesser extent regarding children born to parents with bipolar disorder, have reported impairments such as cognitive deficits,[9–11] language and behavior problems,[12,13] deficits in motor function,[9,10,14] and higher prevalence of psychopathology.[1,10] However, many studies had limitations such as small sample sizes, wide age ranges, inclusion from psychiatric clinics rather than population-based inclusion, and nonmatched controls.[9,15] Furthermore, only a few studies have compared children of parents with schizophrenia with children of parents with bipolar disorder,[16] generally showing children of parents with schizophrenia to be most affected in the domains examined. Furthermore, most have only examined a few of the domains at a time and have thus allowed for conclusions regarding eg prevalence of motor difficulties but not regarding accumulation of other precursors, eg neurocognitive precursors, in those with motor difficulties.

As early as in the first familial high-risk study on schizophrenia, Barbara Fish hypothesized that impairments and possible precursors of illness were found in several domains[2] and while numerous studies have demonstrated impairments in familial high-risk offspring, no studies have analyzed the distribution of impairments from many domains together. Analyses of data across domains are needed to examine whether a group of children are broadly affected and thus, in broad need for support and likely also at higher risk of severe mental illness than other FHR children, considering the extensive literature which have demonstrated premorbid impairments before onset of severe mental illness. Since most FHR studies have only included a few of the domains known to be precursors of severe mental illness each, these studies have not been able to answer whether the same children who are affected in one domain are also affected in other domains (Supplementary Figure 1 A), or if difficulties known to be precursors are more evenly distributed (Supplementary Figure 1 B) among FHR children. This question is of clinical importance since identification of a possible group with multiple impairments could be the first step towards a preventive strategy which focused on this group of familial high-risk children rather than the other groups of children, of which many may not be in need of support and may not be at as high risk of developing a severe mental illness. Further, a possible identification of a FHR child profile which is not affected by known precursors is of importance for antistigmatization and to identify characteristics possibly related to resilience. The Danish High Risk and Resilience Study - VIA 7[17] (hereafter the VIA 7 study) is a population-based familial high-risk cohort study of children all the same age. The test battery of the study was created on the basis of the existing literature concerning precursors for severe mental illness among familial high-risk children and age 7 was chosen because this age allowed for informants from school as well as from parents and further, because it was found suitable since precursors have previously been reported from this age.[17] The VIA 7 Study has identified impairments in many of the above-mentioned domains[18–23] separately but not previously combined. Our study design allows for examination of the distribution of impairments across domains, using cluster analysis to identify children affected across multiple domains to various degrees.

Objectives

We aimed to examine whether we could identify a group of children who were broadly affected in many domains, and to identify the proportions of children of parents with schizophrenia, children of parents with bipolar disorder, and population-based controls belonging to this group. We likewise aimed to examine whether we could identify a group of children who were not affected in any domains. Furthermore, we aimed to analyze how social and genetic characteristics were associated with cluster groups. We hypothesized that the broadly affected profile would be overrepresented among children of parents with schizophrenia. We further hypothesized that the broadly affected children would be characterized by high genetic risk of mental illness and social disadvantages such as low levels of parental functioning and low levels of stimulation and support and likewise, that children who were not affected would have parents with high levels of parental functioning and high levels of stimulation and support in their homes.

Methods

Study Design and Setting

The VIA 7 study is a population-based case-cohort study consisting of 522 7-year-old, Danish children with familial high-risk of schizophrenia (FHR-SZ), familial high-risk of bipolar disorder (FHR-BP), and population-based controls (PBC) matched to the FHR-SZ children on age, sex, and municipality.[17,24]

Children and parents were identified through Danish nationwide registers.[25] Inclusion and data collection were conducted between January 1, 2013 and January 31, 2016. Assessments were performed in research

departments in Aarhus and Copenhagen, and in the children's homes, by trained psychologists, doctors, and nurses. Child assessors were blinded to FHR status. The levels of stimulation and support were measured by using a semistructured home environment interview including several subscales of relevance for the home environment[26] during home visits. The study domains included child motor function, neurocognition, emotional control, behavior, social cognition, self-perception, language, psychotic experiences, and psychopathology.[17] Also, data from biological parents (or nonbiological caregivers if the child was in foster care) regarding their psychopathology, global level of functioning, and socio-economy was collected. Furthermore, biological material including DNA samples from children and parents were collected. The study was approved by the Danish Data Protection Agency and the National Committee for Health Research Ethics – for the latter, only approval of the biological samples was needed.

Participants

Danish children who turned seven between September 1, 2011, and August 31, 2016, born to at least one parent with schizophrenia or bipolar disorder (hereafter the index parent), and controls with neither parents diagnosed with any of these, were identified through national registers as eligible[17] (see Supplementary Table 3, available online). According to the diagnostic ICD-10 hierarchy, children with one parent diagnosed with bipolar disorder and one with schizophrenia spectrum disorder were assigned to the schizophrenia group. The cohort has been described extensively elsewhere.[17] Examined through register-based data concerning socio-economic factors and health characteristics, the cohort was found to be nationwide representative regarding parental severity of illness (as measured by service use and use of coercive measures) but with a selection bias towards inclusion of families from densely populated areas and of families which had not received preventive interventions for their included child.

Further, participants had a higher level of education than non-participants.[27] A total of 514 (8 were excluded due to missing assessments) children and their parents were included in this analysis.

Measures of Child Performance Used for Cluster Analysis

We included instruments from domains frequently affected in familial high-risk children and considered to be precursors of severe mental illness regarding motor function, neurocognition, emotional control, behavior, social cognition, self-perception, language, psychotic experiences (PEs), and psychopathology (see Supplementary Table 1, available online). Validated, comprehensive instruments with the lowest amount of missing answers (fewer than 9 missing total scores or subscale scores, see Supplementary Table 2, available online) were chosen from the assessment battery administered in the VIA 7 study.[17] Data concerning domains which had been the subject of separate studies[18–22] were gathered to examine the distribution of impairments across domains. For neurocognition, four neurocognitive domains were included, based on principle component analysis in a previous study.[21] We thus aimed to include data related to the child's own performance from all the domains which have been found in previous studies to be possible precursors of severe mental illness to examine the distribution of impairments.

Measures Not Included in the Cluster Analysis

In order to illustrate the general function of the children with well-known measures, we further analysed the group level of global functioning (CGAS)[28] and mean estimated IQ (RIST Index)[29] separately. The analysis of the CGAS served to validate cluster findings since this is a clinically well-known measure to estimate overall level of functioning, and the IQ analysis was also shown separately because of its clinical relevance, besides being included in the clustering as part of one of the neurocognitive variables.

Genetic Risk and Social Disadvantages

Supplemental analyses were performed to describe the distribution of genetic and social characteristics within each identified cluster (see Supplementary Table 1, available online). We used the Danish version of the International Standard Classification of Education (DISCED)[30] to measure parental level of education.

We included polygenic risk scores (PRS)[31] for schizophrenia, bipolar disorder, major depression, cognitive performance, and educational attainment, for a subset who provided biological material. The quality control (QC) procedure for the genetic data in the VIA 7 study is described elsewhere.[32] For the full PRS generation protocol, see Supplementary Text 7 (available online).

Statistical Methods

Descriptive statistics estimated the means and standard deviations for all variables by risk status. All nondichotomous scores were converted to z-scores with the control group mean as reference. The principal component analysis for the four neurocognitive variables is described elsewhere.[21] A correlation analysis confirmed that correlations between the chosen tests did not exceed 0.8 (Supplementary Table 4, available online) to avoid multicollinearity. Prior to clustering, missing values were imputed using the regularised iterative principle component analysis algorithm using the first two principle components.[33] Hierarchical cluster analysis (Ward's

criterion) was used to identify latent groups.[34] The hierarchical cluster analysis approach was chosen over other approaches, eg latent class or logistic regression models, because our goal was to perform a descriptive analysis which could find natural groupings in the dataset rather than to identify latent structures in the data, and because clustering is more flexible when boundaries for decision-making are multiple while other approaches, eg logistic regression models, are often too inflexible to identify complex structures in the data.[35] Dissimilarities between clusters were calculated by using the Euclidian squared distance between clusters. A priori we hypothesized that children would distribute across three to four cluster groups; one that would be broadly affected across all domains, one or two with intermediate results and one that was not affected. The final split was based on a data-driven distribution and visual inspection of the dendrogram. Mean differences between cluster groups were estimated and tested for each variable separately using one-way ANOVA. The means and proportions of environmental and genetic variables were compared between cluster groups using one-way ANOVA or, for dichotomous data, chi-square test, to determine differences. The cluster analysis was unadjusted in order to show differences eg in prevalence of diagnosis. Since the study was primarily descriptive and hypothesis-generating, all *P*-values are nominal with a significance level of 5%, ie no correction for multiplicity was applied.

As a few instruments had known norm scores for boys respectively girls, an analysis adjusting for the effect of sex amongst control children was made (Supplementary Table 6, available online).

All analyses were conducted using the statistical software R, version 3.5.3.

Results

FHR-SZ children were significantly more affected than PBC in most domains whilst FHR-BP children were affected to an intermediate level, compared to FHR-SZ and PBC (Table 1). Thus, the schizophrenia group had worst outcomes in 15 out of 17 measures while this was the case for 1 out of 17 measures for the bipolar group. For one other measure (concerning psychotic experiences), the schizophrenia and bipolar groups had equal results, and also in this measure, these groups were more affected than PBC.

The Cluster Analysis

Four overall profiles which differed significantly from each other in the cluster analysis were identified. These displayed the distribution of difficulties across the included domains and showed that one group of children had multiple poor outcomes, two had intermediate outcomes with different profiles and the last had the best outcomes. After inspection and discussion of their content, these were named "broadly affected profile" (N = 56), "selectively affected profile" (N = 80), "intermediate outcome profile" (N = 48), and "best outcome profile" (N = 330) (Table 2). Of PBC children, 78.7% clustered in the best outcome group, 5.1% in the intermediate outcome group, 12.2% in the selectively affected group, and 4.1% in the broadly affected group. Of FHR-SZ children, 51.8% clustered in the best outcome group, 12.1% in the intermediate outcome group, 18.1% in the selectively affected group, and 18.1% in the broadly affected group. Of FHR-BP children, 61.0% clustered in the best outcome group, 11.9% in the intermediate outcome group, 16.9% in the selectively affected group, and 10.2% in the broadly affected group (figure 1 and Supplementary Table 5 (the latter available online)).

Significant differences were found between the cluster groups regarding all the examined domains (figure 2) (see Supplementary Table 8, available online, for pairwise comparisons). The broadly affected group had poor scores regarding motor function, social cognition and neurocognitive function, language, self-perception and symptoms of ADHD, and oppositional defiant disorder. The selectively affected group had poor results regarding present axis 1 diagnosis, emotional control, externalizing, and internalizing behavior. Also, PE's were prevalent more often in the selectively affected group and even more in the intermediate outcome group that clustered children which had all experienced severe PE's but also children with motor and neurocognitive difficulties. Comparing the two middle groups, the selectively affected group thus constituted a group with more difficulties concerning psychopathology, emotion regulation, and behavior while the intermediate outcome group constituted a group with more "neurodevelopmental" difficulties such as motor and neurocognitive difficulties. The best outcome group had best results in all domains except in "Theory of mind" where the results in the selectively affected group were slightly better (8.02 (2.25) versus 8.04 (2.26) (mean, SD)).

The cluster groups did not vary with respect to age of inclusion but showed substantial differences with respect to sex. Most children in the broadly affected profile group were male (71.4%) (Table 2). Adjusting for sex differences as described did not change any levels of significance (see Supplementary Table 6, available online).

Associations between Genetic risk, Environmental Disadvantages, and Clusters

Associations were found between cluster groups and socioeconomic disadvantages of the child and family (figure 3 and Table 2). Children in the best outcome group had caregivers with significantly higher levels of functioning than in other groups. They also had significantly higher levels of stimulation and support at home in contrast to

Table 1. Clinical, Cognitive, Social, and Environmental Characteristics of the 514 Children in the Danish High Risk and Resilience Study – VIA 7

	FHR-SZ		FHR-BP		PBC		Pairwise comparisons, *P*-value (Cohens d)			
							P-value	FHR-SZ vs PBC	FHR-BP vs PBC	FHR-SZ vs FHR-BP
	Mean (SD)/*N* (%)	Z-score	Mean (SD)/*N* (%)	Z-score	Mean (SD)/*N* (%)	Z-score				
N=	199		118		197					
Sex										
Female (*N* (%))	92 (46.2)	-	55 (46.6)	–	90 (45.7)	–		–	–	–
Male (*N* (%))	107 (53.8)	–	63 (53.4)	–	107 (54.3)	–	.986	–	–	–
Age at inclusion (mean (SD))	7.84 (0.22)	–	7.87 (0.20)	–	7.81 (0.20)	–	.085	0.195 (0.130)	0.024 (0.263)	0.30 (0.122)
Measures included in cluster analysis										
Motor function										
Motor function, aiming and catching (Movement ABC)[36] (mean (SD))	8.42 (2.91)	−0.15 (0.97)	8.40 (3.07)	−0.16 (1.03)	8.87 (2.99)	0.00 (1.00)	.243	0.134 (0.151)	0.183 (0.155)	0.945 (0.008)
Motor function, balance (Movement ABC)[36] (mean (SD))	7.64 (3.20)	−0.37 (0.85)	8.30 (3.44)	−0.20 (0.92)	9.04 (3.75)	0.00 (1.00)	**<.001**	**<0.001** (0.400)	0.082 (0.205)	0.086 (0.198)
Motor function, manual dexterity (Movement ABC)[36] (mean (SD))	7.99 (3.44)	−0.41 (0.96)	8.69 (3.58)	−0.21 (1.00)	9.44 (3.57)	0.00 (1.00)	**<.001**	**<0.001** (0.414)	0.074 (0.209)	0.083 (0.201)
Neurocognition										
Processing speed and working memory, z-score (mean (SD))[21]	–	−0.51 (1.07)	–	−0.08 (1.07)		0.00 (1.00)	**<.001**	**<0.001** (0.494)	0.498 (0.078)	**0.001** (0.402)
Verbal functions z-score (mean (SD))[21]	–	−0.26 (1.17)	–	0.03 (1.09)	–	0.00 (1.00)	**.020**	**0.016** (0.243)	0.809 (0.028)	**0.027** (0.260)
Executive and visuospatial functions z-score (mean (SD))[21]	–	−0.28 (1.07)	–	0.10 (1.15)	–	0.00 (1.00)	**.003**	**0.006** (0.275)	0.429 (0.091)	**0.003** (0.345)
Declarative memory and attention z-score (mean (SD))[21]	–	−0.31 (1.14)	–	0.03 (1.08)	–	0.00 (1.00)	**.005**	**0.005** (0.284)	0.818 (0.027)	**0.011** (0.300)
Emotional control										
Executive functions, emotional control (BRIEF)[37] (mean (SD))[a]	16.03 (4.88)	−0.52 (1.31)	15.66 (4.56)	−0.42 (1.23)	14.10 (3.71)	0.00 (1.00)	**<.001**	**<0.001** (0.446)	**0.001** (0.376)	0.505 (0.078)
Problem behavior										
Externalizing problems (CBCL)[38] (mean (SD))[a]	7.67 (7.34)	−0.77 (1.58)	6.04 (6.50)	−0.42 (1.40)	4.08 (4.65)	0.00 (1.00)	**<.001**	**<0.001** (0.585)	**0.002** (0.348)	0.048 (0.234)
Internalizing problems (CBCL)[38] (mean (SD))[a]	6.51 (5.82)	−0.38 (1.32)	6.42 (6.62)	−0.37 (1.50)	4.81 (4.40)	0.00 (1.00)	**.004**	**0.001** (0.329)	**0.010** (0.287)	0.906 (0.013)
Symptoms of ADHD and oppositional defiant disorder (mADHD-RS)[39–41] (mean (SD))[a]	18.33 (13.06)	−0.58 (1.39)	15.86 (12.04)	−0.32 (1.28)	12.86 (9.38)	0.00 (1.00)	**<.001**	**<0.001** (0.481)	**0.014** (0.278)	0.095 (0.196)

Table 1. Continued

	FHR-SZ		FHR-BP		PBC		Pairwise comparisons, *P*-value (Cohens d)			
							P-value	FHR-SZ vs PBC	FHR-BP vs PBC	FHR-SZ vs FHR-BP
	Mean (SD)/*N* (%)	Z-score	Mean (SD)/*N* (%)	Z-score	Mean (SD)/*N* (%)	Z-score				
Social cognition										
Theory of mind (Happe)[42] (mean (SD))	7.23 (2.60)	−0.27 (1.07)	7.81 (2.47)	−0.03 (1.01)	7.89 (2.44)	0.00 (1.00)	**.019**	**0.009** (0.265)	0.780 (0.033)	**0.048** (0.232)
Emotion recognition, percent correct answers (CANTAB)[43] (mean (SD))	48.94 (10.39)	−0.10 (1.05)	50.28 (9.34)	0.03 (0.94)	49.95 (9.91)	0.00 (1.00)	.439	0.324 (0.099)	0.770 (0.034)	0.251 (0.135)
Self-perception										
Self-perception (I think I am)[44] (mean (SD))	20.64 (8.62)	−0.46 (1.30)	22.76 (7.54)	−0.14 (1.14)	23.66 (6.62)	0.00 (1.00)	**<.001**	**<0.001** (0.393)	0.267 (0.127)	**0.028** (0.261)
Language										
Receptive language (TROG)[45] (mean (SD))	13.91 (3.44)	−0.33 (1.20)	14.77 (2.77)	−0.03 (0.97)	14.85 (2.86)	0.00 (1.00)	**.005**	**0.003** (0.297)	0.804 (0.029)	**0.022** (0.274)
Psychotic experiences										
Any moderate to severe psychotic experiences, PE's[28] (N (%))	27 (13.6)	–	16 (13.6)	–	10 (5.1)	–	**.009**	**0.004** (0.294)	**0.008** (0.294)	0.998 (<0.001)
Psychopathology										
Any axis 1 diagnosis, present (K-SADS)[28] (N (%))	64 (32.2)	–	32 (27.1)	–	23 (11.7)	–	**<.001**	**<0.001** (0.510)	**<0.001** (0.397)	0.347 (0.110)
Measures not included in cluster analysis	FHR-SZ		FHR-BP		PBC		*P*-value	FHR-SZ vs PBC	FHR-BP vs PBC	FHR-SZ vs FHR-BP
Measures of key clinical relevance										
Level of functioning, child (CGAS)[28] (mean (SD))[b]	68.07 (15.40)	−0.72 (1.14)	73.55 (14.91)	−0.31 (1.11)	77.71 (13.47)	0.00 (1.00)	**<.001**	**<0.001** (0.666)	**0.011** (0.292)	**0.002** (0.362)
Child intelligence level (RIST),[29] mean (SD)[b]	102.14 (11.35)	−0.29 (1.15)	104.13 (9.32)	−0.09 (0.94)	105.01 (9.90)	0.00 (1.00)	**.021**	**0.008** (0.269)	0.435 (0.092)	0.109 (0.191)
Social characteristics and genetic risk	FHR-SZ		FHR-BP		PBC		*P*-value	FHR-SZ vs PBC	FHR-BP vs PBC	FHR-SZ vs FHR-BP
	Mean (SD)/ N (%)	z-score	Mean (SD)/ N (%)	z-score	Mean (SD)/ N (%)	z-score				
Parental level of functioning										
Level of functioning, index parentc (PSP)[46] (mean (SD))	66.07 (15.74)	−1.83 (1.59)	68.64 (14.51)	−1.57 (1.46)	84.21 (9.92)	0.00 (1.00)	**<.001**	**<0.001** (1.379)	**<0.001** (1.252)	0.180 (0.170)
Level of functioning, primary caregiver (PSP)[46] (mean (SD))d	73.19 (14.10)	−1.23 (1.55)	74.47 (14.12)	−1.09 (1.55)	84.38 (9.12)	0.00 (1.00)	**<.001**	**<0.001** (0.942)	**<0.001** (0.833)	0.437 (0.091)

Table 1. Continued

	FHR-SZ		FHR-BP		PBC		Pairwise comparisons, *P*-value (Cohens d)			
							P-value	FHR-SZ vs PBC	FHR-BP vs PBC	FHR-SZ vs FHR-BP
	Mean (SD)/*N* (%)	Z-score	Mean (SD)/*N* (%)	Z-score	Mean (SD)/*N* (%)	Z-score				
Home environment										
Level of stimulation and support (MC-HOME)[26] (mean (SD))	45.14 (6.16)	−0.89 (1.42)	46.70 (4.68)	−0.54 (1.08)	49.03 (4.35)	0.00 (1.00)	**<.001**	**<0.001** (0.728)	**<0.001** (0.515)	**0.020** (0.284)
Father's level of education[30]										
Primary/lower secondary education (DISCED Level 2) (*N* (%))	48 (27.6)	–	8 (7.6)	–	9 (4.8)	–	–	–	–	–
Upper secondary education (DISCED Level 3 + 5) (*N* (%))	81 (46.6)	–	50 (47.6)	–	105 (55.9)	–	–	–	–	–
Bachelor's degree, equivalent or higher (DISCED Level 6 + 7) (*N* (%))	45 (25.9)	–	47 (44.8)	–	74 (39.4)	–	–	–	–	–
							<.001	**<0.001** (0.661)	0.321 (0.182)	**<0.001** (0.598)
Mother's level of education[30]										
Primary/lower secondary education (DISCED Level 2) (*N* (%))	41 (21.2)	–	7 (6.0)	–	8 (4.1)	–	–	–	–	–
Upper secondary education (DISCED Level 3 + 5) (*N* (%))	84 (43.5)	–	41 (35.0)	–	81 (41.3)	–	–	–	–	–
Bachelor's degree, equivalent or higher (DISCED Level 6 + 7) (*N* (%))	68 (35.2)	–	69 (59.0)	–	107 (54.6)	–	–	–	–	–
							<.001	**<0.001** (0.587)	0.462 (0.145)	<0.001 (0.579)
Single caregiver status										
Parent is a single caregiver (*N* (%))17	74 (37.2)	–	38 (32.2)	–	21 (10.7)	–	**<.001**	**<0.001** (0.654)	**<0.001** (0.544)	0.438 (0.105)
Children with genetic data	*N* = 142		*N* = 94		N = 155					
Polygenic risk score for bipolar disorder[47] (mean (SD)) (10-5)	−198.03 (3.45)	0.20 (0.87)	−−198.07 (4.01)	0.19 (1.01)	−198.83 (3.96)	0.00 (1.00)	.131	0.062 (0.215)	0.141 (0.190)	0.933 (0.011)
Polygenic risk score for schizophrenia[47] (mean (SD)) (10-5)	9.29 (2.70)	0.21 (0.98)	9.58 (2.83)	0.31 (1.03)	8.73 (2.75)	0.00 (1.00)	**.040**	0.071 (0.208)	**0.018** (0.305)	0.428 (0.103)

Table 1. Continued

	FHR-SZ		FHR-BP		PBC		Pairwise comparisons, *P*-value (Cohens d)			
	Mean (SD)/*N* (%)	Z-score	Mean (SD)/*N* (%)	Z-score	Mean (SD)/*N* (%)	Z-score	*P*-value	FHR-SZ vs PBC	FHR-BP vs PBC	FHR-SZ vs FHR-BP
Polygenic risk score for depression[47] (mean (SD)) (10-5)	8.83 (1.63)	0.19 (1.05)	9.00 (1.78)	0.30 (1.15)	8.53 (1.55)	0.00 (1.00)	.073	0.109 (0.184)	**0.030** (0.277)	0.441 (0.100)
Polygenic risk score for educational attainment[47] (mean (SD)) (10-5)	1.44 (0.43)	−0.34 (0.96)	1.58 (0.44)	−0.02 (0.99)	1.59 (0.44)	0.00 (1.00)	**.006**	**0.003** (0.343)	0.848 (0.025)	**0.015** (0.319)
Polygenic risk score, cognition[47] (mean (SD)) (10-5)	0.87 (0.77)	0.00 (0.00)	1.08 (0.62)	0.00 (0.00)	1.04 (0.70)	0.00 (0.00)	**.041**	**0.050** (0.225)	0.609 (0.067)	**0.025** (0.301)

Bold values represent significant at $P = .05$ level.
[a]Higher raw score is indicative of higher level of problem behavior. Low z-score is indicative of higher level of problem behavior.
[b]Child level of global functioning (CGAS) and mean estimated IQ (RIST Index) are also presented in tables to illustrate child function in cluster's with well-known measures although they are not included in the cluster analysis.
[c]The adult who was identified through the Danish registers was named the index parent. In 270 cases, the index parent was also the primary caregiver. In 244 cases, the index parent was not.
[d]The adult who provided information about the child was registered as the primary caregiver.

the broadly affected group where the mean scores nearly equalled the definition of an insufficient home environment[48] (Table 2). Significant differences were also found between parental levels of education across cluster profiles, and between child PRS for educational attainment across cluster profiles (Table 2). PRS for cognitive performance were on average higher in the best outcome group as well ($P = .049$).

We also examined the children's global level of functioning (CGAS) and IQ (not included in Table 2) and found significant differences regarding both. The best outcome group's IQ estimate was 106.01 (SD 8.48) compared to 89.29 (SD 11.35) in the broadly affected group. The best outcome group had a CGAS mean score of 80.07 (SD 10.33) compared to 54.88 (SD 15.06) in the broadly affected group ($P < .001$).

Discussion

In the hitherto largest familial high-risk study with data from multiple domains, we identified four clusters affected to various levels across domains. Such examination of distribution of impairments across multiple domains including known precursors of severe mental illness yields new information to the field since it demonstrates that impairments cluster particularly in a smaller group of children. Particularly if replicated in other FHR studies, this finding has relevance for future preventive strategies towards FHR children since such strategies may thus meaningfully have a special focus on this smaller, broadly affected group of children because their relative risk of having a severe mental illness is likely to be higher than that of other FHR children. A significantly higher proportion of FHR children, particularly FHR-SZ, were broadly affected across numerous domains. The broadly affected profile was 4-5 times more prevalent amongst FHR-SZ and 2-3 times more prevalent amongst FHR-BP, compared to controls. The broadly affected group showed the highest levels of impairments regarding motor function, social cognition, neurocognitive function, language, self-perception and symptoms of ADHD, and oppositional defiant disorder while the selectively affected group had the highest level of impairments concerning axis 1 diagnoses, emotional control, internalizing and externalizing behavior.

The best outcome group had best results in all measures except regarding theory of mind where results were quite similar for the three cluster groups and lower for the broadly affected group. PEs were to a large extent found amongst children in the intermediate outcome group. Inspection of the axis 1 diagnoses of these children versus the children in the broadly affected group showed that children in the broadly affected group often had 2, 3, and 4 diagnoses, frequently including autism, while the children in the intermediate outcome group only had one disorder, frequently ADHD. These diagnostic

Table 2. Hierarchical Cluster Analysis of Outcomes Amongst 514 7-Year-old Children With Familial High-risk of Schizophrenia, Bipolar Disorder, and Population-based Controls

	Best outcome profile		Intermediate outcome profile		Selectively affected profile		Broadly affected profile		*P*-value
	Mean (SD)/*N* (%)	z-score	Mean (SD)/*N* (%)	z-score	Mean (SD)/*N* (%)	z-score	Mean (SD)/*N* (%)	z-score	
N=	330		48		80		56		
High risk status, schizophrenia, row percentage	103 (51.8)	–	24 (12.1)	–	36 (18.1)	–	36 (18.1)	–	–
High risk status, bipolar, row percentage	72 (61.0)	–	14 (11.9)	–	20 (16.9)	–	12 (10.2)	–	–
Controls, row percentage	155 (78.7)	–	10 (5.1)	–	24 (12.2)	–	8 (4.1)	–	**<0.001**
Sex									
Female (*N* (%))	163 (49.4)	–	24 (50.0)	–	34 (42.5)	–	16 (28.6)	–	–
Male (*N* (%))	167 (50.6)	–	24 (50.0)	–	46 (57.5)	–	40 (71.4)	–	**0.028**
Age at inclusion (mean (SD))	7.82 (0.19)	–	7.82 (0.26)	–	7.86 (0.22)	–	7.89 (0.25)	–	0.106
Measures included in cluster analysis									
Motor function									
Motor function, aiming and catching (Movement ABC) (mean (SD))	9.17 (2.86)	0.10 (0.96)	7.81 (2.46)	−−0.35 (0.82)	8.55 (2.82)	−0.11 (0.94)	5.89 (2.72)	−0.99 (0.91)	**<0.001**
Motor function, balance (Movement ABC) (mean (SD))	9.28 (3.40)	0.07 (0.91)	7.85 (3.24)	−0.31 (0.86)	7.36 (2.77)	−0.45 (0.74)	4.46 (2.08)	−1.22 (0.55)	**<0.001**
Motor function, manual dexterity (Movement ABC) (mean (SD))	9.65 (3.37)	0.06 (0.94)	8.31 (3.73)	−0.32 (1.05)	7.71 (3.00)	−0.48 (0.84)	4.95 (2.23)	−1.26 (0.62)	**<0.001**
Neurocognition									
Processing speed and working memory z-score (mean (SD))	–	0.03 (0.94)	–	−0.46 (1.03)	–	−0.17 (0.94)	–	−1.55 (0.96)	**<0.001**
Verbal functions z-score (mean (SD))	–	0.11 (1.02)	–	−0.16 (1.09)	–	−0.02 (0.91)	–	−1.36 (0.92)	**<0.001**
Executive and visuospatial functions z-score (mean (SD))	–	0.14 (1.00)	–	−0.17 (0.99)	–	−0.13 (0.93)	–	−1.30 (0.92)	**<0.001**
Declarative memory and attention z-score (mean (SD))	–	0.11 (0.96)	–	−0.42 (1.29)	–	−0.07 (0.96)	–	−1.24 (1.03)	**<0.001**
Emotional control									
Executive functions, emotional control (BRIEF) (mean (SD))[a]	13.64 (3.24)	0.12 (0.87)	15.67 (3.83)	−0.42 (1.03)	19.19 (4.78)	−1.37 (1.29)	18.34 (5.51)	−1.14 (1.48)	**<0.001**
Problem behavior									
Externalizing behavior (CBCL) (mean (SD))[a]	3.65 (3.85)	0.09 (0.83)	5.88 (5.55)	−0.39 (1.20)	11.59 (8.00)	−1.62 (1.72)	11.20 (8.46)	−1.53 (1.82)	**<0.001**
Internalizing behavior (CBCL) (mean (SD))[a]	4.28 (3.74)	0.12 (0.85)	5.00 (4.69)	−0.04 (1.06)	10.95 (7.74)	−1.39 (1.76)	8.41 (6.47)	−0.82 (1.47)	**<0.001**
Symptoms of ADHD and oppositional defiant disorder (mADHD-RS) (mean (SD))[a]	11.07 (7.47)	0.19 (0.80)	17.40 (10.45)	−0.48 (1.11)	25.44 (12.47)	−1.34 (1.33)	27.36 (15.22)	−1.54 (1.62)	**<0.001**
Social cognition									
Theory of mind (Happe) (mean (SD))	8.02 (2.25)	0.05 (0.92)	7.27 (2.78)	−0.26 (1.14)	8.04 (2.26)	0.06 (0.93)	4.91 (2.50)	−1.22 (1.03)	**<0.001**
Emotion recognition, total correct answers (CANTAB) (mean (SD))	51.01 (9.17)	0.11 (0.93)	50.45 (10.32)	0.05 (1.04)	50.03 (9.74)	0.01 (0.98)	40.28 (9.74)	−0.98 (0.98)	**<0.001**

Table 2. Continued

	Best outcome profile		Intermediate outcome profile		Selectively affected profile		Broadly affected profile		*P*-value
	Mean (SD)/*N* (%)	z-score	Mean (SD)/*N* (%)	z-score	Mean (SD)/*N* (%)	z-score	Mean (SD)/*N* (%)	z-score	
Self-perception									
Self-perception (I think I am) (mean (SD))	24.33 (6.12)	0.10 (0.93)	19.00 (9.41)	−0.70 (1.42)	21.00 (6.88)	−0.40 (1.04)	14.86 (10.03)	−1.33 (1.52)	**<0.001**
Language									
Receptive language (TROG) (mean (SD))	15.17 (2.74)	0.11 (0.96)	13.94 (2.73)	−0.32 (0.96)	14.94 (2.25)	0.03 (0.79)	10.16 (3.01)	−1.64 (1.05)	**<0.001**
Psychotic experiences									
Any moderate to severe psychotic experiences (PE's) (N (%))	0 (0.00)	–	48 (100.0)	–	5 (6.2)	–	0 (0.00)	–	**<0.001**
Psychopathology									
Any axis 1 diagnosis (K-SADS) (N (%))	4 (1.2)	–	17 (35.4)	–	65 (81.2)	–	33 (58.9)	–	**<0.001**
Measures not included in cluster analysis									
Social characteristics and genetic risk:	Best outcome profile		Intermediate outcome profile		Selectively affected profile		Broadly affected profile		*P*-value
	Mean (SD)/*N* (%)	z-scores	Mean (SD)/*N* (%)	z-scores	Mean (SD)/*N* (%)	z-scores	Mean (SD)/*N* (%)	z-scores	
Parental level of functioning									
Level of functioning, index parent (PSP) (mean (SD))	77.44 (14.68)	−0.68 (1.48)	64.46 (16.86)	−1.99 (1.70)	70.69 (16.16)	−1.36 (1.63)	66.04 (14.32)	−1.83 (1.44)	**<0.001**
Level of functioning, primary caregiver (PSP) (mean (SD))	80.68 (12.40)	−0.41 (1.36)	75.67 (14.66)	−0.96 (1.61)	73.10 (13.12)	−1.24 (1.44)	69.31 (13.45)	−1.65 (1.47)	**<0.001**
Home environment									
Level of stimulation and support (MC-HOME) (mean (SD))	48.26 (4.99)	−0.18 (1.15)	45.98 (4.89)	−0.70 (1.12)	45.31 (5.60)	−0.86 (1.29)	42.84 (5.55)	−1.42 (1.28)	**<0.001**
Father's level of education[30]									
Primary/lower secondary education (DISCED Level 2) (*N* (%))	28 (9.2)	—	11 (26.2)	–	10 (14.5)	–	16 (31.4)	–	**<0.001**
Upper secondary education (DISCED Level 3 + 5), (*N* (%))	149 (48.9)	–	24 (57.1)	–	35 (50.7)	–	28 (54.9)	–	
Bachelor's degree, equivalent or higher (DISCED Level 6 + 7), (N (%))	128 (42.0)	–	7 (16.7)	–	24 (34.8)	–	7 (13.7)	–	
Mother's level of education[30]									**<0.001**
Primary/lower secondary education (DISCED Level 2) (*N* (%))	23 (7.1)	–	8 (17.0)	–	15 (19.2)	–	10 (18.2)	–	
Upper secondary education (DISCED Level 3 + 5) (*N* (%))	120 (36.8)	–	22 (46.8)	–	31 (39.7)	–	33 (60.0)	–	
Bachelor's degree, equivalent or higher (DISCED Level 6 + 7) (*N* (%))	183 (56.1)	–	17 (36.2)	–	32 (41.0)		12 (21.8)	–	
Single caregiver status									
Parent is a single caregiver (*N* (%))	79 (23.9)	–	14 (29.2)	–	24 (30.0)	–	16 (28.6)	–	0.607
Children with genetic data	*N* = 259		*N* = 34		*N* = 61		*N* = 37		
Polygenic risk score, depression (mean (SD)) (10-5)	8.67 (1.67)	0.08 (1.07)	8.87 (1.64)	0.21 (1.05)	8.99 (1.52)	0.28 (0.97)	8.62 (1.64)	0.05 (1.05)	0.525
Polygenic risk score, bipolar disorder (mean (SD)) (10-5)	−198.42 (3.76)	0.12 (0.95)	−−199.12 (4.40)	−0.06 (1.11)	−197.86 (3.77)	0.26 (0.95)	−198.62 (3.75)	0.07 (0.95)	0.461

Table 2. Continued

	Best outcome profile		Intermediate outcome profile		Selectively affected profile		Broadly affected profile		*P*-value
	Mean (SD)/*N* (%)	z-score	Mean (SD)/*N* (%)	z-score	Mean (SD)/*N* (%)	z-score	Mean (SD)/*N* (%)	z-score	
Polygenic risk score, schizophrenia (mean (SD)) (10-5)	9.14 (2.81)	0.16 (1.02)	9.26 (2.48)	0.20 (0.90)	9.25 (2.91)	0.20 (1.05)	8.95 (2.74)	0.09 (0.99)	0.953
Polygenic risk score, educational attainment (mean (SD)) (10-5)	1.58 (0.43)	−0.03 (0.96)	1.37 (0.47)	−0.50 (1.06)	1.40 (0.46)	−0.43 (1.03)	1.55 (0.43)	−0.08 (0.97)	**0.005**
Polygenic risk score, cognition (mean (SD)) (10-5)	1.06 (0.71)	0.00 (1.05)	0.77 (0.79)	−0.43 (1.16)	0.85 (0.65)	−0.30 (0.96)	1.00 (0.65)	−0.09 (0.96)	**0.049**

Bold values represent significant at $P = .05$ level.
[a]Higher raw score is indicative of higher level of problem behavior. Low z-score is indicative of higher level of problem behavior.

Fig. 1. Distribution of cluster profiles among 514 children of parents with schizophrenia (FHR-SZ) or bipolar disorder (FHR-BP) and population-based controls (PBC).

characteristics might have relevance with regards to how the children have replied to questions about PE's and how the assessor has interpreted the reply. Furthermore, to some degree, a fairly good function including good verbal function may be required to even express, notice, and remember, psychotic experiences, and the broadly affected children may to a larger extent be impaired in this respect.

Most children in the broadly affected group were boys. This finding might be related to sex differences regarding eg psychopathology or behavior, or to a male maturation delay at the age of 7.[49,50] As adjustment for sex differences did not change levels of significance between the clusters, it is unlikely that the sex differences are driven by general sex differences but rather by differences more specific to FHR children.

Children in the broadly and selectively affected groups had many disadvantages in their daily life such as low levels of stimulation and support at home and low levels of parental functioning and education. Thus, the children most in need of support were also those who received the lowest levels of support by their caregivers. The disadvantages of these children were in this sense double: Not only did they display an accumulation of impairments, as they were themselves affected in domains such as neurocognition, motor function etc., they also had caregivers with lower levels of function, providing lower levels of stimulation and support. Low levels of parental functioning and education, and low levels of stimulation and support at home, have previously been found to affect child development negatively.[51] In contrast, children in the best outcome and two intermediate groups had higher levels of stimulation and support at home and higher levels of parental functioning and education.

The children in the best and intermediate outcome groups neither had many impairments in the cluster domains, nor did they have many disadvantages in their daily life. These findings may provide insight concerning resilience to risk status of mental illness. Causation cannot be determined in this cross-sectional design, and bidirectional effects are likely present – for instance, if a child has severe impairments this can affect the level of

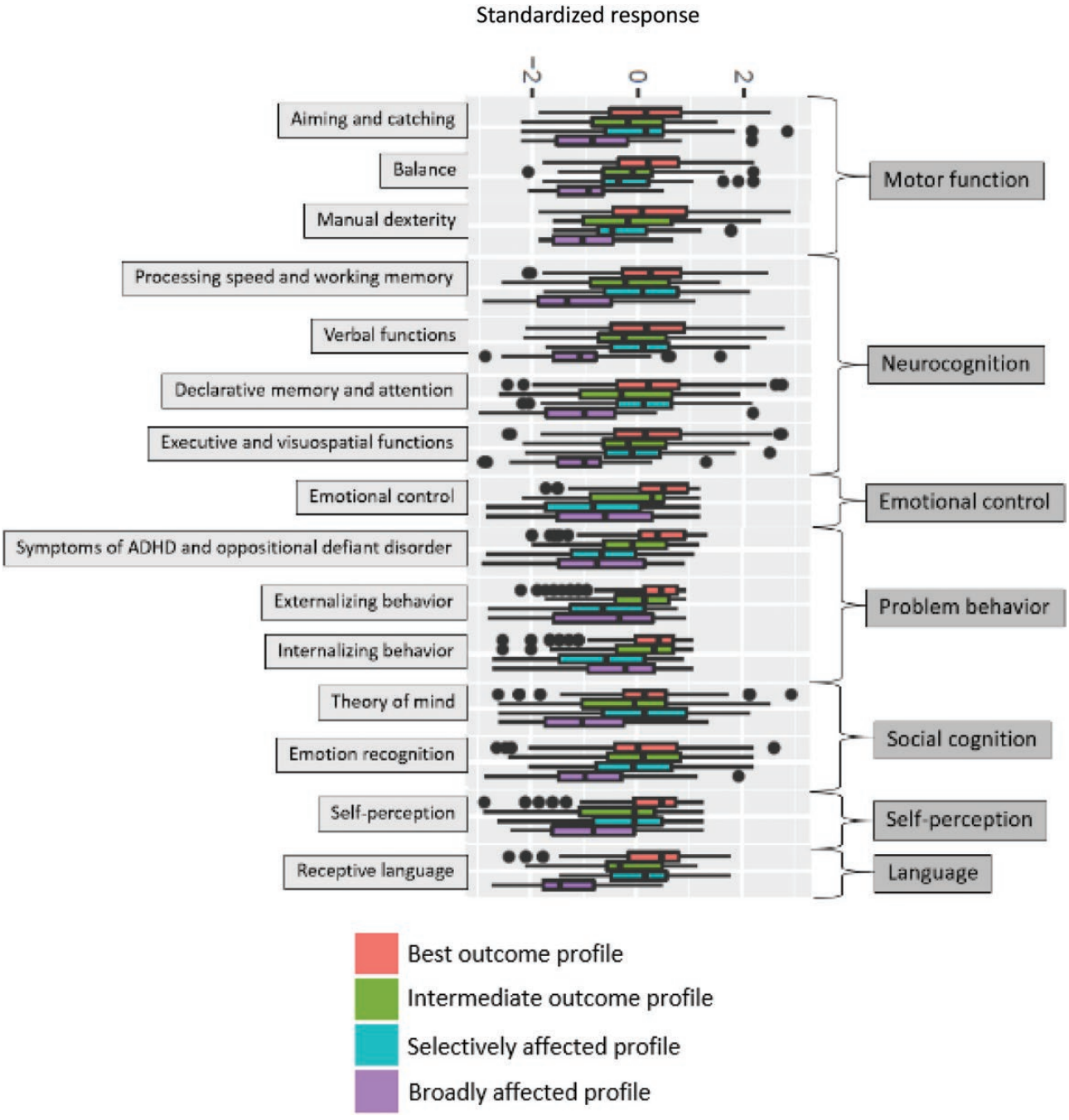

Fig. 2. Distribution of cross-domain test outcomes in four clusters amongst 514 children with familial high risk of schizophrenia or bipolar disorder and matched controls.

stimulation and support in the home because caregivers might choose to avoid activities associated with high scores of stimulation such as including the child in tidying up or going on excursions.

Group mean CGAS levels showed a significant decline from the best outcome group to the broadly affected group and thus confirmed that our analysis succeeded in clustering children in the broadly affected group who had also been evaluated by the VIA 7 Study assessors to have severe impairments.

When examining genetic contributions to the four cluster group outcomes with PRS for schizophrenia, bipolar disorder, major depression, cognitive performance, and educational attainment, we only found significant associations regarding educational attainment and cognition, and the trends were not always consistent across all groups. The child PRS for educational attainment did not display consistent linear increments in the PRS across groups in a decreasing order of affectedness; while the best outcome group had the highest mean PRS, the cluster

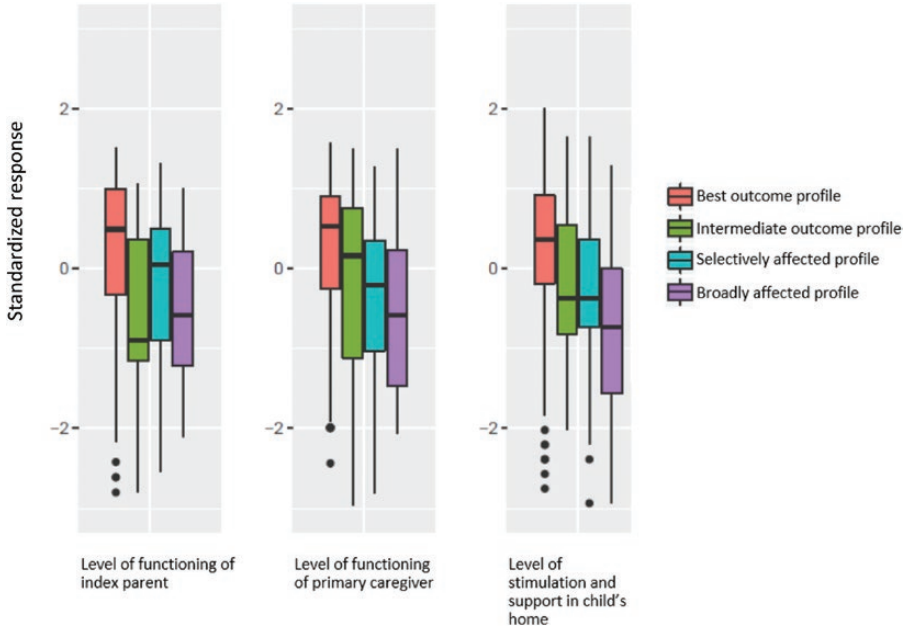

Fig. 3. Distribution of socio-economic exposures across four clusters amongst 514 children with familial high risk of schizophrenia or bipolar disorder and matched controls. a: Parental level of functioning and level of stimulation and support in the child's home. b: Parental level of education and single caregiver status.

group with the second highest mean PRS was the broadly affected group. In this context it is worth mentioning that previous studies have found positive genetic overlaps between schizophrenia, bipolar disorder, and educational attainment.[52]

The predictive power of the PRS depends greatly on the sample size of the discovery GWAS from which the summary statistics are derived. The discovery study for educational attainment was by far the largest in terms of sample size, which could explain the better performance of the PRS for that trait. However, other factors, such as the genetic architecture of the traits themselves, or various parameters of the target sample could also influence the performance of the PRS analyses.

Future studies will show whether the broadly affected profile group will be more likely to develop psychotic symptoms or other severe mental problems compared with FHR children in general. Previous studies have documented that individuals who develop psychotic illness have low premorbid functioning and show early signs of neuro- and social cognitive deficits.[53,54] Other studies report that poor levels of stimulation and support are associated with psychopathology in late adolescence.[55] The broadly affected profile group may be at a higher risk due to the combination of individual impairments, environmental disadvantages and, for some, genetic risk. This assumption would be in line with the existing literature in the field which suggests that precursors of psychosis are multifaceted and consist of many of the domains included in this study.[56] If so, identifying this group at an early stage and intervening already in childhood might be of great future relevance. For now, the broadly affected profile group show significant impairments that, for many, call for supportive strategies not only to prevent the possible development of severe psychopathology but also to support their positive development in general, and the finding of such a broadly affected group highlights the need for future screening and identification of FHR children with multiple individual and family-level impairments so that support can be focused on these rather than on the approximately 50% who display no such impairments.

To our knowledge, the distribution of impairments has previously been examined only within one or a few domains at a time, eg regarding neurocognitive impairments in the prodrome of psychosis in a clinical high-risk and partly familial high-risk sample,[57] and to some degree in multivariate prediction models[6,58,59] which did however not have the distribution as a primary focus. Likewise, to our knowledge, no previous study has examined whether environmental disadvantages (such as low levels of stimulation and support in the home, the level of parental functioning and education) or the included genetic characteristics are associated with accumulation of child impairments from many domains in children with parental schizophrenia or bipolar disorder.

Limitations

Reducing the set of tests from the VIA 7 study to selected domain representatives was necessary to handle data in the cluster analysis. The clustering might also have limitations, as the results depend to a certain degree of the analyst's decisions, but this would however not have altered our conclusions: Elaborating on this possible

limitation, the final split in the dendrogram could have been made between the best outcome group and the remaining three groups but even so, results would indicate that some familial high-risk children are unaffected while others are affected in a range of domains, and that the latter have less support in their family environment.

A latent class analysis could also have been applied but at this stage, we intended to examine the distribution without the assumption of a latent statistical model. Thus, this study can answer to the distribution of impairments across domains but can only hypothesize that the broadly affected children are perhaps also most at risk of severe mental illness.

Furthermore, as Denmark has a universal welfare system[60] which provides economic and practical aid to support family well-being and child development, differences may be larger in countries with no such system. Finally, data are baseline and the impairments assessed at the age of seven could be transient.

Interpretation and Generalizability

We identified cluster groups of FHR-SZ, FHR-BP, and PBC children affected to various degrees in numerous domains, with FHR-SZ children having the highest risk of belonging to the group of broadly affected children. We have demonstrated that familial high-risk children display substantial heterogeneity with regards to whether they are affected across domains known from previous studies to affect familial high-risk children, and that impairments from the various domains examined accumulate in some children rather than distribute evenly across children. Our study further shows that the children most broadly affected in multiple domains receive lower levels of stimulation and support in their homes and have caregivers with low levels of functioning and education. The children are thus disadvantaged in several ways. The broadly and partly also the intermediate groups may constitute certain risk groups for later negative life outcomes since they show high levels of psychopathology as well as impairments across several well-defined and important domains of child development at age seven. If not inspected altogether, the combined load of individual impairments and social disadvantages amongst this group of children and their families might be overseen in the health care and social systems even though evidence from the literature suggests that early interventions may be preventive of further negative developmental course.[61] The broadly affected FHR children stand in contrast to the FHR children in the best outcome group which emphasizes the heterogeneity of FHR children. The results call for an increased focus on identification and targeted, differentiated interventions which integrate child and adolescent and adult mental services and aim towards family as well as child support. Since general VIA 7 study findings are in line with previous studies and as analyses have found our study to be overall nationwide representative, we conclude that our results concerning the heterogeneity of children with familial high-risk of schizophrenia or bipolar disorder are generalizable to industrialized countries with well-established social and health systems.

Supplementary Material

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

Supplementary Figure 1. Possible distributions of difficulties amongst children of parents with severe mental illness. Distribution A: Even distribution of difficulties. Distribution B: Uneven distribution of difficulties.

Supplementary Table 1. Selected outcome variables chosen for cross-domain cluster analysis of 514 children of parents with schizophrenia or bipolar disorder and matched controls.

Supplementary Table 2. Number of missing assessments for variables included in cluster analysis of 514 children of parents with schizophrenia or bipolar disorder and matched controls.

Supplementary Table 3. Flowchart.

Supplementary Table 4. Correlation of variables in cluster analysis of 514 children born to parents with schizophrenia or bipolar disorder and matched controls.

Supplementary Table 5. Number of children of parents with schizophrenia or bipolar disorder and controls by identified cluster group.

Supplementary Table 6. Hierarchical cluster analysis of outcomes amongst 514 7-year-old children with familial high-risk of schizophrenia, bipolar disorder and matched controls, adjusted for sex differences based on controls.

Supplementary Text 7. Protocol for the generation of polygenic risk scores (PRS).

Supplementary Table 8. Pairwise comparisons of all cluster groups. Best outcome=A, Intermediate outcome=B, Selectively affected=C and Broadly affected=D.

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