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Psychotic-Like Experiences in Offspring of Parents With Bipolar Disorder and Community Controls: A Longitudinal Study

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Abstract

Objective: To compare the prevalence and risk factors associated with Psychotic-Like-Experiences (PLE) in offspring of parents with bipolar disorder (BP) and offspring of community control parents.

Method: Delusional and hallucinatory subclinical psychotic experiences were evaluated at intake and longitudinally in a cohort study of 390 offspring of BP parents and 247 offspring of control parents aged 6–18 years old. The sample was followed up every 2.5 years on average for 8.3 years. 91.7% of the sample completed at least one follow up. Risk factors at intake and at each assessment until the onset of PLE were analyzed using survival models.

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This study was presented as an oral communication at the 17th International Conference of ESCAP (European Society for Child and Adolescent Psychiatry), Genève, Switzerland, July 9–11, 2017.

Results: 95 (14.9%) offspring reported PLE at some point of the study, 16.9% of BP parents and 11.7% of controls, without statistically significant differences. Psychotic disorders were less frequent, 16 (2.5%) in both groups. During follow-up, three variables remained as the most significant associated with PLE in the multivariate models: 1) presence of any psychiatric disorder (HR = 3.1; $p = .01$); 2) low psychosocial functioning (HR = 2.94; $p < .0001$); and 3) current or past history of physical or sexual abuse (HR = 1.85; $p = .04$). There were no effects of any subtype of BP, IQ, history of medical illnesses, exposure to medications, or perinatal complications.

Conclusion: In line with previous studies, PLE in our sample were relatively common, and were associated with higher morbidity during the follow-up. Contrary to the literature, neither family risk for bipolar nor early neurodevelopmental insults were associated with PLE.

Keywords

psychosis; psychotic; offspring; bipolar disorder; longitudinal

INTRODUCTION

The prevalence of psychotic-like experiences (PLE) that do not fulfill severity or frequency criteria for a formal psychotic disorder is common in the general population. In an epidemiological cross-sectional study in adults, Van Os *et al*¹ reported rates of 8.2% and 13.5% for threshold and subthreshold psychotic symptoms, respectively. Similar or even higher prevalence rates have been found in youth, ranging from 17%–23% in children and 5%–7% in adolescents, or even as high as 35% in both depending the methodology of the study.^{2,3}

Although the presence of PLE in pediatric populations may be transient and benign,⁴ new evidence highlights their association with a broad range of psychiatric disorders.^{3,4} In fact, the presence of PLE during childhood is associated with increased risk to develop schizophrenia and affective psychotic disorders during adulthood.^{5–7} These findings support the hypothesis of a continuum ranging from isolated and non-pathological PLE to persistent and dysfunctional PLE which may finally transition to full psychosis in some individuals.^{8,9}

Psychosis runs in families, with heritability rates ranging from 40%–70%.¹⁰ Exposure to specific environmental risk factors such as perinatal complications, early neurodevelopmental insults, neurocognitive deficits, lack of social or economic support, and childhood trauma are also associated with the increased risk to develop overt psychosis.¹¹ A combination of above factors together with the absence of protective factors may determine the final pathway towards schizophrenia or affective psychosis such as bipolar disorders.¹²

There are few studies regarding the risk of developing PLE, but it appears that the same risk factors associated with overt psychosis are also associated with increased likelihood to develop PLE^{13–15} Also, whereas some studies have reported a significant association between family loading and PLE,^{14,16} longitudinal twin studies have consistently reported a higher contribution for environmental risk factors (49%–67%) than genetics (15–59%).^{17–19} Moreover, Zammit *et al*²⁰, in a longitudinal birth cohort study, found that only parental history of depression, and not schizophrenia, predicted PLE during adolescence.

To our knowledge, there are no studies evaluating the risk factors associated with PLE in a sample at family risk for bipolar disorder (BP). Thus, using the Pittsburgh Bipolar Offspring Study (BIOS), the largest ongoing cohort of offspring of bipolar parents (BP offspring) that also includes a community control cohort (control offspring), we evaluated the prevalence of PLE and risk factors for developing PLE in the above noted groups. Based on the literature, we hypothesized that: (1) The prevalence of PLE will be higher in BP offspring than in control offspring and (2) PLE will be predicted by high rates of mood and non-mood psychopathology, presence of medical illnesses, exposure to pharmacological treatments (eg, psychotropics); poor psychosocial functioning, lower IQ, and history of physical/sexual abuse, and perinatal exposure to neurodevelopmental insults such as pre- and post-birth complications.

METHOD

The BIOS methods and assessment tools have been described in detail in previous reports and are summarized below.^{21,22} Further information is provided in Supplement 1.

SAMPLE

BP parents (n=235) were recruited through advertisements (124, 53%), other research studies (73, 31%), and at adult outpatient clinics (38, 16%). All BP parents fulfilled criteria for a DSM-IV diagnosis of BP I or II disorders, lived within a 200-mile radius of Pittsburgh, and had offspring between 6 and 17.11 years old. Exclusion criteria for BP parents included the presence of lifetime diagnosis of schizophrenia, mood disorders secondary to substance abuse, medical conditions or medications, and mental retardation (IQ < 70).

Control parents (n=140) were recruited from the community using random digit dialing, at a ratio of one control parent to two bipolar parents, and group matched by age (in years), sex, and neighborhood. They were either healthy or had a psychiatric diagnosis other than bipolar disorder, though could not have any of the exclusionary diagnoses noted above. In addition, control parents could not have first and second-degree relatives with BP.

All available biological co-parents from both groups were invited to participate as well.

All offspring of BP and control parents (n=637, 390 and 247 respectively) were included with the exception of those with mental retardation, autism, or other impairments that prevented their participation (e.g., severe medical illness). One child from the BP group was diagnosed with tuberous sclerosis and was excluded from the final analysis.

PROCEDURES

After obtaining institutional review board approval and consent from parents and children, at intake all families completed questionnaires regarding demographic data. Socioeconomic status (SES) was evaluated using the Hollingshead scale.

Both at intake and during the follow-up, *DSM-IV* psychiatric disorders²³ for parents, 30% of available co-parents, and adult offspring were assessed using the Structured Clinical Interview for *DSM-IV* (SCID),²⁴ complemented with the Attention Deficit and Hyperactive

Disorder (ADHD), Disruptive Behavior Disorders (DBD), and Separation Anxiety Disorder (SAD) sections of the Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime Version (K-SADS-PL).²⁵ The psychiatric history of biological co-parents who were not available for face-to-face interviews was ascertained from the other biological parent using the Family History-Research Diagnostic Criteria (FHR-DC), and the ADHD and DBD items from the K-SADS-PL.²⁶ For the offspring younger than 18 years old, psychiatric disorders were ascertained by interviewing parents about their children and children about themselves using the K-SADS-PL.²⁵

At intake, PLE were reported for the month prior to the evaluation and the worst time in the past. Subsequently, parents and their offspring were evaluated every other year for symptoms, including PLE, since the last interview. Using a methodology similar to that of Poulton et al. (2000),⁵ a composite dichotomous variable — PLE (Yes, No) — was generated scoring as YES any affirmative answer on any of the following: the K-SADS-PL items related to psychosis (PLE Yes for the hallucinatory and delusional items with scores = 2: probably present or subthreshold and 3 = definitely present or threshold); the K-SADS psychosis supplement (5 hallucinatory, 13 delusional, and 6 other psychotic items with scores of 2 for probable and 3 for definite); or the K-SADS Mania Rating Scale (MRS) (items 19: Hallucinations and 20: Delusions with scores of 3: mild, subthreshold and 4: moderate to extreme, threshold). For offspring older than 18 years old and their parents, we used the SCID (8 items on delusions, 5 for hallucinations, and 11 for catatonic or negative symptoms with scores 3 = definitely present, threshold; 2 = probably present, subthreshold) and the SCID summary sheet (scores = 3 or 2 for threshold or subthreshold respectively; or psychotic disorder = 3 or 2). In addition to the information obtained through the KSADS/SCID, the interviewers also wrote a narrative including more details about the symptoms and other important information regarding the participants. This information was also used to complement the data about the psychotic symptoms. Unfortunately, the FHR-DC did not include any information about PLE that could be included for the analyses.

Medical history was ascertained based on a parent-reported questionnaire used in research protocols at the Western Psychiatric Institute and Clinic, and included information on head injuries, endocrine, neurological and other medical illnesses, pharmacological treatments (psychotropics and non-psychotropics), pubertal status and perinatal history. It included specific information about previous and current history of physical or sexual abuse. IQ was evaluated with the Wechsler Intelligence Scale for Children (WISC-IV),²⁷ and the overall psychosocial functioning was assessed with the Child Global Adjustment Assessment (C-GAS)²⁸ for offspring up to age 17 and the Global Assessment of Functioning (GAF)²⁹ for parents and offspring older than 18 years old. In line with the literature, a cut-off of 70 or below was used to define impairment.²⁹

All interviews were conducted by research assistants with at least a Bachelor's or Master's degree, two years of clinical experience, and certified in the use of the assessment tools. To be certified, 80% of agreement with the trainer is required as well as 3 to 6 months of training. Three child psychiatrists supervised their work and reviewed all diagnoses and procedures. The psychiatrists and the interviewers were blind to parental diagnoses. As detailed elsewhere, the reliability (Kappas) for the major psychiatric disorders was between

1.0 for substance abuse to 0.64 for major depressive disorder. We did not test the reliability for PLE phenomena.

STATISTICAL ANALYSES

At intake, demographic and clinical differences between parental groups were examined using t and χ^2 tests. For the longitudinal analyses, different mix models for repeated measures were used. We analyzed socio-demographic and clinical differences between bipolar and control offspring from baseline and last follow-up using General Linear Mixed Models (GLMM) with Least Square Means to control for within-family correlations. The longitudinal risk associations between demographic and clinical variables and the event of interest at each follow-up were estimated first with GLMM, and confirmed with Survival Cox Proportional Hazards Regression Model, with time-varying covariates for multiple events and taking into account within-subject dependence.³⁰ “Age at each follow-up” was the time variable, and censorship was defined as “age when PLE reported” or “age at last follow up”. PLE were considered episodic. For those individuals who were lost during the follow-up, we used the information collected until the last follow-up. Variables that showed group differences at a level of $p < .05$ in univariate models were included as potential covariates in subsequent multivariate models, with a retention criterion of $p < .10$. The number of variables that could enter in those analyses was limited using the $n/10$ rule (where n is the number of observed events) to prevent over-fitting the model. The different multivariate models were assessed using the Akaike information criterion (AIC), with lower values indicating a better fit to our data. Hazard Ratio (HR) and 95% confidence interval were computed for all models.

All analyses were performed using R 3.3.1 for Windows 7 (R project for Statistical Computing; Vienna, Austria), including the Survival library (v2.41–3) and Coxme library (v2.2–5).

RESULTS

The BIOS sample included 637 offspring, 390 from BP parents and 247 from control offspring (Table 1). Each family had on average two children and was followed up every 2.5 years for a period of 8.3 years (0–13 years). 53 (8.7%) offspring dropped out after baseline assessment, whereas the majority ($N = 585$, 91.7%) remained in the study, defined as completing at least one follow-up. Those who dropped out were less likely to live with both biological parents (45.3% vs. 67.3%; $t = 2.39$, $p = .02$) and had lower SES (29.01 ± 9.55 vs. 35.85 ± 13.79 ; $t = 2.67$, $p < .01$) than those who remained in the study. There were no other between-group differences (see Table S1, available online).

PARENTS

Compared with the control parents, BP parents (Table S2, available online) were younger, more likely to be Caucasian (87.7% vs. 72.2%), less often married (49.4% vs. 64.2%), with lower SES (34.0 ± 14.4 vs. 37.4 ± 13.1) and lower psychosocial functioning (all p -values $< .05$). As expected, BP parents reported more post-traumatic stress disorder (PTSD), and 50%

reported psychotic symptoms. All major depression episodes were included as part of the BP disorder.

OFFSPRING

At intake, the mean age for both cohorts was 11.9 ± 3.6 years old, with a median age of 11.2 (6–18) years old. Compared to control offspring, BP offspring were less often living with both biological parents (59.5% vs. 74.9%; $t = 2.81$, $p < .01$), were more Caucasian, and had a slightly lower SES (Table 1).

Prevalence of PLE and psychotic disorders—Ninety-five offspring (14.9%, 95/637) reported PLE at some point in the study, 37 (5.8%) at intake, and 58 (9.1%) during the follow-up (Table S3, available online). The mean age for PLE was 14.6 ± 4.7 years old, with only 16 cases (16.8%) reporting PLE before age 10. About 25% of the PLE symptoms (23/95) were reported more than once over time. Sixteen offspring (2.5%, 16/637) met diagnostic criteria for a psychotic disorder, 7 at intake (5 non-affective psychoses, 2 affective psychoses) and 9 during follow-up (4 non-affective psychoses, 5 affective psychoses). All offspring who developed a psychotic disorder during follow-up reported PLE in the interviews, 2 at intake and 7 at follow up (transition rate 7.9%, 0.99%/year).

Though not significant, BP offspring reported more life-time PLE than control offspring (66/390, 16.9% vs. 29/247, 11.7%), at last assessment. When PLE subtype was differentiated into the most severe diagnosis at the last assessment, there were no differences between offspring groups in rates of psychotic disorder (BP offspring: 2.6% vs. community controls: 2.4%), PLE threshold (BP offspring: 3.3% vs. community controls: 2.4%), and PLE subthreshold (BP offspring: 11.5 % vs. community controls: 6.9%). In both cohorts, hallucinations were the most prevalent PLE, followed by delusions or a combination of the two (8.5% vs. 2.8% vs. 3%, respectively).

Factors associated with PLE—Regarding the association of risk at each follow-up, analyzing the offspring as a whole (PLE, $n = 95$; Table 2) or separating BP and control offspring ($n = 66$ vs. $n = 29$, respectively) (Tables S4 and S5, available online) yielded equivalent results. Therefore, we present the data for the group as a whole, specifying only few significant differences. Excluding from the analyses the 16 cases with psychotic disorders did not change the results.

There were no differences at intake or during follow-up in sex, race, family status (living with both parents). There was not variation in the retention rate either between those with and without PLE. Younger age (HR = 0.93; 95% CI 0.87–0.99, $p = .02$) and lower SES (HR = 0.97; 95% CI 0.95–0.99, $p < .01$) were associated with increased risk of PLE during follow-up (Table 2).

First-degree family history of BP (not all bipolar, neither separately BPI and BP II), or major depression (both with or without psychosis), PLE, or any other affective disorder at intake was not associated with PLE.

Current or past history of any psychiatric disorder at intake or during the follow-up increased six-fold the likelihood of developing PLE (HR = 6.52; 95% CI 2.81–15.16, $p < .0001$) (Table 2), and still significant even after excluding schizophrenia and other psychotic disorders (OR = 2.36 95% CI 1.32–4.23, $p < .01$). Except for other mood disorders and tic disorders, all diagnoses were significant associated with PLE in the univariate analyses of the whole sample and both groups separately (Table 3). Although significant in both, the association between psychiatric disorder and PLE was stronger for BP offspring than for control offspring (Tables S4 and S5, available online).

CGAS/GAF scores below 70 at intake or during the follow-up also increased the likelihood of PLE (current: HR = 5.31; 95% CI 3.41–8.28, $p < .0001$; most severe in the past: HR = 5.02; 95% CI 2.93–8.6, $p < .0001$; highest in the past: HR = 5.49; 95% CI 3.67–8.21, $p < .0001$; minimum at current or past: HR = 5.09; 95% CI 2.98–8.73, $p < .0001$). There was not significant association between IQ and PLE.

History of any physical or sexual abuse at intake or during the follow-up was confirmed associated with PLE (HR = 2.74; 95% CI 1.55–4.85, $p < .001$). However, it was only significant for BP offspring (HR = 2.65; 95% CI 1.45–4.86, $p < .01$).

Exposure to psychotropic and other medications at intake or during follow-up were found significantly related with experiencing PLE in the whole group (HR = 1.78; 95% CI 1.17–2.7, $p < .01$) and also in BP offspring (HR = 1.96; 95% CI 1.15–3.32, $p = .01$). There were no effects of head injury, neurological or other endocrine illnesses, pubertal status, or body mass index. For the whole offspring sample and each one separately, there were no significant associations between the perinatal factors recorded from intake and PLE.

Multivariate analysis: All the significant variables noted above together with sex and years in the study, were entered into a series of multivariate time-varying survival analyses. For the whole offspring group three statistically significant predictors of PLE either at intake or during follow up (Table 3; Figure 1) remained: (1) history of any psychiatric disorders (HR = 3.1; 95% CI 1.3–7.36, $p = .01$), (2) low psychosocial functioning (HR = 2.94; 95% CI 1.79–4.81, $p < .0001$), and (3) history of physical or sexual abuse (HR = 1.85; 95% CI 1.02–3.38, $p = .04$). The effect of previous exposure to medication disappeared when control by other variables. Similar results were found when only BP offspring were analyzed (Table S4, available online). For control offspring, only low psychosocial functioning increased the risk or PLE (Table S5, available online).

DISCUSSION

Contrary to our main hypothesis, BP offspring and control offspring did not significantly differ in terms of prevalence rates for PLE or psychotic disorders. Moreover, having a parent with BP or with a history of PLE was not associated with PLE in their offspring. PLE were common in both BP and control offspring, with 14.9% of offspring, particularly adolescents, reporting probable or definite hallucinations or delusional thoughts at some point in the study. Nearly eight percent (7.9%) of offspring with PLE developed a full psychotic disorder, and twenty-five percent of the PLE symptoms were persistent over time. In the

multivariate analysis, three clinical variables remained as significantly associated with PLE at intake or during follow-up: lifetime history of any psychiatric disorder, poor overall psychosocial functioning (independent of the presence of psychiatric disorders), and lifetime history of either physical or sexual abuse. There were no effects of perinatal complications, head injuries, medical and neurological illnesses, medical and psychiatric pharmacological treatments, substance abuse, IQ, pubertal status, or body mass index.

Before discussing the above findings, the following limitations must be considered. Offspring were recruited across a broad age range (6–18 years old), which may have influenced the results because of the developmental differences regarding perception and the nature of PLE. However, there were no age differences in the prevalence and outcome of the PLE. In addition, most of the sample has not reached yet the period of highest risk to develop psychosis⁸ (mean age at last follow up: 19.9 years old); information regarding the symptoms and PLE was collected retrospectively at intake and for the interval between follow-ups, on average every 2.5 years; existing prodromal scales to ascertain PLE were not available at the time that this study started; and most of the information about the psychopathology of biological co-parents was obtained indirectly. Lastly, the results pertain to offspring of parents with BP and may not be generalizable to other populations.

The high prevalence of PLE in BIOS (14.9%; 5.8% baseline and 9.1% during follow up) was expected in light of previous studies with youth. In a large literature review including community and clinical samples (ages 7–18 years old) with a longitudinal design, Rubio and colleagues³ also reported a baseline-prevalence between 4.9%–9%. Furthermore, the incidence rate was between 0.7%–1.33% per year, as expected with higher prevalence rates for longer follow-up. Kelleher and colleagues also reported prevalence between 7.5%–17%, with higher rates for children ages 9 to 12 than ages 13 to 18 years old.² However, they included PLE from face to face interviews and based on self-reports, which could overestimate the results. On the contrary, in our study, adolescents reported higher prevalence rates of PLE (5% vs. 9.9%), with a mean age of PLE reported at 14 years old. Only 25% of offspring reported PLE more than once over time, less than in previous studies,³¹ which could be related with the younger age of the sample or recall bias. Finally, the prevalence of psychotic disorders (2.5%) was similar to the meta-analysis of Van Os and colleagues⁴ based on 47 studies with youth. Conversion rates (0.99%/year) were also similar to previous studies in youth (range between 0.6%–1.3% on average).³ Thus, according to the literature, it is likely that persistence of PLE and conversions into psychotic disorders in BIOS will increase during future follow-ups.

Contrary to our hypothesis, having a parent with Bipolar or PLE was not associated with PLE in their offspring. The literature regarding the risk to develop PLE in offspring of parents with psychosis and mood disorder is mixed. Van Os and colleagues¹⁴ were the first to highlight the association between first degree family history of a broad range of psychosis (including PLE, mania and depression among others), and the presence of PLE in the general population. More recently, Jeppesen and colleagues¹⁶ in a longitudinal study of 1600 adolescents (11 to 12 years old) confirmed that having a parent or sibling with either schizophrenia or any affective psychosis increased the risk for PLE during follow up. In contrast, Zammit and colleagues²⁰ only found that parental depression and not schizophrenia

was a significant predictor of PLE. Polanczyk and colleagues¹⁷, in a longitudinal twin study, found that correlation for the occurrence of PLE was greater for monozygotic than for dizygotic siblings. Other twin-studies have also shown the contribution of genetics (15%–59%)^{17,18} and environment (49%–67%) and the risk of developing PLE, with a higher heritability for negative PLE (flattened affect, and thought problems) than for positive PLE (delusional and hallucinations).¹⁹ In BIOS, most PLE were hallucinations and delusions; the impact of siblings was not taken into account, which could have weakened the results.

The relation between internalizing and externalizing disorders and the presence of PLE in children is well documented, and also with a broad range of DSMIV disorders later during adolescence.^{32–35} More recently Scott and colleagues³⁶ found a positive correlation between general psychopathology at ages 5 and 14 years old and the presence of PLE at age 21. The presence of any psychiatric disorder was significantly correlated with PLE also in BIOS, with almost all psychiatric disorders associated with increased hazard of PLE either at intake or follow-up. Moreover, this association was stronger for BP offspring than for control offspring. Axelson and colleagues²² have previously reported more psychiatric disorders among BP offspring in this sample, with an increased risk for BP during the follow up. Based in this new evidence, BP offspring also differed in the quality of the psychiatric disorders, with a higher morbidity with PLE over time. Besides, the relation with PLE was spread over a wider range of disorders, including affective, anxiety and eating disorders.

Low psychosocial functioning was associated with increased risk for PLE even after controlling for the impact of psychopathology. Kelleher and colleagues³⁷ also found that adolescents with psychiatric disorders who reported PLE scored more than 10 points lower on the GAF than those with psychiatric disorders who did not report PLE. In fact, a decline in functioning and social isolation is considered as part of a general negative core of symptoms in the earliest stage of psychosis, prior to the onset of subthreshold psychotic symptoms and a subsequent psychotic disorder.^{8,9}

The existing literature has consistently shown a relationship between exposure to trauma and increased risk to develop PLE and psychotic disorders.³⁸ For example, several studies showed that early exposure to any type of maltreatment (bullying, neglect, physical or sexual abuse) that is perceived as a threat also increases the risk of PLE,^{32,38} with a dose-response relationship in terms of intensity and cumulative exposure over time.¹⁵ Moreover, the relation between child abuse and PLE it seems independently of family history of PLE or psychotic disorders.¹⁵ In our study the relation between continuous exposure to abuse and PLE was confirmed, but only in the BP offspring, even after controlling for axis I disorders. We knew from a previous analysis in BIOS³⁹ that, at least at intake, BP offspring and control offspring differed in the number of previous exposures to severe life events, including sexual and physical abuse, which could explain this difference.

In contrast to our results, some studies reported an association between low IQ during childhood and increased risk for PLE during follow up in community samples.^{17,40} A lower IQ has been consistently reported in the early stages of schizophrenia¹¹ as well, but not in the early stages of bipolar disorders⁴¹. More recently, lower IQ has been confirmed in offspring of schizophrenic parents but not in BP offspring or control offspring.⁴² In line with

the existence evidence, it seems that low IQ is only a predictor of PLE in individuals at risk for Schizophrenia but not affective disorders.

In our study we did not find other factors that in the literature have been associated with increased risk for PLE or psychosis such as perinatal complications, head injuries or other medical conditions.^{13,17,42} However, the literature about these factors is mixed and most studies did not control for confounding factors. Finally, in the univariate analyses we found that history of treatment with psychotropic medications was associated with increased risk to develop PLE, but this finding was accounted for by the fact that these offspring had more psychiatric disorders.

In summary, PLE were found to be relatively common phenomena in the offspring of BP and control parents. PLE were correlated with the presence of psychopathology in general, poor psychosocial functioning, and history of exposure to physical or sexual abuse. Based on our findings and the existing literature, during the psychiatric assessments, more attention must be given to the presence of PLE as marker of morbidity. More studies with longer follow-ups are needed to better understand the risk between PLE and functional decline and development of psychiatric disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1:
Multivariate Hazard Ratio (HR) for Predicting Psychotic Like Experiences

Table 1:Socio-Demographic Factors of Bipolar Offspring and Control Offspring^a

	All offspring (N= 637)	Bipolar Offspring (n=390)	Control Offspring (n=247)	Statistic (τ)	p-value
Intake					
Age	11.88 $\pm$ 3.59	11.91 $\pm$ 3.61	11.81 $\pm$ 3.55	0.15	0.88
Gender: Female	50.9%	49.0%	53.8%	0.53	0.59
Race: White	78.2%	81.0%	73.7%	1.99	0.05
Living: both parents	65.5%	59.5%	74.9%	2.81	<0.01
SES	35.32 $\pm$ 13.62	34.15 $\pm$ 13.93	37.18 $\pm$ 12.93	1.95	0.05
N° kids/family	2.37 $\pm$ 1.06	2.35 $\pm$ 1.14	2.38 $\pm$ 0.93	0.53	0.59
Last follow up					
Age	19.91 $\pm$ 5.11	20.01 $\pm$ 5.24	19.75 $\pm$ 4.89	0.24	0.81
Drop outs	8.3%	7.7%	9.3%	0.13	0.89
Years in the study	8.03 $\pm$ 3.43	8.08 $\pm$ 3.40	7.95 $\pm$ 3.48	0.12	0.90
Number of assessments	4.44 $\pm$ 1.58	4.43 $\pm$ 1.62	4.46 $\pm$ 1.52	0.35	0.72
2 FU	85.7%	84.9%	87.0%	0.83	0.41
4 FU	57.1%	55.6%	59.5%	0.63	0.53
6 FU	3.3%	4.6%	1.2%	1.46	0.15
Living: both parents	32.2%	27.9%	38.9%	1.47	0.14
SES	35.18 $\pm$ 13.72	34.69 $\pm$ 13.99	35.97 $\pm$ 13.27	0.91	0.36

Note: In bold p-values indicate <.05. FU = follow-up assessments; SES = Socioeconomic status.

^a GLMM adjusted for within family correlation.

Table 2:

Demographic and Clinical Predictors from Intake and During Follow-Up for the Onset of Psychotic-Like Experiences (PLE) in All Offspring^a

Characteristics	Unadjusted Univariate Analysis, HR (95% CI)	Statistic (z)	p-value	Adjusted Multivariate Analysis, HR (95% CI)	Statistic (z)	p-value
Sociodemographics:						
Gender: Female	1.03 (0.66, 1.61)	0.12	0.90	0.96 (0.62, 1.49)	0.18	0.85
Race: White	0.62 (0.35, 1.09)	1.66	0.09			
Living: Both parents	1.03 (0.67, 1.58)	0.13	0.89			
Age at intake	0.93 (0.87, 0.99)	2.33	0.02	0.92 (0.87, 0.98)	2.44	0.01
Years in the study	0.93 (0.87, 0.99)	2.13	0.03			
SES	0.97 (0.95, 0.99)	2.72	<0.01	0.99 (0.97, 1.00)	1.49	0.13
Drop out	0.87 (0.22, 3.48)	0.19	0.85			
Parent's Psychopathology (proband or coparent)						
Bipolar vs. Control parents	1.46 (0.88, 2.24)	1.47	0.14			
Bipolar with Psy	1.06 (0.69, 1.65)	0.28	0.78			
PLE	0.95 (0.59, 1.52)	0.22	0.83			
Affective DO	0.57 (0.26, 1.23)	1.43	0.15			
DSM-IV-TR Psychopathology:						
Axis I DO	6.52 (2.81, 15.16)	4.36	<0.0001	3.1 (1.3, 7.36)	2.56	0.01
Axis I DO Major	5.93 (2.92, 12.03)	4.94	<0.0001			
Axis I DO wo Psy	2.36 (1.32, 4.23)	2.89	<0.01			
Axis I DO Major wo Psy	2.48 (1.47, 4.17)	3.42	<0.001			
Overall functioning:						
CGAS/GAF min <70	5.09 (2.98, 8.73)	5.94	<0.0001	2.94 (1.79, 4.81)	4.30	<0.0001
CGAS/GAF current <70	5.31 (3.41, 8.28)	7.37	<0.0001			
CGAS/GAF most severe past <70	5.02 (2.93, 8.60)	5.88	<0.0001			
CGAS/GAF highest in the past <70	5.49 (3.67, 8.21)	5.49	<0.0001			
IQ	0.98 (0.97, 1.00)	1.84	0.06			
Medical History:						
Physical or sexual abuse	2.74 (1.55, 4.85)	3.46	<0.001	1.85 (1.02, 3.38)	2.01	0.04
Head injury	1.35 (0.68, 2.69)	0.86	0.39			
Medication	1.78 (1.17, 2.70)	2.68	0.01			
Endocrine illness	0.61 (0.26, 1.45)	1.12	0.26			
Pubertal Status	0.71 (0.42, 1.22)	1.23	0.22			
BMI	1.01 (0.97, 1.06)	0.69	0.49			
Perinatal Hx						
Parental age at offspring's birth	0.96 (0.92, 1.01)	1.57	0.12			
Infections/injuries during pregnancy	1.34 (0.77, 2.36)	1.04	0.3			
Birth weight	0.95 (0.71, 1.27)	0.36	0.72			

Note: In bold *p*-values <.05 included in the multivariate analysis. AIC =1359.23. AIC = akaike information criterion; BMI = body mass index; CGAS/GAF_70 = Child Global Adjustment Scale or Global Assessment of Functioning, cut off 70 or below; DO = disorder; Major DO: excluded unspecified mood/anxiety DO, tics, or other DO. SES = socioeconomic status; w/o Psy = without schizophrenia, schizophreniform, unspecified Schizophrenia and other psychotic DO, or brief psychosis.

^aSurvival Time Varying model, adjusted by gender, age at intake and SES.

Table 3:

Adjusted Prior Diagnoses and Hazard to Develop subsequent Psychotic-Like Experiences (PLE) in all Offspring, Offspring of Bipolar, and Offspring of Controls^a

	Offspring with PLE (n=95) vs. offspring w/o PLE (n=542)			Offspring with PLE (n=66) vs. offspring w/o PLE (n=324)			Offspring with PLE (n=29) vs. offspring w/o PLE (n=218)		
	Hazard ratio	95% CI	P	Hazard ratio	95% CI	P	Hazard ratio	95% CI	P
Affective DO	3.83	2.48, 5.92	<0.0001	4.57	2.65, 7.88	<0.0001	2.5	1.06, 5.91	0.04
Major Depression DO	2.76	1.79, 4.27	<0.0001	2.51	1.48, 4.26	<0.001	3.58	1.54, 8.34	<0.01
Bipolar (I, II, Other and Unspecified)	3.99	2.48, 6.41	<0.0001	4.11	2.45, 6.89	<0.0001	3.21	0.77, 13.38	0.11
Other Mood DO	1.51	0.92, 2.49	0.10	1.81	1.07, 3.06	0.03	0.59	0.13, 2.66	0.49
Psychotic DO	13.23	9.18, 19.06	<0.0001	12.62	8.39, 18.97	<0.0001	13.01	6.67, 25.36	<0.0001
Non-affective Psychotic DO	11.15	6.83, 18.2	<0.0001	10.53	5.92, 18.74	<0.0001	15.15	4.66, 49.19	<0.0001
Affective Psychotic DO	11.34	7.95, 16.17	<0.0001	10.91	7.35, 16.19	<0.0001	12.92	6.21, 26.88	<0.0001
Anxiety DO	3.70	2.41, 5.67	<0.0001	4.04	2.4, 6.79	<0.0001	2.94	1.45, 5.98	<0.01
Major Anxiety DO	3.78	2.41, 5.93	<0.0001	3.95	2.22, 7.03	<0.0001	3.14	1.48, 6.46	<0.01
Other Anxiety DO	2.77	1.80, 4.28	<0.0001	2.83	1.69, 4.73	<0.0001	2.35	1.16, 4.7	0.02
Attention Deficit Hyperactivity DO	2.02	1.28, 3.19	<0.01	1.63	0.97, 2.73	0.06	3.19	1.39, 7.31	<0.01
Conduct/Disruptive Behavioral DO	2.91	1.78, 4.75	<0.0001	2.5	1.4, 4.46	<0.01	4.02	1.8, 8.96	<0.0001
Post-Traumatic Stress DO	2.57	1.17, 5.64	0.02	1.79	0.75, 4.28	0.19	4.23	1.29, 13.82	0.02
Eating DO	3.25	1.66, 6.37	<0.001	3.62	1.87, 7.03	<0.001	NA	NA	NA
Substance Abuse/Dependence DO	1.8	1.11, 2.91	0.02	1.73	0.97, 3.06	0.06	1.88	0.79, 4.46	0.15
Tic DO	2.28	0.71, 7.29	0.16	2.57	0.86, 7.47	0.09	NA	NA	NA
Other DO	1.75	1.06, 2.88	0.03	1.42	0.81, 2.49	0.22	2.76	1.08, 7.06	0.03

Note: Affective Psychotic DO = bipolar, major depression with psychotic features, schizoaffective; DO = disorder; Major Anxiety DO = panic, separation anxiety, avoidant, social phobia, agoraphobia, generalized anxiety, obsessive compulsive; Non-Affective Psychotic DO = schizophrenia, schizopreniform, unspecified schizophrenia and other psychotic DO, brief psychotic; Other Mood DO = dysthymia, unspecified depression, adjustment DO with depression, unspecified mood DO; Other Anxiety DO = specific phobia, unspecified anxiety, adjustment DO with anxiety, enuresis, encopresis; Other DO = learning problems, sleep DO; Unspecified attention-deficit/hyperactivity disorder or unspecified conduct DO, parent-child relational problems, sibling relational problems.

^aSurvival Time Varying model, adjusted by gender, age at intake, and SES at intake. In bold p-values <0.05. NA: Not applicable or convergence problems.