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Longitudinal Course and Risk Factors Associated with Psychosis in Bipolar Youth

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Abstract

Objectives: To compare the longitudinal clinical course of youths with bipolar spectrumdisorders (BD) with lifetime (past, ntake, and/or follow-up) psychosis (BDP+) to youths with BD without lifetime psychosis (BDP−). Also, to identify risk factors associated with increased risk of first onset of psychosis during prospective follow-up.

Method: BD youths (BDP+ = 137, BDP− = 233) ages 7–17 years old were followed on average every 7 months for 11.7 years and were evaluated using standardized instruments. Data were

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Conflict of interest:

Dr. Birmaher has received grants from NIMH during the conduct of the study; royalties from Random House, UpToDate, and Lippincott, Williams and Wilkins, outside of the submitted work. Dr. T. Goldstein has received grants from NIMH, the American Foundation for Suicide Prevention, and the Brain and Behavior Foundation and royalties from Guilford Press, outside the submitted work. Dr. Yen has received research support from NIMH, NICCH, and the American Foundation for Suicide Prevention and has served as a consultant at Janssen Global Services. Dr. Axelson has received grants from NIMH, during the conduct of the study; personal fees from Janssen Research and Development, LLC, and UpToDate, outside the submitted work. Ms. Hower has received funding from NIMH, and honoraria from the DOD. Dr. Weinstock receives funding from NIMH, NIH OBSSR, and NIJ. Dr. B. Goldstein, Dr. Ryan, Dr. Keller, Dr. Strober, Dr. Shalev, Dr. Iyengar, Ms. Liao, Mr. Merranko, and Ms. Gill report no biomedical financial interests or potential conflicts of interest.

Data availability statement: Data from the COBY study were uploaded to NIMH RDOC database to share with the public. It is accessible at https://data-archive.nimh.nih.gov/rdocdb/

analyzed using linear and generalized linear models for the full sample, as well as for youths who developed first period of psychosis (n= 55).

Results: After adjusting for confounders, BDP+ youths with one, and in particular ≥ 2 lifetime psychotic episodes, had higher rates and more severe mood and anxiety symptoms, higher rates of suicidality, psychiatric hospitalizations, and sexual/physical abuse, and poorer psychosocial functioning than BDP− youths. Even before the first onset of psychosis during follow-up, BDP+ youths showed more psychopathology and had more family history of psychiatric illness than those who never developed psychosis. First onset psychosis was associated with low socioeconomic-status, living with one parent, BD-I/II, comorbid anxiety, history of hospitalizations, and family history of mania and suicidality.

Conclusion: BDP+ is associated with poor prognosis and worse clinical picture, even before the onset of psychosis, indicating the need for prompt identification and treatment of these youths. Studies aimed to treat acute symptoms of psychosis, as well as prevent the onset of psychosis, including risk factors amenable to change, are warranted.

Introduction

Bipolar Disorder (BD) is a recurrent illness that affects 1–3% of youth, and is associated with poor psychosocial functioning and increased risk for behavior problems, substance abuse, and suicidality[1, 2].

Depending on the setting and the methodology, prior studies report that between 16%–75% of youths with BD have psychotic symptoms during the course of their disorder[3, 4]. The presence of psychosis in youths and adults with BD (BDP+) is considered a marker of severity that is related to poor outcomes[4, 5]. However, the prognostic significance of BDP+ is not clear; the existing literature in BD youth is scarce, and the results reported in the adult BD literature are inconsistent. Also, it is unknown whether the development of psychosis worsens the course of BD or if more severe psychopathology existed before the onset of the psychosis. Moreover, risk factors associated with the development of psychosis in youth with BD are unknown, making it challenging to predict who will develop psychotic features.

There are few studies evaluating the effects of psychosis in BD youth (Table 1). Three cross-sectional studies reported that, compared to BD youth without psychosis (BDP−), BDP+ youth showed significantly lower Intelligence Quotient (IQ), and more suicidal ideation, psychiatric hospitalizations, family history of anxiety disorders, and suicide attempts[6–8]. The only existing longitudinal study showed that, in comparison with BDP− youth, BDP+ youth had higher rates of comorbid psychopathology, family history of psychosis, and poorer overall functioning in multiple domains[4]. Based on these results, the authors suggested that BDP+ might be considered a separate subtype of BD.

Most, but not all, of the existing studies of BD adults, have shown that the presence of psychosis is generally associated with worse prognosis (Table 1). Both cross-sectional and longitudinal studies report that adults with BDP+ have more severe psychopathology, including mood symptoms, poorer functioning[9–13], and more cognitive deficits[14] than BDP− adults. Nevertheless, some of the cross-sectional studies showed no clinical or functional

differences between BDP+ and BDP− adults[15–17], and some even show a clinical advantage of BDP+ compared to BDP−[18, 19].

The above-noted findings should be considered with caution, because the existing studies had one or more of the following limitations. Most studies were cross-sectional; longitudinal studies were carried out for short periods of time; only small samples were included; psychotic features were diagnosed retrospectively; persistence of psychosis was not considered; standardized tools for diagnosing psychosis were not used; and control groups were not included. Finally, the effects of confounding variables, such as age, sex, socioeconomic status (SES), and parental psychopathology were not always considered.

The Course and Outcome of BD Youth (COBY) study has been prospectively following a large group of youth with BD for over 15 years. COBY reported that BD in youth is a recurrent disorder characterized by syndromal and sub-syndromal mood symptoms[20, 21]. Factors such as early BD onset, comorbid disorders, and lower SES have been found to be associated with worse course and outcome[20]. A prior COBY paper presented a cross-sectional analysis showing that BPD+ was associated with higher rates of suicidality, more time spent with any mood symptoms, and family history of anxiety disorders and suicide attempts, as compared to BDP− youth[7].

The aim of the current study is to extend the above findings, by comparing the demographics/clinical characteristics of psychosis in BDP+ youth, and the effects of psychosis on the longitudinal course of BD. Also, within the BDP+ group we examine: 1) the clinical course of youth who had only one psychotic episode, as compared to those who had two or more lifetime (past, intake and/or during follow-up) psychotic episodes; 2) the clinical symptoms and longitudinal course before and after the onset of a new episode of psychosis, as compared to youth who never developed psychosis; and 3) the risk factors associated with first lifetime onset of psychosis during the follow-up.

Based on the literature, and after adjusting for confounding factors, we hypothesized that 1) the longitudinal clinical course and psychosocial functioning would be poorer in the BDP+ group compared to the BDP− group, particularly in youth with multiple psychotic episodes; 2) the clinical course of the BDP+ group would further deteriorate after the onset of psychosis as compared to the BPD− group, and 3) although there are no studies focusing on the risk of developing first lifetime onset of psychosis in youth with BD, we hypothesized that comorbid psychiatric disorders, early-onset BD, and family history of psychosis would be associated with increased risk for first lifetime onset of psychosis.

METHODS

Participants:

The methods for the COBY study have been described in detail elsewhere[20]. Briefly, 446 youth aged 7–17 years with Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM- IV) BD-I or II, or an operationally defined BD-NOS, were recruited at Brown University, University of California Los Angeles, and the University of Pittsburgh. Age of BD onset was defined as the onset of a DSM- IV mood episode or an episode

fulfilling COBY's BD- NOS criteria. BD-NOS was defined as a distinct period(s) of abnormally elevated, expansive or irritable mood, plus: (i) at least two DSM- IV manic symptoms (three if the mood was irritable only) that were clearly associated with the onset of abnormal mood; (ii) clear change in functioning; (iii) mood and symptoms present for a significant part of the day (minimum of 4 hours); and (iv) a minimum of 4 days (not necessarily consecutive) meeting these mood, symptom, duration, and functional change criteria over the participant's lifetime. Youth with COBY-defined BD-NOS were previously shown to have a comparable, but less severe, clinical picture, similar family history, rates of comorbid disorders, and longitudinal outcome, as compared to BD-I youths, and to have a high risk to convert to BD-I/II. BD youth were enrolled independently of current mood state or treatment status. Youth with schizophrenia, mental retardation, autism, and mood disorders secondary to use of substances, medications, or medical conditions were excluded from the study. BD youth were recruited from outpatient clinics (84.4%), inpatient units (4.4%), advertisements (6.7%) and referrals from other physicians (4.4%), from October 2000 through July 2006. During the follow-up, 12 of the BD youths fulfilled criteria for schizoaffective disorder, and 7 for schizophrenia.

The analyses presented in this report are based on the prospective evaluation of 370 youths with at least four years of follow-up, including 221 (59.7%) with BD-I, 26 (7.0%) with BD-II, and 123 (33.2%) with BD-NOS. At the time this article was written, youths had been prospectively interviewed approximately every seven months for a median of 11.7 years with a retention rate of 83%. Except for higher rates of generalized anxiety disorder (GAD) in youths who dropped from the study (21.4% vs. 13.4%, p=0.05), there were no other demographic or clinical differences between the youths who continued or withdrew from COBY. Each university's Institutional Review Board approved the study before enrollment of any youth, and consents and assents were obtained from parents and youth respectively.

For the analyses, the sample was divided into 2 groups: youths with (BDP+) (n=137), or without (BDPBDP) (n=233), lifetime psychotic symptoms. The average age of BD onset was around 9 years old, with no significant difference between the two groups.

Among the BDP+ group, 40 youths (29%) experienced psychotic symptoms only at/before intake, 55 (40%) experienced symptoms only during follow-up, and 42 (31%) experienced symptoms both at/before intake and during follow-up (For more detailed information see Supplemental Table 1). The psychotic symptoms did not necessarily occur within syndromal mood episodes, but could have also occurred while youths had subsyndromal mood symptoms. Of the BDP+, 31 (32%) never had psychotic symptoms outside of the syndromal mood episodes, 51 (53%) had psychotic symptoms both in and out of syndromal mood episodes, and 15 (15%) had all of their psychotic symptoms outside of the syndromal mood episodes. Of those psychotic symptoms that did not occur during the syndromal mood episode, most occurred together with subsyndromal symptoms. Of note, if the psychotic symptoms occurred without any mood disturbance for the period specified by DSM-IV, the participant was diagnosed with schizoaffective disorder, or where indicated, schizophrenia.

In order to investigate the prognostic role of psychosis in the course of BD, the BDP+ group was further divided into 2 subgroups: BD youth with only one-lifetime psychotic episode

(n=91), and youth with two or more lifetime psychotic episodes (n=46; mean number of episodes = 4.8, median = 3). With the aim to explore the influence of psychosis on the BD trajectory, we also analyzed the data from youth who developed their first lifetime psychotic features during the follow-up (n=55), and contrasted them with youth who never developed psychotic symptoms (n=233).

Examples of psychotic symptoms include: a 14 year-old female, who during a depressed episode, saw angels and heard their voices, dropped to her knees to pray, and begged her mother “not to let them go away”; a 7 year-old female that believed that she could fly while she was manic; a 15 year-old female who reported, while being depressed, seeing a dead man at the foot of her bed, and other dead people in her room; and a 12 year-old female who believed she was being watched by cameras while she was depressed.

Instruments:

At intake, youths and parents (about their children) were directly interviewed for the presence of current and lifetime psychiatric disorders using the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version (K-SADS-PL)[22], the K-SADS Mania Rating Scale (K-MRS), and the K-SADS Depression Rating Scale (K-DRS)[23].

At intake, a youth was considered positive for psychosis if either the hallucinations or delusions item was rated as ‘threshold, definitely present” in the K-SADS-PL screening interview, or as “moderate” or greater on the K-MRS (≥ 4). “Moderate” (K-MRS = 4) in the K-MRS *Hallucinations* item is defined as “generally believes in the reality of the hallucinations, but it has little influence on her/his behavior”; “moderate” (K-MRS =4) for the K-MRS *Delusions* item is: “generally has conviction in her/his belief”.

Longitudinal changes in psychiatric symptomatology since the previous evaluation were assessed every 7 months on average using the Adolescent Longitudinal Interval Follow-up Evaluation (A-LIFE) and tracked on a week-by-week basis using this instrument’s Psychiatric Status Rating scale (PSR)[24]. The Psychiatric Status Ratings are numeric values that have been operationally linked to the DSM-IV criteria. Utilizing a procedure similar to the timeline follow-back (TLFB) method, at each interview there is a retrospective recall of weekly symptomatology from the previous interview to the current interview, utilizing a calendar and several memory aids[25]. The ratings indicate the severity level of an episode, as well as whether the participant has recovered or had a recurrence. For mood disorders, the PSR scores range from 1 for no-symptoms, 2 to 4 for increasing levels of subthreshold symptoms and impairment, and 5 to 6 for full criteria with increasing degrees of severity or impairment. Hallucinations and delusions were rated on a 3-point scale on the PSR: 1 indicates “no psychosis”, 2 means “possible psychosis”, and 3 indicates “definite psychosis”. Only those rated 3 were defined as psychotic in this study.

The consensus scores obtained after interviewing parents and their children were used for the analyses. The K-SADS-PL, K-MRS, and K-DRS, provided data regarding the severity of the psychotic symptoms. These data were complemented by narrative notes written by interviewers after each assessment visit to describe the content of the psychosis. All data and

narrative notes were reviewed by three of the study's senior clinicians to ensure the validity of the psychotic symptoms.

Suicidal ideation, self-injurious behavior, and suicide attempts during follow-up were ascertained using the A-LIFE method to create an A-LIFE Self-Injurious/Suicidal Behavior Scale[26]. Psychosocial functioning was assessed as part of the A-LIFE interview using the instrument's psychosocial functioning scale (PSF), and by the Children's Global Assessment Scale (C-GAS) for those under age 22, and the Global Assessment of Functioning (GAF) for those over age 22, for quantification of functioning at home, school, and work[24, 27]. Anxiety disorders were assessed by the A-LIFE, and by the Screen for Child Anxiety Related Emotional Disorders (SCARED)[28]. Intellectual functioning was assessed using the vocabulary and matrix reasoning subtests of the Wechsler Abbreviated Scales of Intelligence[29]. History of pregnancy and birth complications (e.g., smoking during pregnancy, premature birth) were collected using a clinical child health history questionnaire completed by parents at intake.

All assessments were completed by research staff trained to reliably administer the above-noted interviews, and presented to child psychiatrists/psychologists who confirmed the diagnoses and the K-SADS/PSR ratings. The overall K-SADS kappas coefficients for psychiatric disorders were ≥ 0.8. The intraclass correlation coefficients for the K-MRS and the K-DRS were ≥ 0.95. The intraclass correlation coefficients for syndromal and subsyndromal mood disorders ascertained through the PSRs and using the methods as described elsewhere[30] were 0.75. More specifically, the intraclass coefficient correlations and the Kendall's coefficients of concordance for a major depressive episode were between 0.74 and 0.79, respectively, and for mania/hypomania, 0.6–0.67, respectively.

Statistical Methods

Statistical analyses were all performed in SAS 9.4 and R 3.5.1.

Youths with and without psychosis were compared using chi-squared, Fisher's exact, and t-tests as appropriate. Rates of psychiatric hospitalizations, suicide attempts, and self-injury were contrasted using negative-binomial regression. Contrasts of time-varying measures were tested via mixed linear and generalized linear regressions fitting a random intercept to account for within-subject correlation. Square-root transformations were used to remedy residual nonnormality in SCARED mixed linear regressions, and gamma regressions (after implementation of +1 transformation and estimation of robust standard errors) were used to handle the very skewed distributions of the K-MRS and K-DRS. Longitudinal PSR measures were modeled via mixed logistic regression (dichotomized as 100% threshold vs. otherwise). Mixed regressions were adjusted for age, as well as concurrent demographic and diagnostic factors on which groups significantly differed at the 0.1 level (SES, anxiety, and BD subtype), except for the PSR models, which did not adjust for the diagnostic factors, since they were ascertained via the PSR measures themselves. Group-by-age (mean-centered) interactions were tested in all mixed models and retained where significant, and a quadratic age effect was used in all PSR anxiety models. Satterthwaite approximation was used in all linear models to account for differing subsample variances.

The second phase of the analysis sought to further subdivide the lifetime psychosis subsample by whether youth had only one vs. multiple psychotic episodes. Because the number of lifetime psychotic episodes before intake was not ascertained, but rather the history of presence or absence of psychosis (yes/no), the lifetime psychosis subsample was subdivided based on the number of follow-up episodes. The first subgroup included youths who either had only one psychotic episode during follow-up, or had zero episodes during follow-up, but reported a history of psychotic symptoms before intake (n=91). The second subgroup included youths with 2+ psychotic episodes during follow-up (n=46), disregarding if they had episodes of psychosis before intake. All the above-mentioned statistical tests were then repeated using this three-way grouping variable instead of the initial two-way grouping variable. To account for multiple comparisons, pairwise contrasts implemented Tukey adjustments in linear and generalized linear models, and Bonferroni adjustments in chi-squared tests.

To identify predictors of new psychosis onset among youths who had no history of psychosis at intake, a Cox proportional hazards lasso was implemented to simultaneously perform variable-selection and shrinkage of regression coefficients among dozens of predictor variables, including intake demographics, prenatal/birth factors, categorical and dimensional clinical features, and family history of psychiatric illness. Cross-validation selected the optimal lambda via the one-standard-error rule[31]. Because only 55 youths developed psychosis during follow-up, the number of folds was set to three, and fold-randomization was stratified to ensure balance on the outcome variable. Hazard ratios are reported for predictors with nonzero coefficient estimates (standardized for continuous predictors; Supplemental Table 2).

Comparisons between youths who later went on to develop schizoaffective disorder or schizophrenia, and youths with BPD+ and BPD-, were conducted using linear models and Fisher's exact tests.

Lastly, several sensitivity analyses were performed to test whether findings were driven by youths who went on to develop schizophrenia and schizoaffective disorder, as well as to test whether significant between-group differences held when only considering data outside of psychotic episodes. False discovery rate (FDR) correction was implemented in each section of analysis to account for the multitude of tests performed.

Results:

Clinical course and social functioning between BDP+ and BDP− youths:

As shown in Table 2, BDP+ youths (n=137) had significantly lower SES, and were significantly more likely to have BD-I subtype, history of physical/sexual abuse, anxiety disorders, and family history of mania, suicidality, conduct, and anxiety disorders than BDP − youths (n=233; note that SES, separation anxiety disorder, Post-Traumatic Stress Disorder [PTSD], and family history of conduct and anxiety disorders findings were nonsignificant after FDR correction). BDP+ youths also had higher rates of psychiatric hospitalization, suicidal ideation, suicide attempts, and self-injury. After controlling for age, SES, anxiety, and BD-subtype, BDP+ youths showed worse longitudinal functioning in all areas (Table 2).

During the follow-up, BDP+ youths had significantly more dimensional symptoms of depression, mania, and anxiety, and lower functioning levels than BDP− youths, as reported by parental and child reports. Of these factors, there was a significant group-by-time interaction in psychosocial functioning and anxiety levels (Figure 1). Depression, mania, and anxiety levels were more severe in the BDP+ youths compared to the BDP− youths, and tended to improve gradually in both groups during the years. The psychosocial functioning levels were poorer in the BDP+ youths compared to the BDP− youths. Notably, the functioning levels of the BDP+ youths further deteriorated over follow-up, whereas it remained unchanged in the BDP− youths. Lastly, BDP+ youths had less follow-up time with euthymia, and more follow-up time with threshold episodes of major depression and hypo/mania, and anxiety disorders.

Comparisons between BDP+ youths with one lifetime psychotic episode and BDP+ youths with two or more lifetime psychotic episodes during follow-up:

Similar to the results noted above, youths with ≥ 2 psychotic episodes had significantly more psychopathology and poorer functioning when compared with BDP− youths (Supplemental Table 3). In addition, when compared with youths with one psychotic episode (n=91), the youths with ≥ 2 psychotic episodes (n=46) had significantly more GAD, PTSD, psychiatric hospitalizations, suicide attempts, and worse functioning levels (Supplemental Table 3). Those with one psychotic episode had higher rates of BD-I, panic disorder, specific phobia, and more symptoms of depression and anxiety compared with the BPD− group (note that the specific phobia finding was nonsignificant after FDR correction).

First lifetime onset of psychosis during follow-up:

A total of 55 youths experienced their first psychotic episodes during follow-up (median onset age = 17.8). The majority of the first lifetime psychotic episodes included only hallucinations (55%), followed by only delusions (25%) and a combination of the two (20%). There was no significant association between the type of psychotic symptoms and the age in which the psychosis first emerged. Further, most of the first lifetime psychotic episodes emerged while youths experienced rapid cycling/mixed symptoms (53%); 24% were experiencing only depression, 13% only hypo/mania, and 11% no concurrent mood symptoms. Of these 55 youths, 22 (40%) had subsequent psychotic episodes during follow-up, reporting hallucinations on average during 4% of follow-up time, and delusions during 5% of follow-up time. Most of these subsequent psychotic episodes occurred while experiencing depressive or rapid cycling/mixed symptoms (44% and 40%, respectively); 13% featured only hypo/mania, and 4% featured no concurrent mood symptoms.

Except for lower SES in the youths with first onset of psychosis during the follow-up (n=55), there were no significant between-group differences in demographics and duration of follow-up compared to youths who never had psychosis until the end of follow-up (n=233) (Table 3). Youths who developed psychosis during follow-up had significantly more BD-I, specific phobia, GAD, poorer psychosocial functioning, and depressive, manic, and anxiety symptoms, family history of mania, conduct disorder, and suicidality at intake, and were more likely to have mothers who smoked during pregnancy than BPD- youths. Note that after adjusting for multiple comparisons, all comparisons remained significant, with the

exception of history of prenatal smoking, BD-I, GAD, poor school functioning, and family history of conduct disorder (see Table 3). The differences in severity of depressive and anxiety symptoms and levels of functioning increased as youths aged, and groups did not significantly differ in functioning at intake (Figures 2a, 2b, 2e). Psychosocial functioning, depression severity (K-DRS), and anxiety (SCARED) improved over time in the BDP− youths during follow-up. In contrast, they remained fairly unchanged among those who developed first lifetime onset of psychosis. In addition to the severity scores, we measured the rate of threshold depressive symptoms during the follow-up (Figure 2c). These analyses showed that the rate of threshold depressive symptoms increased over time in the BDP+ group, but not in the BPD- group. The first lifetime onset of psychosis group had significantly higher mania scores as compared to the BPD- group, however, both groups improved similarly over time (the slopes of both groups decreased) (Figure 2d). Finally, youths who developed first psychosis during follow-up were significantly more likely to experience episodes of threshold major depression (which increased with age), hypo/mania, and anxiety disorders during follow-up, than youths with BPD-.

Risk factors associated with first lifetime onset of psychosis:

Any anxiety, history of psychiatric hospitalizations, and family history of mania and suicidality were associated with increased risk to develop psychosis (hazard ratios between 1.25–1.64; Supplemental Table 2). Higher SES, living with both biological parents, and BD-NOS (vs. BD-I/II) were found to be protective factors (hazard ratios between 0.83–0.93).

Schizoaffective Disorder and Schizophrenia

During the follow-up, 12 youths were diagnosed with schizoaffective disorder and 7 with schizophrenia. Of these 19 youths, 6 reported psychosis before intake and 12 developed psychosis over follow-up. Exploratory analyses indicated that, in comparison with BPD- and other BPD+, these youth were more likely to have anxiety disorders, history of suicide attempts, lower SES, and family history of anxiety (p-values<0.04). However, given the small sample size of youths with schizoaffective or schizophrenic disorders, the above findings should be considered with caution. Excluding these youth from the above analyses yielded similar findings.

Discussion:

This is the largest longitudinal study to examine the effects of psychosis in youth with BD. Also, this is the first study to analyze the clinical course and functioning of youth with BD before and after the first onset of psychosis.

In summary, 137 (37%) youth showed significant psychotic symptoms; 91 (24%) had one lifetime psychotic episode, and 46 (12%) had two or more lifetime psychotic episodes. Fifty-five youths (15%) had a new onset of psychosis during the follow-up, with most psychotic episodes occurring during mixed/rapid cycling mood episodes, followed by only depression, and only hypo/mania. This subgroup experienced psychotic symptoms only 5% of the follow-up time. In addition, 12 youths (3%) developed schizoaffective disorder during follow-up, and 7 (1.5%) developed schizophrenia.

As hypothesized, after adjusting for confounders, the clinical and psychosocial longitudinal course of BDP+ youths was characterized by higher rates of mood and anxiety symptoms, suicidality, psychiatric hospitalizations, history of sexual/physical abuse, and poorer psychosocial functioning, than those BDP− youth. Youth with psychosis also showed significantly more family history of suicidality, mania, anxiety, and conduct problems than BDP− youth. The same results were found when the analyses only included youth who had their first psychotic episode during the follow-up.

The presence of two or more lifetime psychotic episodes was associated with the poorest course and outcome, but even one psychotic episode was associated with a worse prognosis when compared with youth with BDP−.

Predictors associated with increased risk of developing first lifetime onset of psychosis included lower SES, living with only one biological parent (vs. both biological parents), being diagnosed with BD-I/II (vs. BD-NOS), having any anxiety disorder, history of psychiatric hospitalizations, and family history of mania and suicidality.

Before discussing the above-noted results in more detail, the following limitations should be considered. First, this is not a study of the relationship of psychosis to mood symptoms. We considered psychosis to function as a comorbidity rather than a specifier of a mood episode (e.g. mania, severe, with psychotic features of depression, severe, with psychotic features). The A-LIFE PSR only recorded presence or absence of hallucinations or delusions over follow-up, not their type, severity, occurrence during depression or mania or mood congruence. Second, for those who reported past psychotic episode(s) at intake, the number of episodes was not ascertained. Third, the majority of participants were self-reported White (reflecting the race distribution of the general population in the metropolitan areas surrounding each study site at the time of original enrollment), and were recruited from clinical settings, which may limit the generalizability of the results. Nonetheless, course and morbidity in non-clinically referred BD youth have been shown to be similar to those in referred populations[32]. Fourth, although this study is prospective, data about psychotic symptoms collected through the A-LIFE (via a method similar to TLFB) was assessed retrospectively at each follow-up visit, and thus subject to recall bias. Nevertheless, TLFB has been used extensively for > 30 years in clinical and nonclinical research studies[25]. Finally, the effects of medications were not analyzed because our study is naturalistic, and therefore the prescription of medications would be confounded by the indication (e.g., youth with more severe symptoms may have been treated more aggressively and sometimes with polypharmacy).

Similar to the existing literature, youths with BDP+, particularly those with more persistent psychosis, had worse clinical course and psychosocial functioning than those with BDP− (Table 1). For example, Hua and colleagues assessed 226 youth with BD, and showed that BDP+ youths had higher rates of comorbid psychopathology, family history of psychosis, and poorer overall functioning in multiple domains, than youth with BDP−[4]. McCarthy and colleagues assessed the cognitive correlates of psychosis in 43 youths with BD, and showed that BDP+ youths have lower IQs and greater working memory deficits than BDP− youths[6]. Caetano and colleagues showed that psychotic symptoms in youth with BD were associated

with more suicidal ideation and plans and psychiatric hospitalizations[8]. Finally, although not consistently, the adult BD literature has also reported that the presence of psychosis in patients with BD is associated with poor course and outcome[9, 10, 12, 13, 15–19, 33, 34].

BDP+ youth appear to be a distinct subgroup of BD, as evidenced by the fact that they had more severe psychopathology, and had families with lower SES and more psychopathology, even before they developed psychosis, compared to BDP− youth. Moreover, once BDP+ youth developed psychosis, their clinical presentation and psychosocial functioning deteriorated (Figure 2), suggesting that psychosis might independently contribute to the deteriorating clinical course, not only as a marker of severity, but also as a course modifier. Although we did not assess mechanisms by which psychosis negatively affects the course of BPD, psychosis has been associated with cognitive and biological changes in the brain. For example, BDP+ youths demonstrated lower IQs and greater working memory deficits than BDP− youths[6], and adults with BDP+ had diminished suppression of the P50 auditory evoked potential and higher dopamine-2 receptors' density in the basal ganglia compared to BDP−[35]. These findings may represent a common physiological mechanism associated with the vulnerability to psychosis in people with BD, and may suggest that the presence of psychosis in BD represents a unique subtype of the disorder[14]. Also, the experience of being psychotic may have a significant impact on one's self-concept (e.g., poor self-esteem, depression, anxiety)[36], and lead to environmental stressors (e.g., peer rejection)[37] and PTSD-like symptoms regarding the traumatic psychotic experience, which may last for months after the psychosis has resolved[38].

In addition, adolescence is a developmentally complex period, characterized by constant changes in the physical and psychosocial domains, with the majority of psychiatric disorders emerging during this timeframe[39, 40]. These developmental changes may be impacted by the onset of BD, and perhaps more severely if the BD is accompanied by psychosis. Also, factors such as lack of adherence to treatment, side effects of medications, and stigma, which are relevant to all mental health problems and especially to psychosis, could also contribute to the poorer outcome[37, 41, 42].

Given that our study included youth with BD who developed first lifetime onset of psychosis during follow-up, we were able, for the first time in the BD literature, to evaluate the risk factors that predate the onset of psychosis. Increased risk of developing psychosis was associated with low SES, living with only one biological parent, BD-I/II subtypes, comorbid anxiety, and family history of suicidality and mania. We cannot compare our results with the literature, because to our knowledge, there are no published studies evaluating the risk factors associated with the onset of psychosis in BD adults or youths. However, a longitudinal high-risk study also showed that BD offspring of parents who are non-responsive to lithium were at increased risk for psychotic features during mood episodes[43]. In addition, a review paper that focused on risk factors for psychosis in general, showed that belonging to an ethnic minority group, having anxiety disorders, history of perinatal complications (e.g., pregnancy and delivery complications, gestational influenza), living with one biological parent, parental history of psychosis and affective disorder, and history of childhood adversity (e.g., physical/sexual abuse) are associated with increased risk of developing psychosis[44, 45].

In our study, family history of psychosis was higher in those who developed first lifetime onset of psychosis during follow-up, compared to BDP− youths. However, the effect was statistically marginal (p=0.06). Although history of abuse was more prevalent in the first lifetime onset of psychosis group, the effect was not statistically significant (p=0.3). Finally, except for smoking during pregnancy, there were no between-group differences in perinatal factors. However, after correction for multiple comparisons, smoking was no longer significant.

Although different pharmacological approaches have been recommended for the acute treatment of patients with BD with psychosis, such as the use of antipsychotics plus a mood stabilizer, there are no randomized control trials to guide clinicians[46–48]. Studies focused on the treatment of BDP+ are warranted in order to improve the course and outcome of these youths. In fact, early interventions during the acute phase of psychosis in general are associated with better outcomes, including decreased hospitalization rates, more rapid recovery, and better social functioning[49, 50].

In conclusion, in this large longitudinal study, we showed that BDP+ in youths, particularly in those with recurrent psychosis, is associated with poorer course and prognosis when compared to BDP−youths, indicating the need for the prompt identification and treatment of these youths. Moreover, it appears that youths who are prone to developing psychosis have more psychopathology at intake, even prior to the first lifetime onset of psychosis, suggesting the need for early identification of BD youths who are at risk of developing psychosis, and the importance of developing preventative interventions focusing on factors amenable for change, such as comorbid disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1a

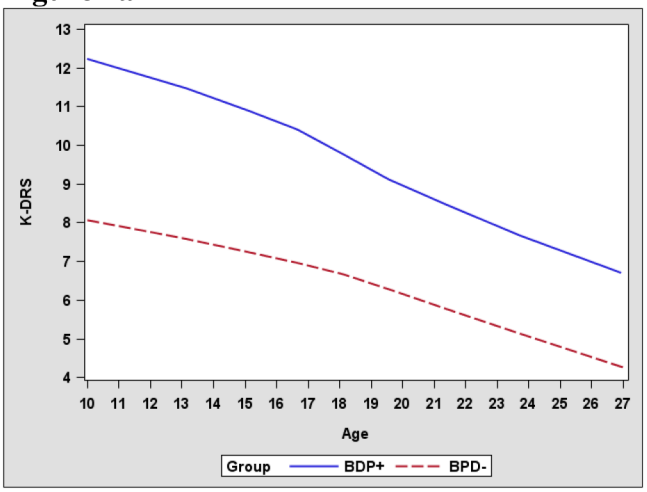


Figure 1b

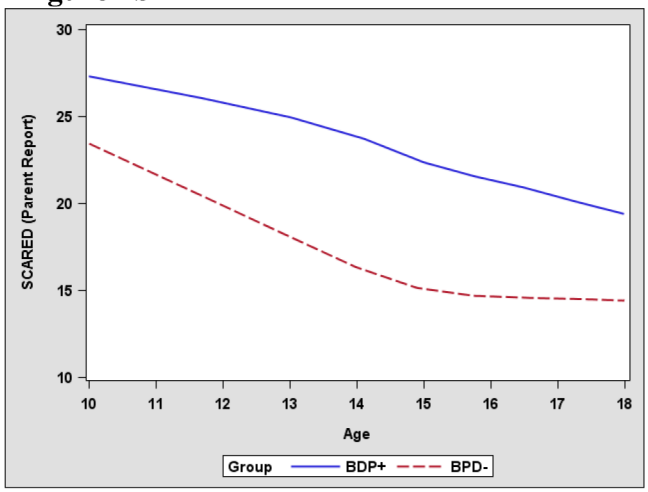


Figure 1c

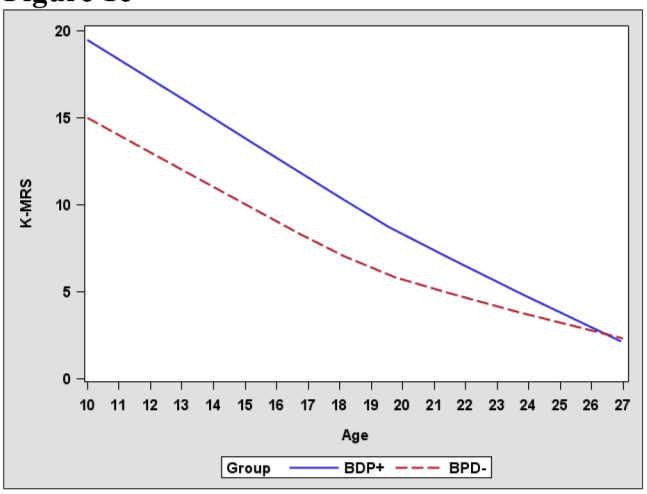


Figure 1d

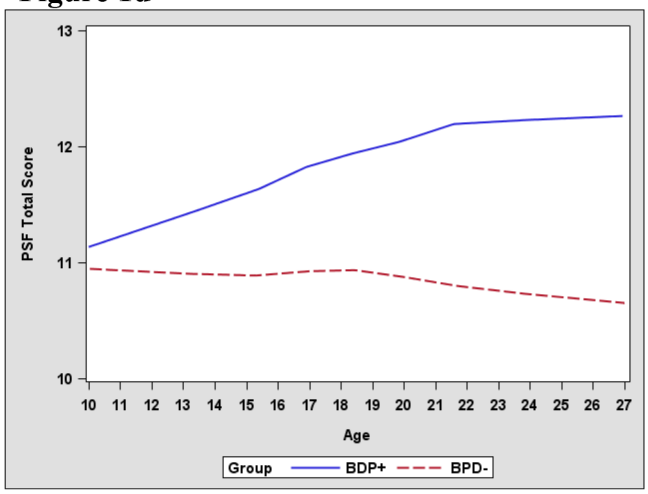


Figure 1: Longitudinal Course of Depressive, Manic and Anxiety Symptoms, and Psychosocial Functioning of Youths with Bipolar Disorder with Lifetime Psychosis (BDP+) Compared to Youths with Bipolar Disorder without Lifetime Psychosis (BDP−)

K-DRS: K-SADS Depression Rating Scale, K-MRS: K-SADS Mania Rating Scale, PSF: Psychosocial Functioning Scale of A-LIFE, SCARED: Screen for Child Anxiety Related Emotional Disorders.

Significant group-by-time interaction stats: SCARED F-stat=14.23, p=0.0002; PSF total score F-stat=14.57, p-value=0.0001

Figure 2a

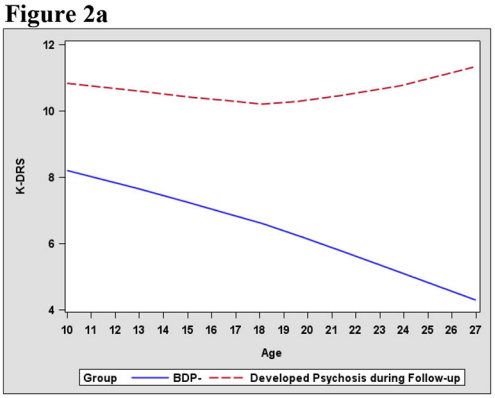


Figure 2b

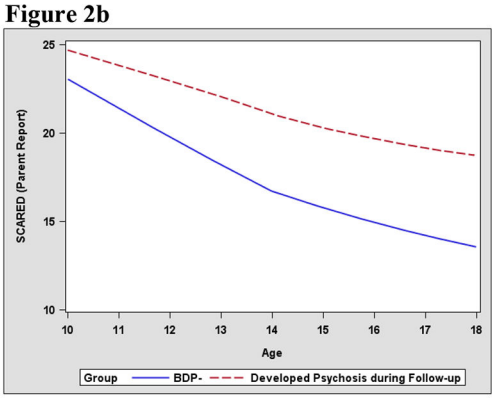
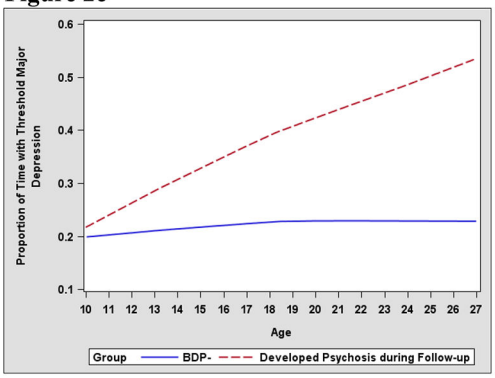


Figure 2c



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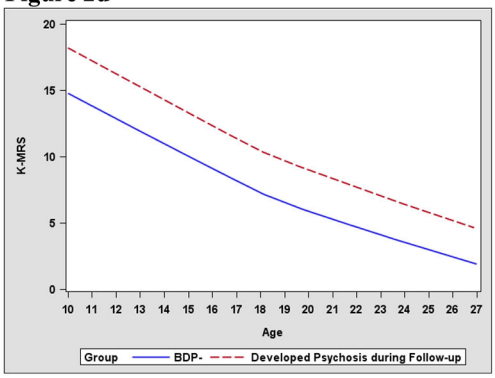

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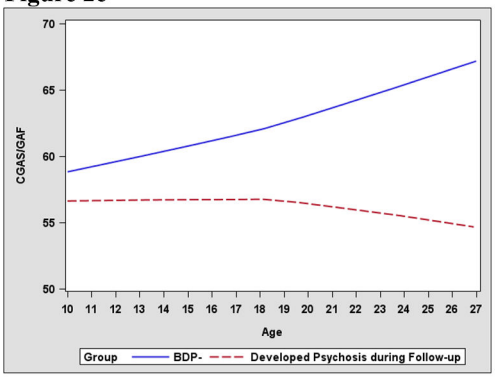

Figure 2: Longitudinal Course of Depressive, Manic, and Anxiety Symptoms and Psychosocial Functioning of Youths with Bipolar Disorder with lifetime psychosis (BDP+) who had First lifetime onset of psychosis during the Follow-Up Compared to Youths with Bipolar Disorder without Lifetime Psychosis (BDP−)

GAF: General Assessment of Functioning, C-GAS: Children's Global Assessment Scale, K-DRS: K-SADS Depression Rating Scale, K-MRS: K-SADS Mania Rating Scale (K-MRS), SCARED: Screen for Child Anxiety Related Emotional Disorders. Significant group-by-time interaction stats: SCARED F-stat=11.24, p-value=0.0008; C-GAS/GAF F-stat=37.87, p-value<0.0001; PSR Depression F-stat=7.51, p-value=0.006

Table 1:

Literature Review Summary of Psychosis in Youths and Adults with Bipolar Disorder

Children and Adolescents					
author-year	**age (years)**	**sample**	**study type**	**instruments**	**main findings**
McCarthy et al 2016	7–18. mean age of14	43 with BD-I or BD-II, 7 with MDD, 30 with mood disorder-NOS	CS	WISC-IV IQ, Coding, Symbol Search (working memory)	BDP+ showed lower IQs and greater working memory deficits than BDP−.
Hua et al 2011 (Biederman)	4–18. mean age of 13.	226 youth with BD-I or BD-II. Amongst them were both BDP+ and BDP−.	Longitudinal	K-SADS, SCID	BDP+ have higher rates of comorbid psychopathology, family history of psychosis, and poorer overall functioning in multiple domains than BDP− youth.
Caetano et al 2006	8–17. mean age of 11.	43 youth with BD spectrum disorder. 17 BDP+ and 26 BDP−.	CS	K-SDAS	Psychotic symptoms in pediatric BD patients are associated with suicidal ideation and plans, and psychiatric hospitalizations.
Birmaher 2006	7–17. mean age of 13.	263 youth with BD-I, BD-II, BD-NOS.	Longitudinal	K-SDAS	Lifetime psychosis is a significant predictor of more time spent with any mood symptoms.
Rende et al 2006	7–17. mean age of 13.	263 youth with BD-I, BD-II, BD-NOS.	CS	K-SADS	BDP+ had a higher percentage of positive family history of anxiety disorders and suicide attempts as compared to BDP−.
Adults					
author-year	**age (years)**	**sample**	**study type**	**instruments**	**main findings**
Jiménez-López et al 2018	mean age of 41	BD spectrum. 50 BDP+, 50 BDP−, 50 patients with schizophrenia (SZ), and 51 (HC).	CS	SCID–I, GAF, FAST, PANSS	History of psychotic symptoms had no relevant impact on level of psychosocial functioning in BD.
Burton et al 2018	>=18, mean age of 41	BD-I, BD-II, BD-NOS. 168 affective-only BD patients (BDP−) and 213 BD patients with a history of psychosis (BDP +). Patients were already suffering from BD for more than 22 years in average.	CS	DIGS	BDP− experienced greater chronicity of affective symptoms and more rapid cycling than BDP+ participants. Results contradict conventional notion that bipolar disorder with psychotic features represents a more severe illness than bipolar disorder without a history of psychosis.
Dell'Osso et al 2017	mean age of 48	BD spectrum. 207 BDP+, 153 BDP−	CS	SCID	BDP+ had more comorbid substance use disorder, lower GAF and more lifetime hospitalizations. However, in the BDP+ group there was shorter duration of most recent episode, lower rates of comorbid anxiety disorders, and less usage of antidepressant medications.
Caldieraro et al 2017	mean age of 39.5	BD-I and BD-II. 32 with current psychotic depression and 271 with current non-psychotic depression.	CS	BISS	Psychosis associated with more severe depressive episode, higher suicidality, more comorbid conditions and worse functioning.
Soni et al 2017	18–55. Mea age of 33.	BD spectrum. 30 BD patients with "low functioning" and 31 BD with "high functioning". All patients were in euthymic state.	CS	GAF, Clinical interview (no specified instrument)	No difference between low and high functioning BD groups in history of psychotic symptoms.

Levi et al 2013	18–59. mean age of 38.	BD-I (20 BDP+ and 35 BDP−)	Longitudinal	SCID, GAF, WASI	At discharge and follow-up, BDP+ exhibited more mood symptoms, lower GAF scores, and poorer cognitive and executive functioning.
Carlson 2012	15–60. mean age of 25.	126 youth and adults with BD-I. Only BDP+.	Longitudinal	SCID, GAF, SAPS, SANS	Poorer premorbid functioning, Schneiderian delusions, greater depressive symptoms, and a younger age of first hospitalization portend a worse course.
Canuso et al 2008	>=18. mean age of 37	BD-I. 259 BDP− and 256 BDP+. All patients present with acute mania.	CS	PANNS	BDP+ had more severe manic scores and worse global functioning.
Keck et al 2003	>=18. mean age of 41	352 adults with BD-I	CS	SCID	In this large cohort of outpatients with BD-I disorder, neither a history of psychosis nor of mood-incongruent psychosis had prognostic significance at entry into the Network.
Coryell et al 2001	>=17. mean age of 35	139 adults with BD-spectrum disorder.	Longitudinal	K-SADS	Psychotic features in mania are associated with greater symptom severity and higher morbidity in the long-term.
Strakowski et al 1999	16–45. mean age of 27.	50 BD spectrum patients with their first manic episode.	Longitudinal (8 months)	SCID, SAPS	Mood-incongruent psychosis that occurs during first manic episode appears to predict increased likelihood of persistent psychotic symptoms and worse overall clinical course, as compared to patients without mood-incongruent psychosis.
Tohen et al 1990	>17. No information about mean.	24 BD spectrum disorder with first manic episode.	Longitudinal (4 years)	BRS, LIFE	Psychotic features during index episode were statistically significant predictors of shorter time in remission (both for developing manic and depressive episodes).

BDP−: bipolar patients without lifetime psychosis, BDP+: bipolar patients with psychotic symptoms, BISS-Bipolar Inventory of Symptoms Scale, BRS- Brief Resilience Scale, CS-cross-sectional, DIGS-Diagnostic Interview for Genetic Studies, FAST-Functioning Assessment Short Test, GAF-Global Assessment of Functioning, K-SDAS- Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children, LIFE- Longitudinal Interval Follow-up Evaluation, PANSS-Positive and Negative Syndrome Scale, SANS-Schedule for the Assessment of Negative Symptoms, SAPS- Scale for the Assessment of Positive Symptoms, SCID-lifetime version of the Structured Clinical Interview for DSM-III-R, WASI-Wechsler Abbreviated Scale of Intelligence, WISC-V IQ-Wechsler intelligence scale for children-V intelligence quotient

Table 2:

Demographic and Clinical Factors between Youths with Bipolar Disorder with lifetime psychosis (BDP+) and Youths with Bipolar Disorder without Lifetime Psychosis (BDP−)

	Variable	Mean ± SD or N (%)		Test Stat	p-values
		No Lifetime Psychosis (n=233)	Lifetime Psychosis (n=137)		
Demographics	Intake Age	12.6 ± 3.4	12.7 ± 3.1	t=0.11	0.9
	SES(Intake + Follow-up)	4.1 ± 0.7	3.9 ± 0.7	F=3.72	**0.05**
	Female %	105 (45.1%)	67 (48.9%)	χ^2=0.51	0.5
	Self-Reported White %	193 (82.8%)	112 (81.8%)	χ^2=0.07	0.8
	Lives with Both Biological Parents at Intake	105 (45.1%)	50 (36.5%)	χ^2=2.60	0.1
Prenatal/Birth Stats	Mother's Age at Birth of Child (years)	26.9 ± 5.8	26.7 ± 5.8	t=0.30	0.8
	Birth Weight	7.1 ± 1.4	6.9 ± 1.4	t=0.66	0.5
	Days in Hospital after Birth	3.2 ± 4.1	3.6 ± 6.3	Z=1.10	0.3
	Drank Alcohol while Pregnant	19 (9.5%)	9 (7.9%)	χ^2=0.23	0.6
	Smoked while Pregnant	49 (24.3%)	36 (31.6%)	χ^2=1.99	0.2
	Premature Birth	21 (10.2%)	9 (8.0%)	χ^2=0.41	0.5
	Any Birth Complications	77 (37.8%)	47 (42.0%)	χ^2=0.54	0.5
Lifetime Clinical Variables	Bipolar Onset Age (years)	9.4 ± 3.9	9.2 ± 4.0	t=0.38	0.7
	Bipolar Disorder Subtype				
	BD-I	150 (64.4%)	115 (83.9%)		
	BD-II	40 (17.2%)	13 (9.5%)	χ^2=16.83	**0.0002**
	BD-NOS	43 (18.5%)	9 (6.6%)		
	Physical/Sexual Abuse	59 (25.5%)	56 (40.9%)	χ^2=9.41	**0.002**
	ADHD	164 (70.4%)	90 (65.7%)	χ^2=0.88	0.3
	Disruptive Behavior Disorders	154 (66.1%)	86 (62.8%)	χ^2=0.42	0.5
	Anxiety Disorder	159 (68.2%)	113 (82.5%)	χ^2=8.99	**0.003**
	Panic Disorder	27 (11.6%)	38 (27.7%)	χ^2=15.54	**<0.0001**
	Separation Anxiety	59 (25.3%)	50 (36.5%)	χ^2=5.18	**0.02**[†]
	Specific Phobia	77 (33.1%)	65 (47.5%)	χ^2=7.56	**0.006**
	Social Phobia	48 (20.6%)	33 (24.1%)	χ^2=0.61	0.4

	GAD	75 (32.2%)	61 (44.5%)	χ^2=5.65	**0.02**
	OCD	36 (15.5%)	25 (18.3%)	χ^2=0.49	0.5
	PTSD	41 (17.6%)	38 (27.7%)	χ^2=5.28	**0.02**†
	Substance Use Disorder	94 (40.3%)	58 (42.3%)	χ^2=0.14	0.7
	Eating Disorders	5 (2.2%)	6 (4.4%)	χ^2=1.49	0.2
	Psychiatric Hospitalizations (days per year)	1.2 ± 3.3	3.7 ± 6.8	Negative Binomial Wald χ2=17.41	**<0.0001**
	Suicidal Ideation	181 (77.7%)	123 (89.8%)	χ^2=8.62	**0.003**
Suicidality, Self-Injury	Suicide Attempts (per year)	0.04 ± 0.1	0.14 ± 0.3	Negative Binomial Wald χ^2=33.07	**<0.0001**
	Self-Injury (per year)	0.18 ± 0.2	0.42 ± 0.7	Negative Binomial Wald χ^2=16.58	**<0.0001**
	Depression	201 (86.3%)	124 (90.5%)	χ^2=1.46	0.2
	Mania	127 (54.5%)	92 (67.2%)	χ^2=5.71	**0.02**
	ADHD	108 (46.4%)	67 (48.9%)	χ^2=0.23	0.6
	CD	77 (33.1%)	60 (43.8%)	χ^2=4.27	**0.04**†
Family History	Schizophrenia	16 (6.87%)	13 (9.49%)	χ^2=0.82	0.4
	Psychosis	38 (16.3%)	31 (22.6%)	χ^2=2.27	0.1
	Anxiety	167 (71.7%)	111 (81.0%)	χ^2=4.04	**0.04**†
	SUD	159 (68.2%)	104 (75.9%)	χ^2=2.47	0.1
	Suicidality	109 (46.8%)	84 (61.3%)	χ^2=7.30	**0.007**
	Variable	**Least-Square Mean (95% Confidence Interval)**		**Test Stat**	**p-value**
		No Lifetime Psychosis (n=233)	**Lifetime Psychosis (n=137)**		
	WASI IQ	108.17 (105.65, 110.69)	104.77 (101.48, 108.06)	F=3.08	0.1
	CGAS/GAF*	63.37 (62.18, 64.56)	59.91 (58.31, 61.51)	F=13.39	**0.0003**
Cognitive and Functioning Variables	PSF Total*	10.66 (10.36, 10.96)	11.39 (10.99, 11.79)	F=9.74	**0.002**
	PSF Work*	3.21 (3.12, 3.30)	3.39 (3.27, 3.51)	F=6.27	**0.01**
	PSF School	2.80 (2.70, 2.91)	2.91 (2.77, 3.06)	F=1.87	0.2
	K-DRS	6.67 (6.04, 7.36)	9.44 (8.43, 10.56)	χ^2=21.23	**<0.0001**
	K-MRS	6.83 (6.10, 7.62)	8.82 (7.77, 10.01)	χ^2=10.07	**0.002**
Symptom Scales	SCARED (Parent Report)*	15.86 (14.23, 17.58)	20.78 (18.32, 23.38)	F=11.97	**0.0006**
	SCARED (Child Report)	13.30 (11.77, 14.90)	19.82 (17.39, 22.41)	F=23.73	**<0.0001**

	Follow-up Variables	Odds Ratio (95% Confidence Interval)	F-Stat	p-value
PSR Measures	Euthymia	0.46 (0.32, 0.66)	17.89	**<0.0001**
	Major Depression	2.27 (1.66, 3.11)	26.11	**<0.0001**
	Hypo/Mania	2.33 (1.71, 3.18)	28.41	**<0.0001**
	Anxiety	2.71 (1.73, 4.23)	19.07	**<0.0001**
	ADHD	1.27 (0.74, 2.18)	0.77	0.4
	DBD	0.89 (0.56, 1.41)	0.26	0.6
	SUD	1.02 (0.60, 1.74)	0.01	0.9

*Age interaction significant

"†" Superscripts indicate p-values were significant at the 0.05 level but nonsignificant after adjustment for false discovery rate (FDR).

ADHD: attention deficit hyperactivity disorder, BD-NOS: bipolar disorder not otherwise specified, CD: conduct disorder, C-GAS: Children's Global Assessment Scale, DBD: disruptive behavior disorder, including Conduct Disorder (CD) and Oppositional Defiant Disorder (ODD), GAD: generalized anxiety disorder, GAF: global assessment of functioning, K-DRS: K-SADS Depression Rating Scale, K-MRS: K-SADS Mania Rating Scale, OCD: obsessive compulsive disorder, PSF: psychosocial functioning scale from the Adolescent Longitudinal Interval Follow-Up Evaluation (A-LIFE), PTSD: post-traumatic stress disorder, SCARED: Screen for Child Anxiety Related Emotional Disorders, SUD: substance use disorder (including all alcohol and substance abuse and dependence disorders), WASI: Wechsler Abbreviated Scales of Intelligence

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Table 3:

Comparison of Demographic and Clinical Factors between Youths with First lifetime onset of psychosis during the Follow-up vs. Youths with Bipolar Disorder without Lifetime Psychosis (BDP−)

	Intake Variables	Developed Psychosis during Follow-up (n=55)	Never Developed Psychosis (n=233)	Test Stat	p-value
Demographics	Intake Age	12.6 ± 3.4	12.6 ± 3.4	t=0.08	0.9
	Socioeconomic Status	3.0 ± 1.2	3.5 ± 1.2	t=2.87	**0.004**
	% Female	30 (54.6%)	105 (45.1%)	χ^2=1.61	0.2
	% Self-Reported White	44 (80.0%)	193 (82.8%)	χ^2=0.25	0.6
	Lives with Both Biological Parents	18 (32.7%)	105 (45.1%)	χ^2=2.77	0.1
Prenatal/Birth Stats	Mother's Age at Birth of Child	26.2 ± 5.9	26.9 ± 5.8	t=0.74	0.5
	Birth Weight	6.9 ± 1.4	7.1 ± 1.4	t=0.65	0.5
	Days in Hospital after Birth	3.8 ± 8.6	3.2 ± 4.1	Z=0.11	0.9
	Drank Alcohol while Pregnant	5 (10.6%)	19 (9.5%)	Fisher's Exact	0.8
	Smoked while Pregnant	19 (40.4%)	49 (24.3%)	χ^2=5.02	**0.03**†
	Premature Birth	2 (4.4%)	21 (10.2%)	Fisher's Exact	0.2
	Any Birth Complications	18 (40.0%)	77 (37.8%)	χ^2=0.08	0.8
Clinical Variables	Bipolar Onset Age	9.3 ± 4.2	9.4 ± 3.9	t=0.10	0.9
	Bipolar Disorder Subtype				
	BD-I	39 (70.9%)	122 (52.4%)		
	BD-II	4 (7.3%)	18 (7.7%)	χ^2=6.75	**0.03**†
	BD-NOS	12 (21.8%)	93 (39.9%)		
	Physical/Sexual Abuse	12 (21.8%)	36 (15.5%)	χ^2=1.30	0.3
	ADHD	31 (56.4%)	140 (60.1%)	χ^2=0.26	0.6
	Disruptive Behavior Disorders	31 (56.4%)	113 (48.5%)	χ^2=1.10	0.3
	Anxiety	26 (47.3%)	82 (35.2%)	χ^2=2.77	0.1
	Panic Disorder	4 (7.3%)	8 (3.4%)	Fisher's Exact	0.3
	Separation Anxiety	14 (25.5%)	50 (21.5%)	χ^2=0.41	0.5
	Specific Phobia	15 (27.3%)	30 (12.9%)	χ^2=7.00	**0.008**
	Social Phobia	2 (3.6%)	11 (4.7%)	Fisher's Exact	~1
	GAD	11 (20.0%)	24 (10.3%)	3.92	**0.05**†

	Intake Variables	Developed Psychosis during Follow-up (n=55)	Never Developed Psychosis (n=233)	Test Stat	p-value
Family History	OCD	1 (1.8%)	14 (6.0%)	Fisher's Exact	0.3
	PTSD	4 (7.3%)	13 (5.6%)	Fisher's Exact	0.7
	Eating Disorders	1 (1.8%)	3 (1.3%)	Fisher's Exact	0.6
	Psychiatric Hospitalizations (per year)	0.17 ± 0.1	0.15 ± 0.1	Poisson Wald χ^2=0.88	0.3
	Depression	51 (92.7%)	201 (86.3%)	χ^2=1.70	0.2
	Mania	43 (78.2%)	127 (54.5%)	χ^2=10.31	**0.001**
	ADHD	24 (43.6%)	108 (46.4%)	χ^2=0.13	0.7
	CD	27 (40.1%)	77 (33.1%)	χ^2=4.96	**0.03**†
	Schizophrenia	8 (14.6%)	16 (6.9%)	Fisher's Exact	0.1
	Psychosis	15 (27.3%)	38 (16.3%)	χ^2=3.56	0.06
	Anxiety	44 (80.0%)	167 (71.7%)	χ^2=1.57	0.2
	SUD	40 (72.7%)	159 (68.2%)	χ^2=0.42	0.5
	Suicidality	38 (69.1%)	109 (46.8%)	χ^2=8.86	**0.003**
	Follow-up Variables	**Least-Square Mean (95% Confidence Interval)**		**Test Stat**	**p-value**
		Developed Psychosis during Follow-up (n=55)	**Never Developed Psychosis (n=233)**		
Cognitive and Functioning Variables	WASI IQ	105.41 (100.34, 110.49)	108.29 (105.31, 111.27)	F=1.12	0.3
	CGAS/GAF*	57.61 (54.98, 60.25)	62.93 (61.39, 64.47)	F=15.27	**0.0001**
	PSF Total*	12.03 (11.39, 12.66)	10.87 (10.50, 11.24)	F=12.32	**0.0005**
	PSF Work*	3.50 (3.32, 3.68)	3.23 (3.12, 3.34)	F=8.09	**0.005**
	PSF School*	3.11 (2.89, 3.34)	2.84 (2.71, 2.97)	F=5.75	**0.02**†
Symptom Scales	K-DRS	11.09 (9.32, 13.16)	7.21 (6.50, 7.99)	χ^2=12.60	**0.0004**
	K-MRS	10.13 (8.44, 12.13)	7.28 (6.35, 8.33)	χ^2=9.25	**0.002**
	SCARED (Parent Report)*	121.51 (118.04, 125.03)	118.71 (116.61, 120.83)	F=2.46	0.1
	SCARED (Child Report)	122.88 (119.31, 126.49)	115.97 (113.83, 118.13)	F=14.40	**0.0002**
	Follow-up Variables	**Odds Ratio (95% Confidence Interval)**		**F-Stat**	**p-value**
PSR Measures	Euthymia	0.35 (0.21, 0.61)		14.34	**0.0002**
	Major Depression*	2.61 (1.68, 4.07)		17.24	**<0.0001**
	Hypo/Mania	2.33 (1.55, 3.50)		16.73	**<0.0001**

	Intake Variables	Developed Psychosis during Follow-up (n=55)	Never Developed Psychosis (n=233)	Test Stat	p-value
	Anxiety	3.00 (1.62, 5.57)		12.12	**0.0005**
	ADHD	1.17 (0.56, 2.41)		0.10	0.8
	DBD	1.45 (0.78, 2.73)		1.21	0.3
	SUD	0.93 (0.45, 1.93)		0.04	0.8

* Age interaction significant

"†" Superscripts indicate p-values were significant at the 0.05 level but nonsignificant after adjustment for false discovery rate (FDR).

ADHD: attention deficit hyperactivity disorder, BD-NOS: bipolar disorder not otherwise specified, CD: conduct disorder, C-GAS: Children's Global Assessment Scale, DBD: disruptive behavior disorder, including Conduct Disorder (CD) and Oppositional Defiant Disorder (ODD), GAD: generalized anxiety disorder, GAF: global assessment of functioning, K-DRS: K-SADS Depression Rating Scale, K-MRS: K-SADS Mania Rating Scale, OCD: obsessive compulsive disorder, PSF: psychosocial functioning scale from the Adolescent Longitudinal Interval Follow-Up Evaluation (A-LIFE), PTSD: post-traumatic stress disorder, SCARED: Screen for Child Anxiety Related Emotional Disorders, SUD: substance use disorder (including all alcohol and substance abuse and dependence disorders), WASI: Wechsler Abbreviated Scales of Intelligence