NEW RESEARCH

Check for updates

A Risk Calculator to Predict the Individual Risk of Conversion From Subthreshold Bipolar Symptoms to Bipolar Disorder I or II in Youth

Boris Birmaher, MD, John A. Merranko, MA, Tina R. Goldstein, PhD, Mary Kay Gill, MSN, Benjamin I. Goldstein, MD, PhD, Heather Hower, MSW, Shirley Yen, PhD, Danella Hafeman, MD, Michael Strober, PhD, Rasim S. Diler, MD, David Axelson, MD, Neal D. Ryan, MD, Martin B. Keller, MD

Objective: Youth with subthreshold mania are at increased risk of conversion to bipolar disorder (BP) I/II. Predictors for conversion have been published for the group as a *whole.* However, risk factors are heterogeneous, indicating the need for personalized risk assessment.

Method: One hundred forty youth with BP not otherwise specified (BP-NOS; 6–17 years old) followed through the Course and Outcome of Bipolar Youth (COBY) study with at least 1 follow-up assessment before conversion to BP-I/II were included. Youths were assessed on average every 7 months (median 11.5 years) using standard instruments. Risk predictors reported in the literature were used to build a 5-year risk calculator. Discrimination was measured using the time-dependent area under the curve after 1,000 bootstrap resamples. Calibration was evaluated by comparing observed with predicted probability of conversion. External validation was performed using an independent sample of 58 youths with BP-NOS recruited from the Pittsburgh Bipolar Offspring Study.

Results: Seventy-five (53.6%) COBY youths with BP-NOS converted to BP-I/II, of which 57 (76.0%) converted within 5 years. Earlier-onset BP-NOS, familial hypomania/mania, and high mania, anxiety, and mood lability symptoms were important predictors of conversion. The calculator showed excellent consistency between the predicted and observed risks of conversion, good discrimination between converters and non-converters (area under the curve 0.71, CI 0.67–0.74), and a proportionally increasing rate of converters at each successive risk class. Discrimination in the external validation sample was good (area under the curve 0.75).

Conclusion: If replicated, the risk calculator would provide a useful tool to predict personalized risk of conversion from subsyndromal mania to BP-I/II and inform individualized interventions and research.

Key words: risk calculator, bipolar disorder, youth, subsyndromal mania, bipolar disorder not otherwise specified

J Am Acad Child Adolesc Psychiatry 2018;57(10):755–763.

Youth and adults with subthreshold manic symptoms, many of whom are diagnosed with bipolar disorder not otherwise specified (BP-NOS), have significant psychosocial functioning impairment and are at increased risk for suicidality, substance abuse, and other comorbid disorders.[1-9] Also, they are at high risk to develop BP-I/II, but the rates of conversion vary.[7-11] For example, the Course and Outcome of Bipolar Youth (COBY) study showed that in a period of 5 years, 45% of youth who at intake fulfilled an operationalized criterion for BP-NOS (see Supplement 1 for criteria, available online) developed BP-I/II, 41% continued to have BP-NOS, and 14% had full or partial remission.[9]

Clinical and epidemiologic studies of adults and youth with subthreshold mania or BP-NOS have shown that persistent subsyndromal manic symptoms, severe manic symptomatology, early BP onset, mood lability, depression, psychosis, and/or anxiety, and in particular family history of mania/hypomania increase the risk to develop BP-I/II.[3-6,8,9,11-13] Although 1 study predicted personalized manic symptomatology classification profiles,[14] most studies predicted conversion to BP-I/II for the group as a *whole* and not for a *specific individual,* a key issue because there is substantial heterogeneity in the rates and risk factors associated with the increased likelihood to convert to BP-I/II.[3,5,6,8-13,15] Thus, there is a need to specifically identify which of these youths are at risk to convert to BP-I/II to develop individualized interventions that might delay or, ideally, prevent the onset of BP-I/II.

Quantification of an individual's risk could inform treatment decisions, such as the use and specific choice of antidepressant medications for a depressed youth with BP-NOS at high risk for conversion versus a depressed youth with BP-NOS at low risk for conversion. Moreover, quantification of an individual's risk will enable the youth (and the family) to more accurately understand the youth's level of risk, which in turn can have a positive effect on treatment engagement and adherence.[16]

To determine an individual's risk, based on the available data for a particular disease, risk prediction models ("risk calculators") have been developed to identify the optimal set of factors to estimate the probability that an individual will develop a specific condition in the future.[17-20] Risk calculators have been successfully developed, validated, and implemented to enhance clinical decision making across several health conditions (eg, cardiovascular disease and cancer).[19-22] For example, to determine risk for myocardial infarction, patients enter responses to questions on key risk variables (eg, age, weight, exercise, smoking) into a calculator, which then generates an individualized risk estimate that can be used to guide treatment decisions (eg, the need for statins to lower cholesterol).[18-20]

In adults, risk models have been developed to predict factors associated with the risk for major depressive disorder and generalized anxiety disorders and, in one study, the conversion of major depressive disorder to BP.[20] However, these studies reported factors for the overall sample and not individualized risk, and the use of internal and external validations within these studies was limited. To our knowledge, only 3 studies in psychiatry have reported on individualized risk calculators. The North American Prodrome Longitudinal Study (NAPLS) built and externally validated in an independent sample a risk calculator to predict 2-year conversion to psychosis for a very high-risk sample of adolescents and young adults.[23,24] By including variables such as unusual thought content, poor functioning, younger age, and lower verbal and memory performance, the model showed an area under the curve (AUC) of 0.79 in the validation sample. Fusar-Poli *et al.*[25] developed and externally validated a risk calculator in a large clinical registry cohort of adults with nonpsychotic psychiatric disorders to predict 6-year risk of psychosis. Diagnosis of transient psychotic disorders, brief limited intermittent psychotic symptoms or BP, age, sex, age-by-sex interaction, and race predicted onset of psychosis with an AUC of 0.79. The Pittsburgh Bipolar Offspring Study (BIOS), a longitudinal study aimed at evaluating the psychopathology of offspring of parents with BP compared with offspring of community controls, developed a risk calculator to predict 5-year risk of developing BP spectrum disorders in offspring of parents with BP.[15] By including dimensional measures of mania, depression, anxiety, and mood lability, psychosocial functioning, and parental age at diagnosis of mood disorder, the model predicted onset of BP with an AUC of 0.76.

The COBY previously reported risk factors for progression to BP-I/II for the sample as a *whole*.[9] The goal of this study was to extend these findings by developing a risk calculator to predict 5-year individual risk of conversion from BP-NOS to BP-I/II. This risk calculator was externally validated using an independent sample of youth with BP-NOS recruited from the BIOS.

METHOD

The COBY is a multisite naturalistic longitudinal study being conducted at Brown University, the University of Pittsburgh, and the University of California at Los Angeles. The COBY enrolled 413 youth 7 to 17.11 years old with *DSM-IV* BP-I (n = 244), BP-II (n = 28), or operationalized criteria for BP-NOS (n = 141; Supplement 1, available online). The analyses in this report are based on the prospective evaluation of 140 youths with BP-NOS with at least 1 follow-up assessment before diagnosis of BP-I/II or right-censoring (ie, conversion did not occur at last available assessment). Twenty subjects dropped out of the study before a BP-I/II diagnosis could be made after an average follow-up of 4.0 ± 3.9 years (mean dropout age 17 years).

The COBY methods have been presented in detail in other articles.[9,26] Briefly, participants were mainly recruited from outpatient clinics (67.6%) and directly interviewed for psychiatric disorders and exposure to treatment using the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (K-SADS-PL).[27] Youth with schizophrenia, IQ lower than 70, autism, and mood disorders secondary to substances, medications, or medical conditions were excluded. The most severe past mood symptomatology, and 1 month before the assessment, was recorded through an interview using the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) Kiddie Mania Rating Scale (KMRS)[9,28] and the Kiddie Depression Rating Scale (KDRS).[9,29] In addition, parents and children completed the Screen for Child Anxiety Related Emotional Disorders (SCARED)[30] and parents completed the Behavior Control Scale (BCS).[31]

Participants were interviewed on average every 7 months (median 11.5 years). Week-by-week longitudinal change in psychiatric symptoms and exposure to treatment was assessed using the Longitudinal Interval Follow-up Evaluation (LIFE) and quantified using the instrument's Psychiatric Status Rating (PSR) scale.[32] The PSR uses numeric values linked to *DSM-IV* criteria and the participant's functioning. For mood disorders, PSR scores no

higher than 2 indicate euthymia, scores of 3 to 4 indicate subsyndromal symptoms, and scores of at least 5 indicate syndromal symptomatology. Onset of BP was determined by the presence of a score of at least 5 for hypomania or mania. The consensus scores obtained after interviewing parents and their children were used for the analyses.

Psychiatric family history was ascertained using a modified version of the Family History Screen,[33] and socioeconomic status (SES) was ascertained using the Hollingshead Scale.[34] Current and most severe past global functioning was assessed using the Children's Global Assessment Scale (CGAS).[35]

Parents were interviewed at intake using the Structured Clinical Interview (SCID).[36] Family psychiatric histories of first- and second-degree relatives were obtained through the Family History Screen[37] and are presented in this article as the summary of data collected during the full length of the study.

Assessments were conducted by research staff trained to reliably administer the interviews. Psychiatrists or psychologists confirmed all diagnoses. Overall K-SADS-Present and Lifetime Version (PL) κ values for psychiatric disorders were at least 0.8. Intraclass correlation coefficients for the KMRS, the KDRS, and syndromal/subsyndromal mood disorders ascertained through the PSR were at least 0.75. Maximum scores for depression and mania on the PSR for the 4 weeks before each follow-up assessment and maximum scores on the KMRS and the KDRS for the same period showed Spearman correlations of 0.82 ($p < .0001$) and 0.77 ($p < .0001$), respectively.

The COBY risk calculator was externally validated with 58 youth with BP-NOS of parents with BP recruited through the BIOS (for method, see Supplement 2, available online). The 2 studies used the K-SADS at intake, but to ascertain *DSM-IV* psychiatric disorders during follow-up, the BIOS used the K-SADS-PL, whereas the COBY used the LIFE. Also, although the 2 studies used the same methods to ascertain family history, the BIOS used a different instrument, the Family History–Research Diagnostic Criteria method.[37]

To avoid the circular logic of testing the prognostic power of variables previously shown to be predictive within the COBY sample, we chose predictor variables from the results of a recent meta-analysis that identified prodromal symptoms in youth and adults who later developed BP (Table S1, available online).[13] This meta-analysis found 26 items to be common (>25%) in individuals before conversion, including manic and depressive symptoms, mood lability, lower global functioning, and anxiety. For the analyses in this study, items from the KMRS and KDRS that were in common with the mood items in the meta-analysis were selected (Table S1, available online). Other predictors noted in the meta-analyses were ascertained through the SCARED parent and child reports, the BCS parent report on lability, the CGAS, family history of mania, age at each assessment, duration of BP illness, and demographic factors including sex and race. Family history of mania was entered because there is a high correlation between this factor and earlier onset of BP.[5,9,38] To further ensure external generalizability of the risk calculator, all these predictors were included in the final mode, even if estimated effect sizes were nonsignificant when modeling the COBY sample. Other risk factors reported in the literature but not included in the meta-analysis also were analyzed (eg, comorbid disorders).[2-6,8,9,11,12,26]

Each participating university's institutional review board approved the study. Consent or assent was obtained from the participating youth and their parents.

Statistical Analyses

To make use of the full extent of longitudinal data, assessment was the unit of analysis. This allowed the use of symptoms at intake and follow-up visits and for modeling the time to BP-I/II onset (or censoring) separately from each assessment. Inclusion of data from follow-up visits allowed incorporating symptoms that might occur closer to BP-I/II conversion, which is especially important because worsening or new symptoms could emerge proximal to conversion.[5] Predictor variables included in the analyses were ascertained before the onset of BP-I/II and before 18 years of age, because different self-report scales were completed by participants after 18 years.

An interaction term was fit between assessment age and duration of BP (which implicitly also captures the effect of age at BP onset) because preliminary analyses demonstrated a significant interaction between these predictors. We imputed missing data using multiple multivariate imputations by chained equations[39] (5 imputations).

Baseline-resetting Cox regression was used to model time to event (conversion) from each index assessment using a generalized estimating equations model parameterization to account for clustering of visits within the individual. The final trained model was used to predict the cumulative hazard (ie, risk) of BP-I/II conversion at 5 years. Median follow-up time for the baseline-resetting Cox regression was 6.0 years, thus allowing for sufficient data to test the cumulative hazard within a 5-year window.

To account for overfitting, training and testing were performed and internally validated using the algorithm of Harrell *et al.*[40] for bootstrap optimism correction (implementing 1,000 bootstrap resamples). Discrimination and calibration were evaluated within the bootstrap procedure; discrimination was measured using the time-dependent AUC, predicting the 5-year risk of an event.[41]

The final model was externally validated on the BIOS sample and evaluated by the time-dependent AUC (predicting the 5-year risk of an event) and by the non–time-dependent AUC. Calibration was tested by Hosmer-Lemeshow testing[42] and by plotting and comparing observed with predicted probability of conversion to BP-I or BP-II. Sensitivity, specificity, positive predictive value, and negative predictive value were assessed at a range of thresholds. To test the internal predictive importance of each variable, 3 measures were used: hazard ratios, 5-year AUC of a model with only that variable, and decrement in 5-year AUC with removal of that variable from the full model. To assess statistical significance, parametric 95% CIs were estimated for hazard ratios, and bootstrapped 95% CIs were estimated for all AUCs. To test the external predictive importance of each variable, the decrement in the external 5-year AUC with the removal of that variable from the full model was calculated.

RESULTS

Internal Validation Using COBY Data

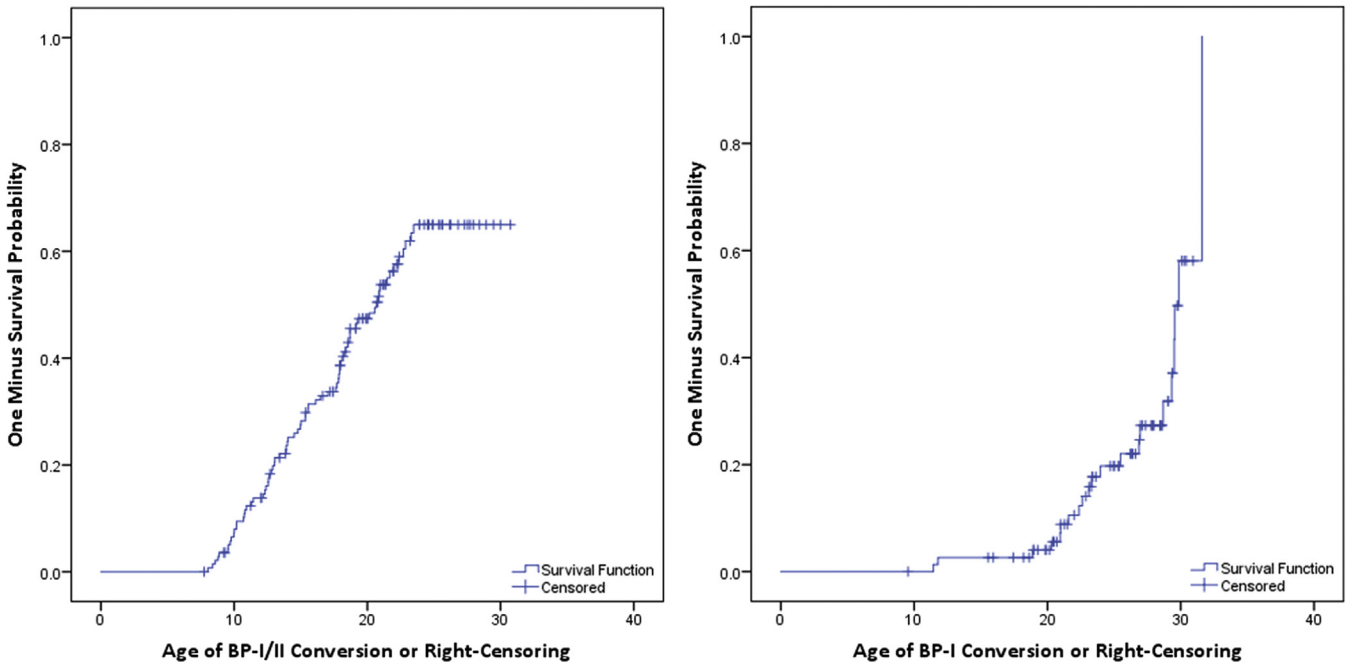
Table 1 presents the demographic and clinical characteristics of the 140 COBY participants included in this study. COBY youths were followed for a median of 11.5 years (range 0.5–15.3 years) with a median of 7 months between assessments, during which time 75 (53.6%) converted from BP-NOS to BP-I (n = 27) or BP-II (n = 48). Of the 75 BP-I/II converters, 57 (76.0%) converted within 5 years (median time to conversion 2.7 years, range 0.5–11.2 years). Risk of conversion increased with age until the early 20s, after which conversion was observed to be unlikely (Figure 1). However, because only 42% of the non-converting sample had assessments after 22 years of age (age range at last assessment 22–31 years old, mean and median age 26 years), more follow-up throughout this age range is needed before definitive conclusions can be made concerning risk of conversion in the mid to late 20s. The COBY sample used to train the risk calculator consisted of 763 follow-up assessments. Mean age at conversion to BP-I/II was 15.3 ± 4.4 years (range 8–23 years). Using the risk factors reported in the meta-analyses (Table S1, available online), after bootstrapping internal validation, the risk calculator discriminated between converting to BP-I/II and non-converting with a 5-year AUC of 0.71 (95% CI 0.67–0.74; BP-I: AUC 0.74; BP-II: AUC 0.70), indicating good discrimination. A model using parent-reported SCARED in lieu of the child report yielded similar results.

TABLE 1 Course and Outcome of Bipolar Youth (COBY) Versus Bipolar Offspring Study (BIOS) Demographic, Clinical, and Family History

Demographic Variables	**COBY (n = 140)**	**BIOS (n = 58)**	**Test Statistic**	***p***
Age, mean (SD)	11.9 (3.2)	11.9 (3.3)	$z = 0.10$	.9
SES, mean (SD)	3.4 (1.1)	2.7 (1.2)	$z = 4.03$	**<.0001**
Male, n (%)	85 (60.7)	24 (41.4)	$\chi^2 = 6.20$	**.01**
Caucasian, n (%)	115 (82.1)	43 (74.1)	$\chi^2 = 1.63$	.2
Live with both biological parents, n (%)	62 (44.3)	21 (36.2)	$\chi^2 = 1.10$	.3
Clinical Variables	**COBY (n = 140)**	**BIOS (n = 58)**	**Test Statistic**	***p***
Age at BP-NOS onset, mean (SD)	8.7 (3.5)	11.8 (3.5)	$z = 5.20$	**<.0001**
Major depressive disorder, n (%)	58 (41.4)	16 (27.6)	$\chi^2 = 3.36$	.07
Anxiety, n (%)	54 (38.6)	30 (51.7)	$\chi^2 = 2.90$	.09
ADHD, n (%)	88 (62.9)	31 (53.5)	$\chi^2 = 1.51$	.2
DBD, n (%)	67 (47.9)	27 (46.6)	$\chi^2 = 0.02$	.9
Psychosis, n (%)	19 (13.6)	1 (1.7)	Fisher's Exact	**.009**
Family History	**COBY (n = 140)**	**BIOS (n = 58)**	**Test Statistic**	***p***
Depression, n (%)	127 (90.7)	55 (94.8)	Fisher's Exact	.4
Mania/hypomania, n (%)	81 (57.9)	58 (100.0)	Fisher's Exact	**<.0001**
Anxiety, n (%)	110 (78.6)	51 (87.9)	$\chi^2 = 2.36$	.1
ADHD, n (%)	73 (52.1)	18 (31.0)	$\chi^2 = 7.36$	**.007**
CD, n (%)	54 (38.6)	17 (29.3)	$\chi^2 = 1.53$	.2
Psychosis, n (%)	24 (17.1)	18 (31.0)	$\chi^2 = 4.74$	**.03**
SUD, n (%)	104 (74.3)	36 (62.1)	$\chi^2 = 2.96$	.09

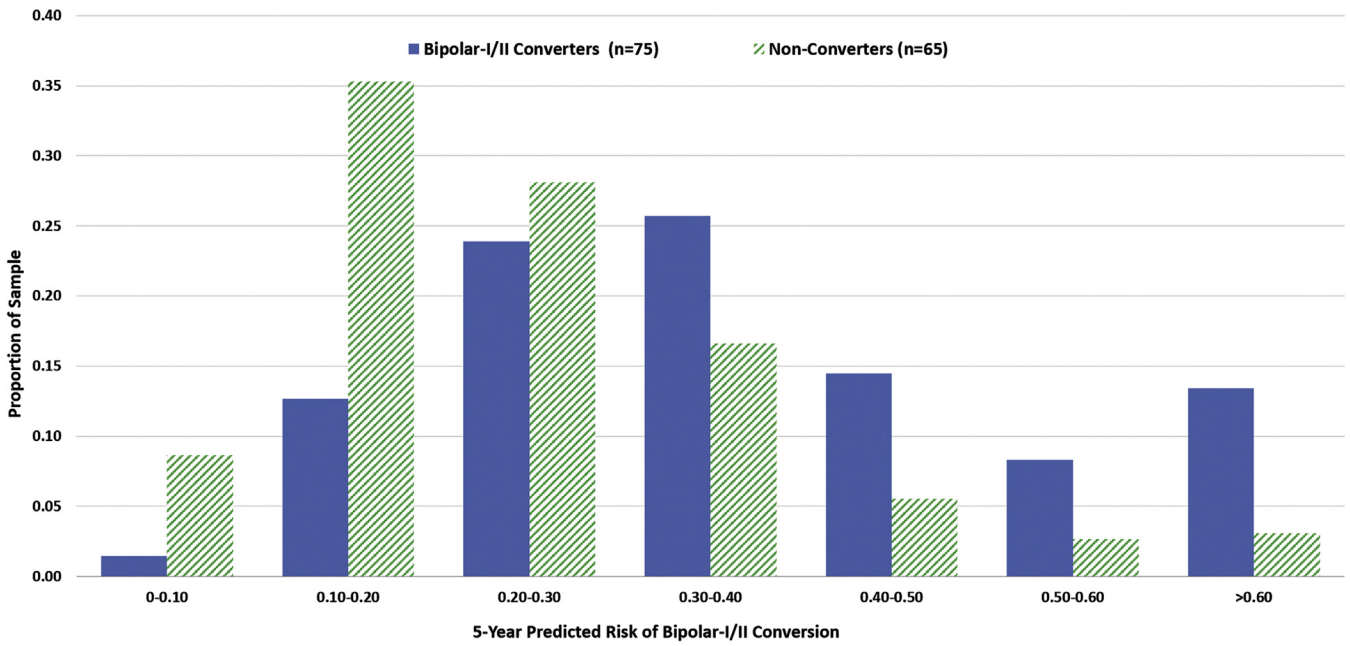
Note: Bold text indicates statistical significance. ADHD = attention-deficit/hyperactivity disorder; BP-NOS = bipolar disorder not otherwise specified; CD = conduct disorder; DBD = disruptive behavior disorders (includes oppositional defiant and conduct disorders); SES = socioeconomic status; SUD = substance use disorder.

FIGURE 1 Course and Outcome of Bipolar Youth Progression From Subthreshold Mania to Bipolar Disorder (BP) I/II and from BP II to I



Note: *Please note color figures are available online.*

FIGURE 2 Frequency Distributions of Predicted 5-Year Risk Among Course and Outcome of Bipolar Youth Converters and Non-Converters



Note: *Please note color figures are available online.*

As presented in Figure 2, conversions occurred at a proportionally increasing rate when observing participants with progressively higher predicted risk, indicating clinically relevant discrimination between converters and non-converters. The calibration plot (Figure S1, available online) indicated that the predicted and observed risks of conversion were consistent throughout the range of risk scores, and the median predicted 5-year risk (25.9%) closely matched the observed 5-year rate of conversion (27.5%). Further, predicted risk and observed rates of conversion within a decile did not significantly differ (Hosmer-Lemeshow $\chi^2_8 = 6.79, p = .56$), which indicates no evidence of mis-calibration.

Table 2 presents internal model prediction metrics at a range of predicted risk thresholds. For example, a less stringent threshold of 0.20 positively identified 86% of internal cases (sensitivity), but only 46% of the positively predicted sample converted to BP-I/II within 5 years (positive predictive value). Increasing the threshold to 0.30 resulted in a higher positive predictive value (56%) but only positively identified 62% of cases.

Estimated model coefficients indicated that youths with increased mania, depression, anxiety, and mood lability symptoms who also had a positive family history of mania were at greater risk of conversion to BP-I/II. Youths with early mood onset were at greater risk of conversion to BP-I/II, predominantly in the years closest to their initial diagnosis of subthreshold manic symptoms. Further, boys and African Americans showed less risk of conversion. Estimates of the magnitude and predictive value of each effect using standardized hazard ratios and concordance statistics are presented in Table 3 (also shown in Figure S2, available online). As depicted, univariate 5-year AUCs indicated that the 4 individual predictors with the strongest univariate discrimination were the KMRS, KDRS, SCARED, and BCS Lability scores. All predictors except age, duration of illness, and age-by-duration of illness interaction triplet yielded 5-year internal AUC decrements of at least 0.01 when removed from the model. Race featured the largest AUC decrement at 0.06, which was the only decrement significantly larger than 0 (bootstrapped 95% CI 0.03–0.09). Estimated standardized hazard ratios indicated that the KMRS, SCARED, race, family history of mania, and sex predictors had the largest effect sizes (all hazard ratios > 1.2).

Adding other potential predictors, including SES, living with 1 biological parent, comorbid disorders, suicidality, physical/sexual abuse, history of psychiatric hospitalization, and family history of non-BP psychopathology, did not appreciably improve internal discrimination (all 5-year internal AUC improvements ≤ 0.01).

External Validation Using BIOS Data

The 58 youth with BP-NOS recruited through the BIOS were followed for a median of 6.1 years with a median of 24 months between assessments, during which time 14 (24.1%) converted to BP-I/II. Compared with the COBY sample, BIOS youths had significantly lower SES and older age at mood onset, were less likely to have family history of

TABLE 2 Performance Measures for a Range of Dichotomous Risk Score Cutoffs

Internal Validation (COBY)

Risk Score Cutoff	Proportion of Sample in Risk Group	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
0.20	0.67	0.86	0.44	0.46	0.85
0.25	0.52	0.75	0.61	0.52	0.81
0.30	0.40	0.62	0.72	0.56	0.77
0.35	0.29	0.47	0.82	0.60	0.73
0.40	0.20	0.36	0.89	0.65	0.71

External Validation (BIOS)

Risk Score Cutoff	Proportion of Sample in Risk Group	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
0.20	0.83	1.00	0.19	0.15	1.00
0.30	0.65	0.78	0.37	0.15	0.92
0.40	0.49	0.78	0.55	0.20	0.94
0.50	0.38	0.67	0.66	0.22	0.93
0.60	0.23	0.56	0.82	0.31	0.93
0.70	0.14	0.56	0.92	0.50	0.93

Note: *BIOS = Bipolar Offspring Study; COBY = Course and Outcome of Bipolar Youth.*

TABLE 3 Individual Predictive Value of Each Variable in the Risk Calculator[a]

Predictor	Standardized Hazard Ratio (95% CI)[a]	Internal Univariate 5-y AUC (95% CI)[a]	Internal AUC Decrement[b]	External AUC Decrement[b]
KMRS[c]	1.26 (0.99–1.60)	0.65 (0.61–0.69)	0.02 (−0.02 to 0.05)	0.05
KDRS[c]	1.03 (0.83–1.27)	0.60 (0.56–0.65)	0.01 (−0.03 to 0.03)	0.00
SCARED	1.26 (1.02–1.56)	0.62 (0.58–0.66)	0.02 (−0.02 to 0.04)	0.04
BCS Lability	1.15 (0.92–1.45)	0.60 (0.56–0.64)	0.01 (−0.03 to 0.03)	−0.02
Age at assessment	1.02 (0.75–1.39)	0.56 (0.52–0.60)	0.00 (−0.03 to 0.03)	0.05
Duration of BP illness	0.94 (0.66–1.34)			
Age × duration of BP illness	0.91 (0.72–1.14)			
Caucasian	1.51 (1.09–2.08)	0.58 (0.55–0.61)	0.06 (0.03–0.09)	0.11
CGAS	1.01 (0.83–1.26)	0.59 (0.55–0.65)	0.01 (−0.03 to 0.0.3)	0.01
Family history of mania	1.31 (0.96–1.78)	0.56 (0.52–0.60)	0.02 (−0.02 to 0.04)	0.04
Female	1.23 (0.89–1.70)	0.55 (0.52–0.59)	0.01 (−0.02 to 0.03)	−0.05

Note: AUC = area under the curve; BCS = Behavior Control Scale; BP = bipolar disorder; CGAS = Children's Global Assessment Scale; COBY = Course and Outcome of Bipolar Youth; KDRS = Kiddie Depression Rating Scale; KMRS = Kiddie Mania Rating Scale; SCARED = Screen for Child Anxiety Related Emotional Disorders.

[a]*Hazard ratios and internal concordance statistics were computed on the COBY sample; external concordance statistics were computed on the BIOS sample.*

[b]*AUC decrements represent decrease in AUC when each predictor is removed from the model.*

[c]*Only items of the KMRS and KDRS that were in common with the mood items in the meta-analysis of Van Meter* et al.[13] *were included (Table S1, available online).*

attention-deficit/hyperactivity disorder (ADHD), and were more likely to be female and have psychosis and family history of psychosis (Table 1). Unlike the COBY sample, all BIOS subjects in the external validation sample had a family history of mania/hypomania. The risk calculator externally validated on the BIOS sample had a 5-year AUC equal to 0.75 and a non–time-dependent AUC equal to 0.78, indicating strong overall external discrimination between converters and non-converters. External prediction metrics presented in Table 2 indicated that the risk calculator predictions were more sensitive and less specific in the BIOS sample compared with those in the COBY sample.

DISCUSSION

In this study, 53.6% (n = 75) of COBY youth with BP-NOS within an average period of approximately 11 years converted to BP-I/II (mean conversion age 15 years), of which 76.0% converted within 5 years of intake. As noted in the existing literature, family history of hypomania and mania and increased levels of manic, mood lability, and anxiety symptoms were strong predictors of increased conversion risk.[5,13] Early onset of BP-NOS also was associated with increased risk for conversion to BP-I/II; in general, if conversion did not occur within 4 years of the initial BP-NOS diagnosis, then the risk decreased considerably. Using the variables described earlier, a risk calculator to predict onset of BP-I/II was constructed. The risk calculator showed excellent consistency between the predicted and observed risks of new-onset BP-I/II, good discrimination between converters to BP-I/II and non-converters, and a proportionally increasing rate of converters at each successive risk class (Figure 2). More specifically, the risk calculator predicted BP-I conversion with 74% discrimination and BP-II conversion with 70% discrimination, comparable to the performance of risk calculators developed to predict psychosis and new-onset BP in offspring of parents with BP and risk calculators currently used in medicine.[18,19,21,22,24] The external validation of the model in an independent sample recruited through the BIOS predicted with an even stronger 75% discrimination, indicating that the risk calculator is generalizable to other samples. Predictions were more sensitive and less specific in the BIOS sample compared with those in the COBY sample, which is likely due to the BIOS sample's higher risk of conversion because all subjects have family history of BP. Overall, further validation of the model on other samples will help to pinpoint the ideal predicted risk range to optimize sensitivity and specificity, so we hope to further validate the model in future samples.

Other variables that have been associated with course and outcome of BP in the literature and in the COBY, such as SES, comorbid disorders, family history of unipolar depression, and exposure to negative events, did not influence the results of the risk calculator. Because the COBY is

a naturalistic study, the prescription of medications is confounded by indication. Thus, exposure to treatment was not included in the analyses.

A different sample of BIOS offspring of parents with BP who did not have BP-NOS before developing BP-I/II[5,15] also showed that increased depressive symptoms, mood lability, manic-like symptoms, and parental history of early-onset BP increased risk to develop new-onset BP to 50%. Thus, our results and those of the existing literature provide convergent evidence that the presence of these symptoms increases the risk for developing BP-I/II.[3-13,15]

If replicated, then the risk calculator provided in this study would offer a useful tool for clinicians to predict an individual child's risk of converting from subsyndromal mania to BP-I/II and thus inform personalized treatment decisions. As presented in Table 2, the internal and external models provided a range of predicted risk thresholds, which can be used depending on whether the risk calculator is being used epidemiologically or clinically to inform treatment and research. For example, the risk calculator can be used to select samples at very high risk and low risk to convert BP for biological studies or to develop early intervention treatment trials that require samples at very high risk for conversion.

The results of this study should be considered within the context of the following limitations. Most participants were Caucasian (reflecting the race distribution for the study sites) and were recruited from clinical settings, which could limit the generalizability of the results. Nonetheless, course and morbidity in non-clinically referred BP youth have been shown to be similar to those in non-referred populations.[7,43] Moreover, the risk calculator built using the COBY data was externally validated in the BIOS, a sample that was recruited from the community. The risk calculator was designed for patients 6 to 17 years old with the goal of predicting BP-I/II conversion by young adulthood, and the success of the risk predictions on the COBY and BIOS samples indicates good generalization to patients in this age range. The use of the modified KMRS and KDRS to ascertain current symptoms of mania and depression, respectively, requires some training. However, these scales are easy to use, brief, free of cost, and include information that is part of standard clinical practice. Parental age at BP onset for COBY participants was not available, an important factor because early parental BP onset is strongly associated with increased risk to develop BP in their offspring.[5,13,15] Although the risk calculator yields a risk value, like other calculators, its ability to predict outcomes in clinical settings should be viewed with caution. Moreover, the presence of factors associated with high risk for conversion is not stable and can change over time.

In conclusion, like existing risk calculators in medicine, if replicated, the proposed risk calculator has the potential to become a useful tool for research and clinical practice. This risk calculator uses instruments that can be disseminated to various settings and used as an aid to predict whether an individual youth with BP-NOS is at risk to develop BP-I/II. The risk calculator and the rating scales used to build it are available at www.pediatricbipolar.pitt.edu. It is important to mention that, at this stage, the use of the calculator is experimental.

Accepted June 21, 2018.

Drs. Birmaher, T.R. Goldsetin, Hafeman, Diler, Ryan, and Mr. Merranko and Ms. Gill are with the University of Pittsburgh School of Medicine, PA. Dr. B.I. Goldstein is with Sunnybrook Health Sciences Centre, University of Toronto Faculty of Medicine, Ontario, Canada. Ms. Hower and Drs. Yen and Keller are with the Warren Alpert Medical School of Brown University, Butler Hospital, Providence, RI. Dr. Strober is with the David Geffen School of Medicine at the University of California, Los Angeles. Dr. Axelson is with the Nationwide Children's Hospital and The Ohio State College of Medicine, Columbus.

This report represents original material that has never been published before, is not under consideration for publication elsewhere, and has been approved by each author. The work was completed at the Department of Psychiatry, Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine and the Department of Psychiatry and Human Behavior, Warren Alpert Medical School of Brown University.

This study was supported by National Institute of Mental Health (NIMH) grants MH059929 and MH59691.

Dr. Merranko served as statistical expert for this research.

The authors thank the studies' participants and their families, the research assistants, and Rita Scholle, BA, of Western Psychiatric Institute and Clinic, for preparation of this report. The authors also acknowledge Stacia Friedman-Hill, PhD, and Shelli Avenevoli, PhD, of the NIMH, for their continued encouragement and support.

Disclosure: Dr. Birmaher has received grants from the NIMH during the conduct of the study and royalties from Random House, UpToDate, and Lippincott, Williams and Wilkins, outside the submitted work. Dr. T. Goldstein has received grants from the 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 the NIMH and the American Foundation for Suicide Prevention and has served as a consultant at Janssen Global Services. Dr. Hafeman has received grants from the NIMH and the Klingenstein Third Generation Foundation. Dr. Strober has received research support from the NIMH and as the Resnick Endowed Chair in Eating Disorders at the University of California, Los Angeles. Dr. Diler has received research support from the NIMH. Dr. Axelson has received grants from the NIMH during the conduct of the study and personal fees from Janssen Research and Development, LLC, and UpToDate, outside the submitted work. Dr. Ryan has received grants from the National Institutes of Health. Dr. Keller has received research support from the NIMH. Ms. Hower has received funding from the NIMH. Dr. B. Goldstein, Mr. Merranko, and Ms. Gill report no biomedical financial interests or potential conflicts of interest.

Correspondence to Boris Birmaher, MD, Western Psychiatric Institute and Clinic, 3811 O'Hara Street, Bellefield Towers, Room 612, Pittsburgh, PA 15213; e-mail: birmaherb@upmc.edu

https://doi.org/10.1016/j.jaac.2018.05.023

REFERENCES

1. Angst J, Gamma A, Benazzi F, Ajdacic V, Eich D, Rossler W. Toward a re-definition of subthreshold bipolarity: epidemiology and proposed criteria for bipolar-II, minor bipolar disorders and hypomania. J Affect Disord. 2003;73:133-146.
2. Wozniak J, Uchida M, Faraone SV, *et al*. Similar familial underpinnings for full and subsyndromal pediatric bipolar disorder: a familial risk analysis. Bipolar Disord. 2017;19:168-175.
3. Axelson D, Goldstein B, Goldstein T, *et al*. Diagnostic precursors to bipolar disorder in offspring of parents with bipolar disorder: a longitudinal study. Am J Psychiatry. 2015;172:638-646.
4. Faedda GL, Marangoni C, Serra G, *et al*. Precursors of bipolar disorders: a systematic literature review of prospective studies. J Clin Psychiatry. 2015;76:614-624.
5. Hafeman DM, Merranko J, Axelson D, *et al*. Toward the definition of a bipolar prodrome: dimensional predictors of bipolar spectrum disorders in at-risk youths. Am J Psychiatry. 2016;173:695-704.
6. Correll CU, Hauser M, Penzner JB, *et al*. Type and duration of subsyndromal symptoms in youth with bipolar I disorder prior to their first manic episode. Bipolar Disord. 2014;16:478-492.
7. Lewinsohn PM, Klein DN, Seeley JR. Bipolar disorders in a community sample of older adolescents: prevalence, phenomenology, comorbidity, and course. J Am Acad Child Adolesc Psychiatry. 1995;34:454-463.
8. Tijssen MJ, van Os J, Wittchen HU, *et al*. Prediction of transition from common adolescent bipolar experiences to bipolar disorder: 10-year study. Br J Psychiatry. 2010;196:102-108.
9. Axelson DA, Birmaher B, Strober MA, *et al*. Course of subthreshold bipolar disorder in youth: diagnostic progression from bipolar disorder not otherwise specified. J Am Acad Child Adolesc Psychiatry. 2011;50:1001-1016 e1003.
10. Nadkarni RB, Fristad MA. Clinical course of children with a depressive spectrum disorder and transient manic symptoms. Bipolar Disord. 2010;12:494-503.
11. Regeer EJ, Krabbendam L, de Graaf R, ten Have M, Nolen WA, van Os J. A prospective study of the transition rates of subthreshold (hypo)mania and depression in the general population. Psychol Med. 2006;36:619-627.
12. Ratheesh A, Cotton SM, Davey CG, *et al*. Ethical considerations in preventive interventions for bipolar disorder. Early Interv Psychiatry. 2017;11:104-112.
13. Van Meter AR, Burke C, Youngstrom EA, Faedda GL, Correll CU. The bipolar prodrome: meta-analysis of symptom prevalence prior to initial or recurrent mood episodes. J Am Acad Child Adolesc Psychiatry. 2016;55:543-555.
14. Jo B, Findling RL, Hastie TJ, *et al*. Construction of longitudinal prediction targets using semisupervised learning. Stat Methods Med Res. 2016. 962280216684163.
15. Hafeman DM, Merranko J, Goldstein TR, *et al*. Assessment of a person-level risk calculator to predict new-onset bipolar spectrum disorder in youth at familial risk. JAMA Psychiatry. 2017;74:841-847.
16. Harle CA, Downs JS, Padman R. Effectiveness of personalized and interactive health risk calculators: a randomized trial. Med Decis Making. 2012;32:594-605.
17. Tripepi G, Heinze G, Jager KJ, Stel VS, Dekker FW, Zoccali C. Risk prediction models. Nephrol. Dial Transplant. 2013;28:1975-1980.
18. Department of Quantitative Health Sciences. Cleveland Clinic Risk Calculator Library. http://rcalc.ccf.org. Accessed March 30, 2018.
19. D'Agostino RB Sr, Vasan RS, Pencina MJ, *et al*. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation. 2008;117:743-753.
20. Bernardini F, Attademo L, Cleary SD, *et al*. Risk prediction models in psychiatry: toward a new frontier for the prevention of mental illnesses. J Clin Psychiatry. 2017;78:572-583.
21. Ankerst DP, Hoefler J, Bock S, *et al*. Prostate cancer prevention trial risk calculator 2.0 for the prediction of low- vs high-grade prostate cancer. Urology. 2014;83:1362-1367.
22. Wells BJ, Kattan MW, Cooper GS, Jackson L, Koroukian S. Colorectal cancer predicted risk online (CRC-PRO) calculator using data from the multi-ethnic cohort study. J Am Board Fam Med. 2014;27:42-55.
23. Cannon TD, Yu C, Addington J, *et al*. An individualized risk calculator for research in prodromal psychosis. Am J Psychiatry. 2016;173:980-988.
24. Carrión RE, Cornblatt BA, Burton CZ, *et al*. Personalized prediction of psychosis: External validation of the NAPLS-2 psychosis risk calculator with the EDIPPP project. Am J Psychiatry. 2016;173:989-996.
25. Fusar-Poli P, Rutigliano G, Stahl D, *et al*. Development and validation of a clinically based risk calculator for the transdiagnostic prediction of psychosis. JAMA Psychiatry. 2017;74:493-500.
26. Birmaher B, Gill MK, Axelson DA, *et al*. Longitudinal trajectories and associated baseline predictors in youths with bipolar spectrum disorders. Am J Psychiatry. 2014;171:990-999.
27. Kaufman J, Birmaher B, Brent D, *et al*. Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. J Am Acad Child Adolesc Psychiatry. 1997;36:980-988.
28. Axelson D, Birmaher BJ, Brent D, *et al*. A preliminary study of the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children mania rating scale for children and adolescents. J. Child Adolesc Psychopharmacol. 2003;13:463-470.
29. Chambers WJ, Puig-Antich J, Hirsch M, *et al*. The assessment of affective disorders in children and adolescents by semistructured interview. Test-retest reliability of the schedule for affective disorders and schizophrenia for school-age children, present episode version. Arch Gen Psychiatry. 1985;42:696-702.
30. Birmaher B, Brent DA, Chiappetta L, Bridge J, Monga S, Baugher M. Psychometric properties of the Screen for Child Anxiety Related Emotional Disorders (SCARED): a replication study. J Am Acad Child Adolesc Psychiatry. 1999;38:1230-1236.
31. Kolko DJ, Baumann BL, Bukstein OG, Brown EJ. Internalizing symptoms and affective reactivity in relation to the severity of aggression in clinically referred, behavior-disordered children. J Child Fam Stud. 2007;16:745-759.
32. Keller MB, Lavori PW, Friedman B, *et al*. The longitudinal interval follow-up evaluation. A comprehensive method for assessing outcome in prospective longitudinal studies. Arch Gen Psychiatry. 1987;44:540-548.
33. Weissman MM, Wickramaratne P, Adams P, Wolk S, Verdeli H, Olfson M. Brief screening for family psychiatric history: the family history screen. Arch Gen Psychiatry. 2000;57:675-682.
34. Hollingshead AB. Four-Factor Index of Social Status. New Haven, CT: Yale University Department of Sociology; 1975.
35. Shaffer D, Gould MS, Brasic J, *et al*. A Children's Global Assessment Scale (CGAS). Arch Gen Psychiatry. 1983;40:1228-1231.
36. Spitzer RL, Williams JB, Gibbon M, First MB. The Structured Clinical Interview for DSM-III-R (SCID). I: history, rationale, and description. Arch Gen Psychiatry. 1992;49:624-629.
37. Andreasen NC, Endicott J, Spitzer RL, Winokur G. The family history method using diagnostic criteria. Reliability and validity. Arch Gen Psychiatry. 1977;34:1229-1235.
38. Smoller JW, Finn CT. Family, twin, and adoption studies of bipolar disorder. Am J Med Genet C Semin Med Genet. 2003;123C:48-58.
39. Raghunathan TE, Lepkowski JM, Van Hoewyk J, Solenberger P. A multivariate technique for multiply imputing missing values using a sequence of regression models. Surv Methodol. 2001;27:85-96.
40. Harrell FE, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med. 1996;15:361-387.
41. Heagerty PJ, Lumley T, Pepe MS. Time-dependent ROC curves for censored survival data and a diagnostic marker. Biometrics. 2000;56:337-344.
42. May S, Hosmer D. Hosmer and Lemeshow type goodness-of-fit statistics for the cox proportional hazards model. In: Srinivasa Rao ASR, Pyne S, Rao CR, eds. *Handbook of Statistics*. Amsterdamn: Elsevier; 2003:383-394.
43. Lewinsohn PM, Klein DN, Seeley JR. Bipolar disorder during adolescence and young adulthood in a community sample. Bipolar Disord. 2000;2:281-293.

SUPPLEMENT 1.

Criteria for Bipolar Disease Not Otherwise Specified (BP-NOS) From the Course and Outcome of Bipolar Youth (COBY) Study[1-3]

A. Child does not meet *DSM-IV* criteria for BP-I/II.
B. A distinct period of abnormally elevated, expansive, or irritable mood plus the following:
   1. At least 2 *DSM-IV-TR* "B" manic symptoms (3 if the mood is irritability only) that are clearly associated with the onset of abnormal mood.
   2. A clear change in functioning.
   3. The presence of elated and/or irritable mood and manic symptoms for a significant part of the day (a *minimum* of 4 hours, although this did not necessarily need to be expressed consecutively).
   4. A *minimum* of 4 days (not necessarily consecutive) meeting criteria B.1 to B.3 over the youth's lifetime.
C. Mood and affective symptoms must be abnormal for the youth's level of development and environment.
D. Symptoms or mood changes that occur during substance use or antidepressant treatment do not count toward a BP diagnosis.
E. Exclusion criteria
   1. Current or lifetime *DSM-IV* diagnosis of schizophrenia, mental retardation, autism, or severe autism spectrum disorders.
   2. Mood disorders from substance abuse, from a medical condition, or secondary to use of medications (eg, corticosteroids).
F. Youth determined to have onset of BP before comorbid substance use disorders are included.
G. Youth with mild comorbid Asperger disorder or pervasive developmental disorder not otherwise specified are included if their mood symptomatology was clearly episodic and best accounted for by the BP diagnosis.

Recently, Towbin *et al.*[3] proposed a modification to the COBY criteria for bipolar disorder not otherwise specified (BP-NOS), which could facilitate the use of these criteria and perhaps limit the number of false positives in clinical practice.

1. Recurrent ($\geq$4) distinct episodes meeting full criteria for a manic or hypomanic episode, except for the duration criterion. Each episode must last at least 1 day, and at least 1 episode must last a minimum of 2 consecutive days. For a day to "count" toward an episode, symptoms must be present for most of that day.
2. A hypomanic episode without a history of a major depressive episode.

SUPPLEMENTAL REFERENCES

1. Birmaher B, Axelson D, Strober M, *et al.* Clinical course of children and adolescents with bipolar spectrum disorders. Arch Gen Psychiatry. 2006;63:175-183.
2. Axelson D, Birmaher B, Strober M, *et al.* Phenomenology of children and adolescents with bipolar spectrum disorders. Arch Gen Psychiatry. 2006;63:1139-1148.
3. Towbin K, Axelson D, Leibenluft E, Birmaher B. Differentiating bipolar disorder-not otherwise specified and severe mood dysregulation. J Am Acad Child Adolesc Psychiatry. 2013;52:466-481.

SUPPLEMENT 2.

The Bipolar Offspring Study (BIOS)—Summary of Methodology

The method of the BIOS has been described in detail elsewhere.[1-5] The study was approved by the institutional review board of the University of Pittsburgh.

The sample was recruited through the parent probands. Parents with BP were recruited through advertisements (53%), other research studies (31%), and outpatient clinics (16%). Parents with BP had to meet *DSM-IV* criteria for BP-I or BP-II and live within 200 miles of Pittsburgh. Exclusion criteria were a lifetime diagnosis of schizophrenia, mental retardation, a mood disorder secondary to medical illness, substance use, or use of psychoactive medications. Comparison parents were recruited from the community using random digit dialing and were matched by group to parents with BP by age, sex, and neighborhood. Comparison parents could not have a parent or sibling with BP and the biological co-parent could not have BP. The study included all offspring of the parent probands who were 6 to 18 years old (including siblings and half-siblings), unless the child had mental retardation.

Study procedures were initiated after informed consent was obtained from the parents and assent was obtained from the children. Parent probands and participating biological co-parents (31%) were assessed for *DSM-IV*[6] disorders by direct interview using the Structured Clinical Interview (SCID)[7] and the ADHD, oppositional defiant disorder, conduct disorder, and separation anxiety disorder sections of the Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime Version (K-SADS-PL).[8] The psychiatric history of nonparticipating biological co-parents was obtained from the parent proband using the Family History–Research Diagnostic Criteria method[9] plus the ADHD, oppositional defiant disorder, conduct disorder, and separation anxiety items from the K-SADS-PL.

At intake, parents were interviewed about their offspring, and the children were directly interviewed using the K-SADS-PL for non-mood disorders and the K-SADS Kiddie Mania Rating Scale (KMRS) and depression items

from the KDRS.[8,10,11] Symptoms that are criteria for more than 1 diagnosis (eg, distractibility) were not rated as fulfilling criteria for a mood disorder unless they had their onset or significantly intensified during a period of abnormal mood. BP-NOS (or subthreshold mania or hypomania) was diagnosed using BP-NOS criteria from the COBY study[12-14] (Supplement 1).

Parents (about the child) and offspring completed several rating scales covering a range of psychopathologies, including the Child Affective Lability Scale[15] and the SCARED.[16] Parents completed the Child Behavior Checklist.[17]

Interviewers completed the Children's Global Assessment Scale (CGAS)[18] to measure overall functioning and the Hollingshead Scale[19] to determine SES.

Follow-up evaluations were performed approximately every 2 years using the same diagnostic instruments cited earlier for parents and offspring younger than 18 years. Offspring at least 18 years old were assessed using the SCID for non-mood disorders and the KMRS and the KDRS.[7,9] If a participant could not complete an interview at the 2-year interval, attempts to schedule and complete the evaluation would continue unless the participant or the parent or guardian asked to withdraw from the study. Follow-up evaluations focused on assessment of the interval since the previous interview. The current retention in the BIOS is approximately 85%.

Assessments were performed by interviewers with a bachelor's or a master's degree who had intensive training with the diagnostic instruments and were required to achieve 80% agreement with a certified rater. Interviewers who assessed offspring were blind to the parents' diagnoses, because different interviewers were used to assess the parents. All information was presented to a child psychiatrist, who reviewed the data to confirm diagnoses. Psychiatrists were blind to parental diagnoses. As specified in the K-SADS instructions, all available data were used to assign summary symptom and diagnostic scores, and discrepant information was discussed at a case conference with the psychiatrist.

Diagnostic reliability was assessed using audiotapes of 44 actual BIOS assessments, which were rated by 2 to 8 BIOS interviewers (mean 5.4). The κ statistics for diagnostic reliability were 0.86 for BP spectrum disorders, 0.77 for BP-I/II versus BP-NOS versus no BP, 0.64 for major depressive episode, 0.71 for any depressive episode, 0.86 for ADHD, 0.78 for anxiety disorders, 0.84 for oppositional defiant disorder and/or conduct disorder, and 1.0 for substance use disorders.

The onset age of specific disorders and mood episodes was set to the estimated age at which the participant met full *DSM-IV* criteria. For consistency with other longitudinal high-risk studies, the onset of full-threshold BP in the offspring was set to when they first met *DSM-IV* criteria for a manic, mixed, or hypomanic episode. The onset age of BP spectrum disorder was set to the age at the first time the participant met criteria for subthreshold mania or hypomania or full-threshold BP.

SUPPLEMENTAL REFERENCES

1. Birmaher B, Axelson D, Monk K, *et al*. Lifetime psychiatric disorders in school-aged offspring of parents with bipolar disorder: the Pittsburgh Bipolar Offspring study. Arch Gen Psychiatry. 2009;66:287-296.
2. Axelson D, Goldstein B, Goldstein T, *et al*. Diagnostic precursors to bipolar disorder in offspring of parents with bipolar disorder: a longitudinal study. Am J Psychiatry. 2015; 172:638-646.
3. Birmaher B, Goldstein BI, Axelson DA, *et al*. Mood lability among offspring of parents with bipolar disorder and community controls. Bipolar Disord. 2013;15:253-263.
4. Hafeman DM, Merranko J, Axelson D, *et al*. Toward the definition of a bipolar prodrome: dimensional predictors of bipolar spectrum disorders in at-risk youths. Am J Psychiatry. 2016;173:695-704.
5. Hafeman DM, Merranko J, Goldstein TR, *et al*. Assessment of a person-level risk calculator to predict new-onset bipolar spectrum disorder in youth at familial risk. JAMA Psychiatry. 2017;74:841-847.
6. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington, DC: American Psychiatric Association; 2004.
7. First MB, Spitzer RL, Williams JBW, Gibbon M. Structured Clinical Interview for DSM-IV (SCID). Washington, DC: American Psychiatric Association; 1995.
8. Kaufman J, Birmaher B, Brent D, *et al*. Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. J Am Acad Child Adolesc Psychiatry. 1997;36:980-988.
9. Andreasen NC, Endicott J, Spitzer RL, *et al*. The family history method using diagnostic criteria: reliability and validity. Arch Gen Psychiatry. 1977;34:1229-1235.
10. Axelson D, Birmaher BJ, Brent D, *et al*. A preliminary study of the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children mania rating scale for children and adolescents. J Child Adolesc Psychopharmacol. 2003;13:463-470.
11. Chambers WJ, Puig-Antich J, Hirsch M, *et al*. The assessment of affective disorders in children and adolescents by semistructured interview. Test-retest reliability of the schedule for affective disorders and schizophrenia for school-age children, present episode version. Arch Gen Psychiatry. 1985;42:696-702.
12. Birmaher B, Axelson D, Strober M, *et al*. Clinical course of children and adolescents with bipolar spectrum disorders. Arch Gen Psychiatry. 2006;63:175-183.
13. Axelson D, Birmaher B, Strober M, *et al*. Phenomenology of children and adolescents with bipolar spectrum disorders. Arch Gen Psychiatry. 2006;63:1139-1148.
14. Hafeman D, Axelson D, Demeter C, *et al*. Phenomenology of bipolar disorder not otherwise specified in youth: a comparison of clinical characteristics across the spectrum of manic symptoms. Bipolar Disord. 2013;15:240-252.
15. Gerson AC, Gerring JP, Freund L, *et al*. The Children's Affective Lability Scale: a psychometric evaluation of reliability. Psychiatry Res. 1996;65:189-198.
16. Birmaher B, Brent DA, Chiappetta L. Psychometric properties of the Screen for Child Anxiety Related Emotional Disorders (SCARED): a replication study. J AmAcad Child Adolesc Psychiatry. 1999;38:1230-1236.
17. Achenbach TM. Manual for the Child Behavior Checklist/4-18 and 1991 Profile. Burlington: University of Vermont Department of Psychiatry; 1991.
18. Shaffer D, Gould MS, Brasic J, *et al*. A Children's Global Assessment Scale (CGAS). Arch Gen Psychiatry. 1983;40:1228-1231.
19. Hollingshead AB. Four-Factor Index of Social Status. New Haven, CT: Yale University Department of Sociology; 1975.

FIGURE S1 Calibration Plot of Model-Predicted 5-Year Risk of Course and Outcome of Bipolar Youth Bipolar Disorder I/II Conversion

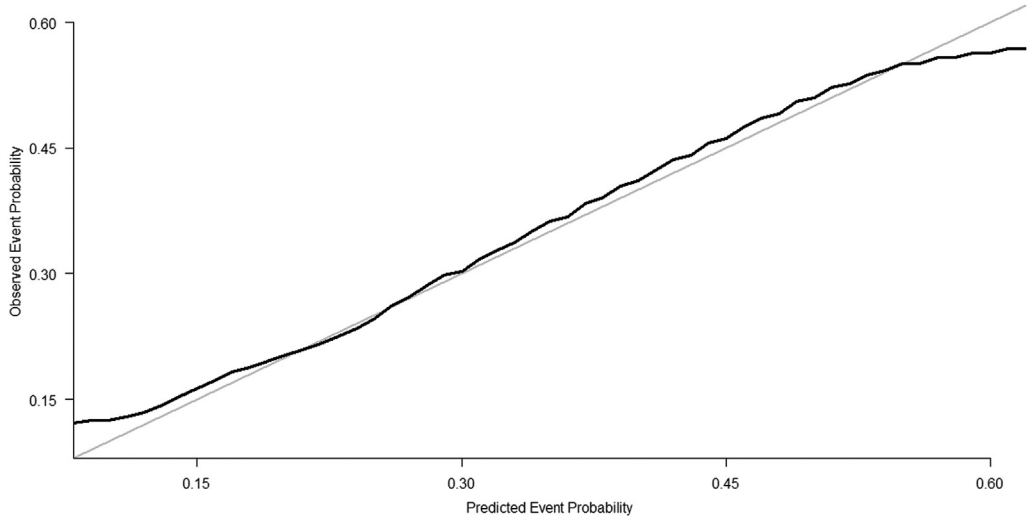
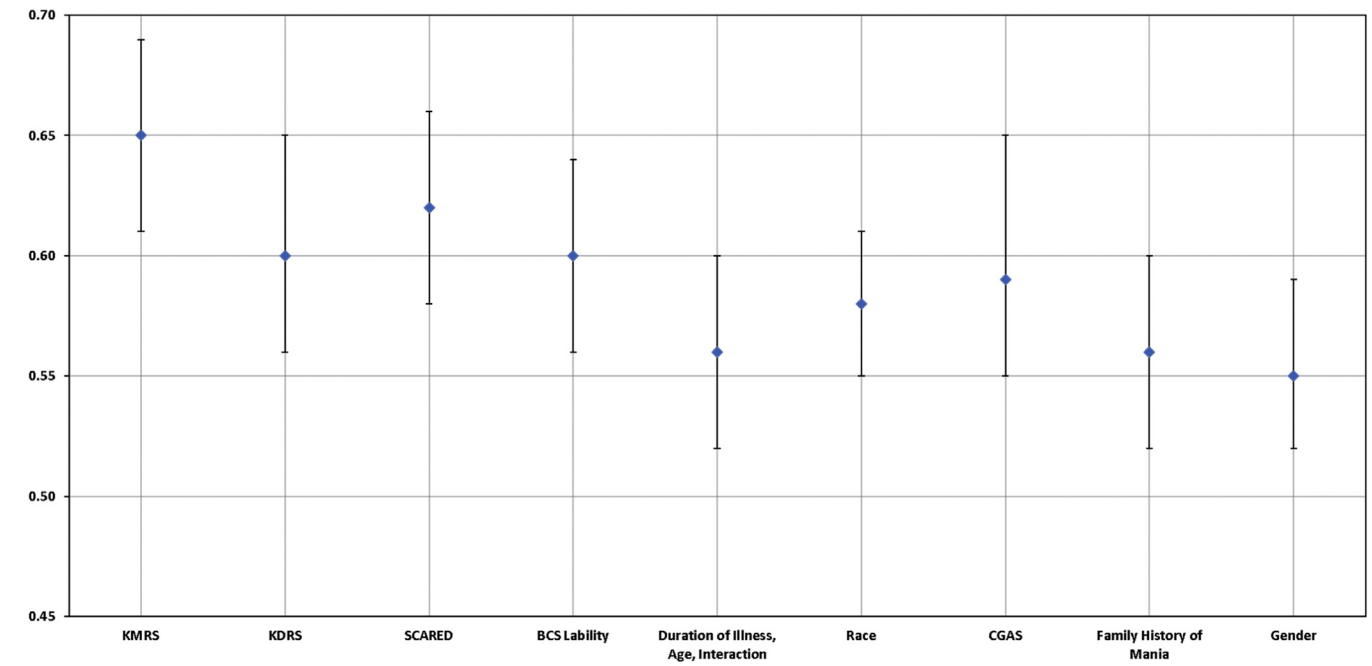


FIGURE S2 Course and Outcome of Bipolar Youth Univariate 5-Year Areas Under the Curve With 95% Bootstrap Intervals



Note: *BCS = Behavior Control Scale; CGAS = Children's Global Assessment Scale; KDRS = selected items from the Kiddie Depression Rating Scale; KMRS = selected items from the Kiddie Mania Rating Scale; SCARED = Screen for Child Anxiety Related Emotional Disorders*

TABLE S1 26 Common (>25%) Bipolar Prodromal Symptoms Noted in Meta-Analyses of Van-Meter *et al.*[13]

Prodromal Symptoms in Meta-Analyses of Van-Meter *et al.*	Ascertained Through KMRS	Ascertained Through KDRS	Ascertained Through Other Scales
Too much energy	Unusually energetic		
Diminished ability to think		Difficulty concentrating	
Indecisiveness		Difficulty concentrating	
Pressured speech	Accelerated speech		
Talkative	Accelerated speech		
Elated mood	Elation		
Academic or work difficulties			CGAS
Insomnia		Insomnia	
Depressed mood		Depressed mood	
Overproductive/goal-oriented	Increase in goal-directed activity Increased productivity		
Agitation		Psychomotor agitation	
Rage attacks	Irritability	Irritability	
Grandiosity	Grandiosity		
Racing thoughts	Racing thoughts		
Anxiety			SCARED Parent, SCARED Child
Decreased need for sleep	Decreased need for sleep		
Irritable mood	Irritability	Irritability	
Fatigue		Fatigue Daytime sleepiness	
Distractibility	Distractibility		
Sleep disturbance		Middle insomnia Nonrestorative sleep	
Disinhibited	Poor judgment People seeking Inappropriate laughter		
Weight loss/loss of appetite		Anorexia Weight loss	
Hyperactive	Motor hyperactivity		
Suicidal thoughts		Suicidal ideation	
Feelings of worthlessness		Negative self-image	
Mood lability	Mood lability		BCS Lability subscale

Note: BCS = Behavior Control Scale; CGAS = Children's Global Assessment Scale; KMRS = selected items from Kiddie Mania Rating Scale; KDRS = selected items from Kiddie Depression Rating Scale; SCARED = Screen for Child Anxiety Related Emotional Disorders.