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

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Abstract

Objective: Youth with subthreshold mania are at elevated 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: 140 BP Not-Otherwise-Specified (BP-NOS) youths (6–17 years old) followed through the Course and Outcome of Bipolar Youth (COBY) study with at least one follow-up assessment prior to conversion to BP-I/II were included. Youths were assessed on average every 7 months for a median of 11.5 years using standard instruments. Risk predictors reported in the literature were utilized to build a 5-year risk calculator. Discrimination was measured using the time-dependent area under the curve (AUC) after 1000 bootstrap resamples. Calibration was evaluated comparing observed vs. predicted probability of conversion. External validation was performed using an independent sample of 58 BP-NOS youths recruited from the Pittsburgh Bipolar Offspring Study.

Results: Seventy-five (53.6%) COBY BP-NOS youths 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/observed risks of conversion, good discrimination between converters/non-converters (AUC: 0.71, CI: 0.67–0.74), and a

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proportionally increasing rate of converters at each successive risk class. Discrimination in the external validation sample was good (AUC: 0.75).

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

Introduction

Youth and adults with subthreshold manic symptoms, of which many 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 criteria for BP-NOS (see Supplement 1 for the criteria, available online) developed BP-I/II, 41% continued to have BP-NOS, and 14% had full or partial remission.[9]

Clinical and epidemiological 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 one 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 since 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 in order to develop individualized interventions that may delay or, ideally, prevent the onset of BP-I/II.

The quantification of an individual's risk could inform treatment decisions, such as the use and specific choice of antidepressant medications for a depressed BP-NOS youth at high risk for conversion vs. a depressed BP-NOS youth at low risk for conversion. Moreover, quantification of an individual's risk will enable the youth (and the family) to more accurately understand his/her own level of risk, which may in turn 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 key risk variable questions (eg, age, weight, exercise, smoking) into a calculator, which then generates an individualized risk estimate that may be utilized to guide treatment decisions (eg, the need for the use of statins to lower cholesterol).[18–20]

In adults, risk models have been developed to predict factors associated with the risk for Major Depressive Disorder (MDD) and Generalized Anxiety Disorders (GAD), and in one study, the conversion of MDD to BP.[20] However, these studies reported factors for the overall sample and not individualized risk, and the use of internal and external validation within these studies was limited. To our knowledge, only three studies in psychiatry have reported individualized risk calculators. The North American Prodrome Longitudinal Study (NAPLS) built and externally validated in an independent sample, a risk calculator to predict the 2-Year conversion to psychosis for a very high risk sample of adolescents and young adults.[23,24] 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 and colleagues[25] developed and externally validated a risk calculator in a large clinical registry cohort of adults with non-psychotic psychiatric disorders to predict the 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. Finally, the Pittsburgh Bipolar Offspring Study (BIOS), a longitudinal study aimed to evaluate the psychopathology of offspring of parents with BP compared with offspring of community controls developed a risk calculator to predict the 5-year risk of developing BP Spectrum Disorders in offspring of parents with BP.[15] Including dimensional measures of mania, depression, anxiety, and mood lability, psychosocial functioning, and parental age of mood disorder, the model predicted onset of BP with an AUC of 0.76.

COBY previously reported risk factors for progression to BP-I/II for the sample as a *whole*.[9] The goal of this paper is to extend these findings, by developing a risk calculator to predict the 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 BIOS.

Method

COBY is a multi-site naturalistic longitudinal study being conducted at Brown University, the University of Pittsburgh, and the University of California at Los Angeles. COBY enrolled 413 youth between the ages of 7 and 17.11 years with DSM-IV BP-I (n=244), BP-II (n=28), or operationalized criteria for BP-NOS (n=141) (See Supplement 1, available online). The analyses in this report are based on the prospective evaluation of 140 youths with BP-NOS with at least one follow-up assessment prior to diagnosis of BP-I/II or right-censoring (i.e., 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 of 4.0 ± 3.9 years of follow-up (mean dropout age = 17 years old).

COBY methods have been presented in detail in other papers.[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, Intelligence Quotient (IQ) < 70, autism, and mood disorders secondary to substances, medications, or medical conditions were excluded. The most severe

past mood symptomatology, and also one month before the assessment, was recorded through an interview using the K-SADS Kiddie Mania Rating Scale (KMRS)[9,28] and 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 for a median of 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 the *DSM-IV* criteria and participant's functioning. For mood disorders, PSR scores ≤ 2 indicate euthymia, 3–4 for subsyndromal symptoms, and ≥ 5 for syndromal symptomatology. Onset of BP was determined by the presence of a score of ≥ 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 history in first/second-degree relatives was obtained through the Family History Screen[37] and presented in this paper 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. The overall KSADS-PL kappas for psychiatric disorders were ≥0.8. The intraclass correlation coefficients for the KMRS, the KDRS, and syndromal/subsyndromal mood disorders ascertained through the PSR were ≥ 0.75. The maximum scores for depression and mania on the PSR for the 4 weeks prior to each follow-up assessment and the maximum scores on the KMRS and the KDRS for the same period showed Spearman correlations of 0.82 ($p<0.0001$) and 0.77 ($p<0.0001$), respectively.

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

To avoid the circular logic of testing the prognostic power of variables that have 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 prior to conversion, including manic and depressive

symptoms, mood lability, lower global functioning, and anxiety. For the analyses of this paper, items from the KMRS and KDRS that were in common with the mood items in the above meta-analysis were selected (Table S1, available online). Other predictors noted in the meta-analyses were ascertained through the SCARED parent and child-report, the BCS parent-report-Lability, 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] In order to further ensure external generalizability of the risk calculator, all of the above 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 were also 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 both 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 may emerge proximal to conversion.[5] Predictor variables included in the analyses were ascertained prior to the onset of BP-I/II and prior to the age of 18 years old, since different self-report scales were completed by participants after age 18.

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

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

To account for overfitting, training and testing were performed and internally validated via Harrell's algorithm for bootstrap optimism correction (implementing 1000 bootstrap resamples).[40] 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 via the time-dependent AUC (again predicting the 5-year risk of an event) as well as via non-time-dependent AUC. Calibration was tested via Hosmer-Lemeshow testing[42] and by plotting and

comparing observed vs. predicted probability of conversion to BP-I or 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, three measures were used: (1) hazard ratios, (2) 5-year AUC of a model with only that variable, and (3) the decrement in 5-year AUC with removal of that variable from the full model. To assess statistical significance, parametric 95% confidence intervals were estimated for hazard ratios, and bootstrapped 95% confidence intervals 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 shows 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) with a median of 7 months between assessments, during which time 75 (53.6%) converted from BP-NOS to BP-I (n=27) or II (n=48). Among the 75 BP-I/II converters, 57 (76.0%) converted within 5 years (median time to conversion was 2.7 years, with range = 0.5–11.2 years). Risk of conversion increased with age until the early twenties, after which conversion was observed to be unlikely (Figure 1). However, given that only 42% of the non-converting sample had assessments after age 22 years old (age at last assessment ranging from 22–31 years old, mean and median = 26 years old), more follow-up throughout this age range is needed before definitive conclusions may be made concerning risk of conversion in the mid-to-late twenties. The COBY sample used to train the risk calculator consisted of 763 follow-up assessments. The mean age of conversion to BP-I/II was 15.3 ± 4.4 years old (range=8–23). 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 vs. non-converting with a 5-year AUC of 0.71 (95% confidence interval-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.

Figure 2 shows that 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) indicates 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 decile did not significantly differ (Hosmer-Lemeshow χ^2=6.79, df=8, p=0.56), which indicates there is no evidence of miscalibration.

Table 2 shows 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 five 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 have 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, males and African Americans showed less risk of conversion. The magnitude and predictive value of each effect is estimated in Table 3 via standardized hazard ratios and concordance statistics (also shown in Figure S2, available online). As depicted, univariate 5-year AUCs indicate that the four individual predictors with the strongest univariate discrimination were the KMRS, KDRS, SCARED, and BCS Lability scores. All predictors except the age, duration of illness, and age-by-duration of illness interaction triplet yielded 5-year internal AUC decrements ≥0.01 when removed from the model. Race featured the largest AUC decrement at 0.06, which was the only decrement significantly larger than zero (bootstrapped 95% CI: 0.03–0.09). Estimated standardized hazard ratios indicated that the KMRS, SCARED, race, family history of mania, and gender predictors had the largest effect sizes (all HRs > 1.2).

Lastly, adding other potential predictors including SES, living with one 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 were ≤0.01).

External validation using BIOS data.

The 58 youth with BP-NOS recruited through BIOS were followed for a median of 6.1 years with a median of 24 months between assessments, during which time fourteen (24.1%) converted to BP-I/II. As compared to the COBY sample, BIOS youths had significantly lower SES and older age of mood onset, were less likely to have family history of ADHD, and were more likely to be female and have psychosis and family history of psychosis (Table 1). Note that unlike the COBY sample, all BIOS subjects in the external validation sample had family history of mania/hypomania. The risk calculator externally validated on the BIOS sample had a 5-year AUC=0.75 and non-time-dependent AUC=0.78, indicating strong overall external discrimination between converters/non-converters. External prediction metrics as shown in Table 2 indicate that the risk calculator predictions were more sensitive/less specific in the BIOS sample as compared to those in the COBY sample.

Discussion

In this study, 53.6% (n=75) of COBY youth with BP-NOS in an average period of about 11 years converted to BP-I/II (mean conversion age = 15), of which 76.0% converted within 5 years of intake. As noted in the existing literature, family history of hypo/mania and elevated levels of manic, mood lability, and anxiety symptoms were strong predictors of increased conversion risk).[5,13] Early onset of BP-NOS was also associated with increased risk for conversion to BP-I/II, and in general, if conversion did not occur within four years of the initial BP-NOS diagnosis, the risk dropped considerably. Using the above-noted variables, 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 70% for BP-II, comparable to the performance of risk calculators developed to predict psychosis, 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 BIOS predicted with an even stronger 75% discrimination, indicating that the risk calculator is generalizable to other samples. Predictions were more sensitive/less specific in the BIOS sample as compared to those in the COBY sample, which is likely due to the BIOS sample's higher risk of conversion since all subjects have family history of bipolar disorder. Overall, further validation of the model on other samples will help to pinpoint the ideal predicted risk range to optimize sensitivity/specificity though, so we hope to further validate the model on future samples.

Other variables that have been associated with course and outcome of BP in the literature and in 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. Since COBY is a naturalistic study, the prescription of medications is confounded by indication, the 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, were up to 50% greater risk to develop new onset BP. Thus, our results together with the existing literature, provides convergent evidence that the presence of the above noted symptoms increases the risk for developing BP-I/II.[3–13,15]

If replicated, the risk calculator provided in this study offers a useful tool for clinicians to predict an individual's child's risk of converting from subsyndromal mania to BP-I/II, and thus inform personalized treatment decisions. As depicted in Table 2, the internal and external models provided a range of predicted risk thresholds, which can be utilized depending on whether the risk calculator is being used epidemiologically, 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. The majority of participants were Caucasian (reflecting the race distribution for the study sites) and were recruited from clinical settings, which may limit the generalizability of the results. Nonetheless, course/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 COBY's data was externally validated in BIOS, a sample that was recruited from the community. The risk calculator was designed for patients ages 6–17 with the goal of predicting BP-I/II conversion by young adulthood, and the success of the risk predictions on both 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 BP age of 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] Finally, 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 are not stable and may change over time.

In conclusion, like the 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 utilized as an aid to predict whether an individual youth with BP-NOS is at risk to develop BP-I/II. The risk calculator together with 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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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 1 2003;73(1–2):133–146. [PubMed: 12507746]
2. Wozniak J, Uchida M, Faraone SV, et al. Similar familial underpinnings for full and subsyndromal pediatric bipolar disorder: A familial risk analysis. Bipolar disorders. 5 2017;19(3):168–175. [PubMed: 28544732]
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 7 2015;172(7):638–646. [PubMed: 25734353]
4. Faedda GL, Marangoni C, Serra G, et al. Precursors of bipolar disorders: a systematic literature review of prospective studies. J. Clin. Psychiatry 5 2015;76(5):614–624. [PubMed: 26035191]

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 7 01 2016;173(7):695–704. [PubMed: 26892940]
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 disorders. 8 2014;16(5):478–492. [PubMed: 24597782]
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 4 1995;34(4):454–463. [PubMed: 7751259]
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 2 2010;196(2):102–108. [PubMed: 20118453]
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 10 2011;50(10):1001–1016 e1003. [PubMed: 21961775]
10. Nadkarni RB, Fristad MA. Clinical course of children with a depressive spectrum disorder and transient manic symptoms. Bipolar disorders. 8 2010;12(5):494–503. [PubMed: 20712750]
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 5 2006;36(5):619–627. [PubMed: 16438739]
12. Ratheesh A, Cotton SM, Davey CG, et al. Ethical considerations in preventive interventions for bipolar disorder. Early Interv Psychiatry. 4 2017;11(2):104–112. [PubMed: 27027848]
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. 7 2016;55(7):543–555. [PubMed: 27343882]
14. Jo B, Findling RL, Hastie TJ, et al. Construction of longitudinal prediction targets using semisupervised learning. Stat. Methods Med. Res 1 1 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. 8 01 2017;74(8):841–847. [PubMed: 28678992]
16. Harle CA, Downs JS, Padman R. Effectiveness of personalized and interactive health risk calculators: a randomized trial. Med. Decis. Making Jul-Aug 2012;32(4):594–605. [PubMed: 22247421]
17. Tripepi G, Heinze G, Jager KJ, Stel VS, Dekker FW, Zoccali C. Risk prediction models. Nephrol. Dial. Transplant 8 2013;28(8):1975–1980. [PubMed: 23658248]
18. Department of Quantitative Health Sciences CC. 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. 2 12 2008;117(6):743–753. [PubMed: 18212285]
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 5 2017;78(5):572–583. [PubMed: 27337225]
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. 6 2014;83(6):1362–1367. [PubMed: 24862395]
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 Jan-Feb 2014;27(1):42–55. [PubMed: 24390885]
23. Cannon TD, Yu C, Addington J, et al. An Individualized Risk Calculator for Research in Prodromal Psychosis. Am. J. Psychiatry 10 01 2016;173(10):980–988. [PubMed: 27363508]
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(10):989–996. [PubMed: 27363511]

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 5 01 2017;74(5):493–500. [PubMed: 28355424]
26. Birmaher B, Gill MK, Axelson DA, et al. Longitudinal trajectories and associated baseline predictors in youths with bipolar spectrum disorders. Am. J. Psychiatry 9 2014;171(9):990–999. [PubMed: 24874203]
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.[see comment]. J. Am. Acad. Child Adolesc. Psychiatry 7 1997;36(7):980–988. [PubMed: 9204677]
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. Winter 2003;13(4):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 7 1985;42(7):696–702. [PubMed: 4015311]
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 10 1999;38(10):1230–1236. [PubMed: 10517055]
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. Journal of Child and Family Studies. 12 01 2007;16(6):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 6 1987;44(6):540–548. [PubMed: 3579500]
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 7 2000;57(7):675–682. [PubMed: 10891038]
34. Hollingshead AB. Four-Factor Index of Social Status. New Haven, Connecticut: 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 11 1983;40(11):1228–1231. [PubMed: 6639293]
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 8 1992;49(8):624–629. [PubMed: 1637252]
37. Andreasen NC, Endicott J, Spitzer RL, Winokur G. The family history method using diagnostic criteria. Reliability and validity. Arch. Gen. Psychiatry 10 1977;34(10):1229–1235. [PubMed: 911222]
38. Smoller JW, Finn CT. Family, twin, and adoption studies of bipolar disorder. Am. J. Med. Genet. C Semin. Med. Genet 11 15 2003;123C(1):48–58. [PubMed: 14601036]
39. Raghunathan TE, Lepkowski JM, Van Hoewyk J, Solenberger P. A multivariate technique for multiply imputing missing values using a sequence of regression models. Survey Methodology. 2001;27(1):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(4): 361–387. [PubMed: 8668867]
41. Heagerty PJ, Lumley T, Pepe MS. Time-dependent ROC curves for censored survival data and a diagnostic marker. Biometrics. 2000;56(2):337–344. [PubMed: 10877287]
42. May S, Hosmer D. Hosmer and Lemeshow type goodness-of-fit statistics for the cox proportional hazards model In: Rao ASRSRSPCR, ed. Handbook of Statistics. North Holland: Elsevier; 2003:383–394.
43. Lewinsohn PM, Klein DN, Seeley JR. Bipolar disorder during adolescence and young adulthood in a community sample. Bipolar disorders. 9 2000;2(3 Pt 2):281–293. [PubMed: 11249806]

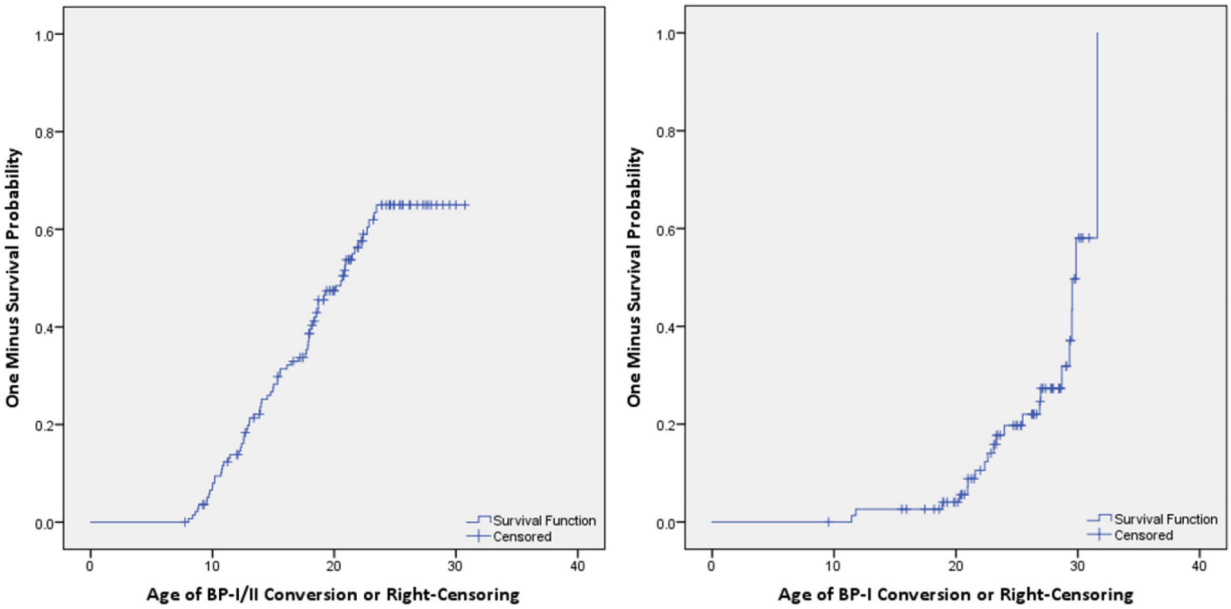

Figure 1.

Course and Outcome of Bipolar Youth (COBY) Progression From Subthreshold Mania to Bipolar-I/II, and From Bipolar-II to Bipolar-I

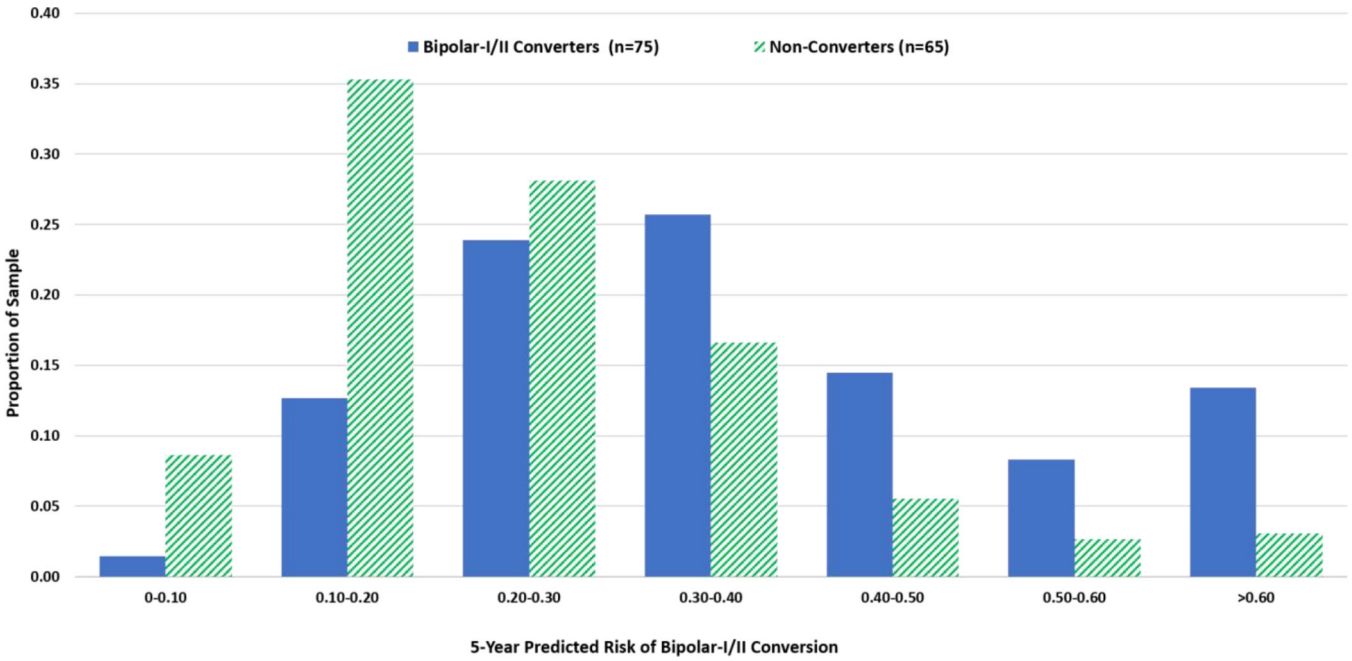

Figure 2.

Frequency Distributions of Predicted 5-Year Risk Among Course and Outcome of Bipolar Youth (COBY) Converters and Non-Converters

Table 1.

COBY vs. BIOS Demographic, Clinical, and Family History

Demographic Variables	COBY (N=140)	BIOS (N=58)	Test Stat	p-value
Mean Age (SD)	11.9 (3.2)	11.9 (3.3)	z=0.10	0.9
Mean SES (SD)	3.4 (1.1)	2.7 (1.2)	z=4.03	**<0.0001**
Male (%)	85 (60.7)	24 (41.4)	χ^2=6.20	**0.01**
Caucasian (%)	115 (82.1)	43 (74.1)	χ^2=1.63	0.2
Live with Both Biological Parents (%)	62 (44.3)	21 (36.2)	χ^2=1.10	0.3

Clinical Variables	COBY (N=140)	BIOS (N=58)	Test Stat	p-value
Mean Age of BP-NOS Onset (SD)	8.7 (3.5)	11.8 (3.5)	z=5.20	**<0.0001**
Major Depressive Disorder (%)	58 (41.4%)	16 (27.6%)	χ^2=3.36	0.07
Anxiety (%)	54 (38.6)	30 (51.7)	χ^2=2.90	0.09
ADHD (%)	88 (62.9)	31 (53.5)	χ^2=1.51	0.2
DBD (%)	67 (47.9)	27 (46.6)	χ^2=0.02	0.9
Psychosis (%)	19 (13.6)	1 (1.7)	Fisher's Exact	**0.009**

Family History	COBY (N=140)	BIOS (N=58)	Test Stat	p-value
Depression (%)	127 (90.7)	55 (94.8)	Fisher's Exact	0.4
Mania/Hypomania (%)	81 (57.9)	58 (100.0)	Fisher's Exact	**<0.0001**
Anxiety (%)	110 (78.6)	51 (87.9)	χ^2=2.36	0.1
ADHD (%)	73 (52.1)	18 (31.0)	χ^2=7.36	**0.007**
CD (%)	54 (38.6)	17 (29.3)	χ^2=1.53	0.2
Psychosis (%)	24 (17.1)	18 (31.0)	χ^2=4.74	**0.03**
SUD (%)	104 (74.3)	36 (62.1)	χ^2=2.96	0.09

Note: ADHD = attention-deficit/Hyperactivity disorder; BIOS = Bipolar Offspring Study; BP-NOS = Bipolar Disorder Not Otherwise Specified; CD = Conduct Disorder; COBY = Course and Outcome of Bipolar Youth; DBD = Disruptive Behavior Disorders (includes both, oppositional defiant and conduct disorders); SES = Socio-economic Status; SUD = Substance Use Disorder

Table 2.

Performance Measures for a Range of Dichotomous Risk Score Cutoffs

Internal Validation (COBY)					
Risk Score Cutoff	**Proportion of Sample in RiskGroup**	**Sensitivity**	**Specificity**	**Positive PredictiveValue**	**Negative PredictiveValue**
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 RiskGroup**	**Sensitivity**	**Specificity**	**Positive PredictiveValue**	**Negative PredictiveValue**
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]	InternalUnivariate 5-YearAUC (95% CI)[a]	InternalAUC Decrement[b]	ExternalAUC Decrement[b]
KMRS [c]	1.26 (0.99, 1.60)	0.65 (0.61, 0.69)	0.02 (−0.02, 0.05)	0.05
KDRS [c]	1.03 (0.83, 1.27)	0.60 (0.56, 0.65)	0.01 (−0.03, 0.03)	0.00
SCARED	1.26 (1.02, 1.56)	0.62 (0.58, 0.66)	0.02 (−0.02, 0.04)	0.04
BCS Lability	1.15 (0.92, 1.45)	0.60 (0.56, 0.64)	0.01 (−0.03, 0.03)	−0.02
Age at Assessment	1.02 (0.75, 1.39)			
Duration of BP Illness	0.94 (0.66, 1.34)	0.56 (0.52, 0.60)	0.00 (−0.03, 0.03)	0.05
Age x 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, 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, 0.04)	0.04
Female	1.23 (0.89, 1.70)	0.55 (0.52, 0.59)	0.01 (−0.02, 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 computed on COBY sample; external concordance statistics computed on BIOS sample.

[b]AUC decrements represent reduction to Area Under the Curve 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 Van Meter's meta-analysis[13] were included (see Table S1, available online).