### Title

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Research paper

# Validation of the youth mood recurrences risk calculator in an adult sample with bipolar disorder

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ABSTRACT

*Background:* The ability to predict an individual's risk of mood episode recurrence can facilitate personalized medicine in bipolar disorder (BD). We sought to externally validate, in an adult sample, a risk calculator of mood episode recurrence developed in youth/young adults with BD from the Course and Outcome of Bipolar Youth (COBY) study.

*Methods:* Adult participants from the National Institute of Mental Health Collaborative Depression Study (CDS; N=258; mean(SD) age=35.5(12.0) years; mean follow-up=24.9 years) were utilized as a sample to validate the youth COBY risk calculator for onset of depressive, manic, or any mood episodes.

*Results:* In this older validation sample, the risk calculator predicted recurrence of any episode over 1, 2, 3, or 5-year follow-up intervals, with Area Under the Curves (AUCs) approximating 0.77. The AUC for prediction of depressive episodes was about 0.81 for each of the time windows, which was higher than for manic or hypomanic episodes (AUC=0.72). While the risk calculator was well-calibrated across the range of risk scores, it systematically underestimated risk in the CDS sample by about 20%. The length of current remission was a highly significant predictor of recurrence risk in the CDS sample.

*Limitations:* Predominantly self-reported White samples may limit generalizability; the risk calculator does not assess more proximal risk (e.g., 1 month).

*Conclusions:* Risk of mood episode recurrence can be predicted with good accuracy in youth and adults with BD in remission. The risk calculators may help identify higher risk BD subgroups for treatment and research.

## 1. Introduction

Bipolar disorder (BD) is classically characterized by episodes of depressive and manic syndromes. The frequency, duration, and severity of these mood episodes can vary substantially across those affected and over time (Judd et al., 2003a, 2002, 2003b). One person may have infrequent and brief episodes, while another suffers a more chronic course with persistent symptoms. Although a lot of attention is paid to

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differences in course by diagnostic subtype (e.g., BD-I or BD-II), there is considerable variability in course of illness within each subtype (Judd et al., 2003b). The clinical utility of these broad BD diagnoses alone in predicting recurrence is limited, and clinicians lack validated tools to predict the course of illness for a particular patient. Risk calculators, which integrate information from various predictor variables to provide a quantitative estimate, are one such tool.

While validated risk calculators are commonly used for cardiovascular disease (Preiss and Kristensen, 2015) and cancer (Ankerst et al., 2014), psychiatry has arguably been slow to adopt quantitative measures of individualized risk into routine clinical practice. Published psychiatric risk calculators have focused primarily on predicting transition to psychosis in those with prodromal symptoms (Cannon et al., 2016; Carrion et al., 2016; Ciarleglio et al., 2019; Fusar-Poli et al., 2019; Osborne and Mittal, 2019; Studerus et al., 2020; Worthington et al., 2021; Zhang et al., 2021). Other risk calculators have addressed suicide risk,(Fazel et al., 2019; Marcon et al., 2020) violence risk,(Fazel et al., 2016, 2017; Negatsch et al., 2019), and psychopathology following child victimization (Meehan et al., 2020). There are few risk calculators focused on mood disorders, which is striking given the well-known heterogeneity in course of illness exemplified by mood disorders (Suppes et al., 2000). Another risk calculator looks at the likelihood of having a treatment refractory depression (Perlis, 2013).

Our group has recently developed three risk calculators predicting BD disease prognosis in individuals over a period of 5 years. One is based on a high-risk sample of offspring of BD patients to predict the likelihood of a child in turn developing BD themselves (The Pittsburgh Bipolar Offspring Study; BIOS) (Hafeman et al., 2017; Hanford et al., 2019). Important univariate predictors of outcome were dimensional measures of mania, depression, anxiety, and mood lability, psychosocial functioning, and parental age at mood disorder. The other two risk calculators are based on samples from the Course and Outcome of Bipolar Youth (COBY) study. The first of these risk calculators from COBY (Birmaher et al., 2018) is focused on conversion to BD-I or BD-II in youth who were originally diagnosed with a COBY study operationalized definition of BD Not Otherwise Specified (BD-NOS) (Birmaher et al., 2006). Earlier onset BD-NOS, familial hypomania/mania, and high mania, anxiety, and mood lability symptoms were important predictors of conversion. The second COBY-derived risk calculator estimate risk of depressive, manic, or any mood episode recurrence in youth and young adults with BD who were in remission (Birmaher et al., 2020). This latest risk calculator was derived in a sub-sample of 182 participants and tested in the remaining "holdout" sub-sample of 181 participants (total N=363). In the test sample, the 5-year risk Area Under the Curves (AUCs) were 0.82 (95% Confidence Interval (C.I.) 0.81–0.84) for any mood episode, 0.80 (95% C.I. 0.78–0.82) for depressive episodes, and 0.89 (95% C.I. 0.85–0.91) for manic episodes. These values are noteworthy in that they generally exceed that observed with more commonly used conventional models to predict risk of cardiovascular events (Echouffo-Tcheugui and Kengne, 2013; Robinson et al., 2012; Wang et al., 2006). At its optimal cutoff for 5-year risk, this BD specific risk calculator demonstrated a sensitivity and a specificity of 0.74, with a positive predictive value of 0.78. Any tool that facilitates a reasonable risk estimate of recurrence of mood episodes in BD has the potential to promote clinical and research advances, akin to that fostered by the clinically high-profile cardiovascular disease risk estimators.

Internal validation can still exaggerate model performance, and external validation is necessary to support the use of any prediction model in clinical practice. We sought to conduct a second and external validation of the COBY BD risk calculator to see if its predictive utility extends from a youth and young adult sample with BD, to an adult sample with BD. For this, we analyzed historical data from a large, long-term prospective cohort study of adults with mood disorders, the National Institute of Mental Health Collaborative Depression Study (CDS), which used similar longitudinal assessments to COBY. This sample includes participants with an intake diagnosis of BD-I and BD-II as well as those with major depressive disorder (MDD) who later developed hypomania or mania. In this CDS sample, the performance of the youth BD risk calculator can be similarly assessed for its ability to individually predict recurrence of depressive episodes, manic episodes, and risk of any mood episode in adults with BD.

## 2. Method

### 2.1. Participants

Descriptions for the COBY and CDS studies have been described in detail previously (Birmaher et al., 2006; Rice et al., 1989). Relevant to this article, COBY initially enrolled 413 BD youths who met Diagnostic and Statistical Manual of Mental Disorders -IV (DSM-IV) (American Psychiatric Association, 2000) criteria for BD-I, BD-II, or operationalized COBY criteria for BD-Not Otherwise Specified (BD-NOS) (see Birmaher et al. 2006, for criteria). For the COBY risk calculator that was developed to predict recurrence in the young adult BD sample, participants needed to have a history of full-threshold mood episode, and had to be in recovery (at least 2 months of no or minimal mood symptoms), yielding 363 participants in the risk calculator sample (Birmaher et al., 2020). This risk calculator was derived in a sub-sample of 182 COBY participants and tested in the remaining "holdout" sub-sample of 181 COBY participants to give an unbiased assessment of how well the model might do if applied to new data).

For the current external validation study, we started with a sample of 435 CDS participants who met diagnostic criteria for BD-I or BD-II over prospective follow-up (detailed in a prior publication) (Fiedorowicz et al., 2009). In addition to those diagnosed with BD at intake, this sample also includes those who had MDD at intake and developed hypomania or mania over follow-up, thus meeting Research Diagnostic Criteria (RDC) (Spitzer et al., 1978) for BD-I or BD-II, respectively. This prospective cohort study recruited a self-reported White, English-speaking sample, between 1978 and 1981 at five centers: Massachusetts General Hospital and Harvard University in Boston, MA; Rush Presbyterian-St. Luke's Medical Center in Chicago, IL; University of Iowa in Iowa City, IA; New York State Psychiatric Institute and Columbia University in New York, NY; and Washington University in St. Louis, MO. Participants had to know about their biological parents in order to provide family history in this study which tested genetic hypotheses. For the current external validation study, we included those CDS participants with at least one period of remission from mood symptoms for at least two consecutive months followed by a recurrence. After considering inclusion and exclusion criteria, the sample used for this analysis included 258 CDS participants (intake BD-I n=114, BD-II n=66, MDD n=78). Note that all CDS participants with MDD at intake later developed BD, thus becoming eligible for inclusion in the external validation sample. As compared to CDS participants with BD at intake, participants with MDD at intake were significantly less likely to have psychotic symptoms (23.1% vs. 49.4%, $p<0.0001$), marginally less likely to family history of depression (43.6% vs. 57.2%, $p=0.06$), and marginally older when mood symptoms onset (mean age 24.7±10.1 vs. 22.4±8.7, $p=0.07$); there were no other significant demographic or clinical differences.

### 2.2. Procedure

For both the COBY and CDS studies, each participating university's Institutional Review Board approved the study before enrollment. Informed consent/assent was obtained from participants and their parents at intake (COBY), and informed consent was obtained from participants at intake (CDS). Trained research staff administered semi-structured interview assessments, which were reviewed by a study investigator, who was ultimately responsible for the clinical ratings. Please see prior publications for more details about the procedures (Birmaher et al., 2006; Rice et al., 1989).

#### 2.2.1. Measures

At intake, CDS participants were assessed using the Schedule for Affective Disorders and Schizophrenia (Endicott and Spitzer, 1978) and the Personal History of Depressive Disorders (Katz et al., 1979). Similar to the COBY study, the Longitudinal Interval Follow-up Evaluation (LIFE) was used to assess the type and severity of mood symptoms over follow-up in the CDS (Keller et al., 1987). It was administered every six months in the first five years, and annually thereafter. Using a validated calendar method, the onsets and offsets of changes in mood symptom severity were recorded using the LIFE's weekly Psychiatric Status Ratings (PSRs). The intraclass correlation coefficients for the PSR data was estimated at 0.9 (Keller et al., 1987). Severity of symptoms was rated on a 6-point PSR scale for major depression, schizoaffective depression, mania, or schizoaffective mania. A 3-point PSR scale was used for minor depression, intermittent depression, or hypomania. These scales are detailed in **Supplemental Table 1**. RDC diagnoses of schizoaffective manic (mainly affective) and schizoaffective depressed (mainly affective) are consistent with diagnoses of psychotic major depression and mania in that they require psychotic symptoms to be concurrent with the mood episode.

The assessment of family history of BD in the CDS differed between those who participated in a family study and those who did not, as has been detailed elsewhere (Andreasen et al., 1987; Fiedorowicz et al., 2011). For the 192 CDS participants who also participated in the family study, a total of 1621 biological relatives were directly interviewed in person or by telephone. For the 66 CDS participants who did not participate in the family study, consensus diagnosis for 546 relatives was based on Family History RDC from interviews of one or more family members, with estimated diagnoses for those not interviewed. Unlike COBY, family history data on second-degree relatives was available only for half-siblings.

### 2.3. Statistical analyses

To formulate the recurrence risk calculator datasets, participants' remission periods were divided into 6-month intervals, beginning with the onset of each remission period, which enabled analysis of the effect of current remission length on future recurrence risk. Each data point defined the multinomial outcome variable as recurrence status (depression recurrence vs. hypomania/mania recurrence vs. no recurrence) at each distinct point during remission. The risk calculator was built from the COBY dataset with predictors based on factors from the existing literature, rather than results from COBY (Birmaher et al., 2018). The risk calculator included general variables (age, age of mood disorder onset, family history of mania), variables from the previous mood episode (maximum PSR depression score, number of weeks with threshold major depression, maximum PSR hypomania/mania score, number of weeks with threshold mania/hypomania), remission variables (current remission length, prior remission length), and past episode history variables (number of recurrences (none vs. one vs. two or more), and whether episodes usually included hypomanic/manic symptoms). The model was trained using boosted multinomial classification trees, a useful model for these data because it implicitly incorporates interactions between predictors. Predictions were then calibrated via Platt scaling (Niculescu-Mizil and Caruana, 2005).

The COBY recurrence model was externally validated using the longitudinal data from the CDS. Since the risk calculator was designed to be effective at any point in remission, a validation algorithm was developed to consider each CDS remission period and randomly choose a single point in time during remission from which to estimate risk. For example, if a participant had a remission period of two years, the algorithm would choose a point in time between 0 and 2 years into the remission and estimate risk from that point. After doing this for each observation in the dataset, the AUC was computed. This was repeated for 1,000 iterations allowing estimation of the overall AUC as well as a 95% C.I.

## 3. Results

### 3.1. CDS external validation sample characteristics

The CDS external validation sample included 258 participants with a prospective diagnosis of BD I or BD II (mean (SD) age at intake 35.5 (12.0); 63% female; 59% BD I). Participants were followed for a mean of 24.9 years. The relevant sociodemographic and clinical characteristics for this analysis are shown in **Table 1**.

### 3.1. Comparison between cds external validation and COBY sample characteristics

The CDS external validation sample was clearly distinct from the COBY sample, with a substantially later mean age of mood episode onset (23.1 vs. 9.4 years), a greater representation of female participants (63% vs. 47%), less frequent co-occurring generalized anxiety disorder (5% vs. 40%), and less loading for various mental disorders on family history. The observed course of illness for each sample also varied as shown in **Table 2**, with a higher recurrence rate and a lower proportion of recurrences involving depression in the CDS sample.

### 3.2. CDS external validation sample risk calculator

The risk calculator model showed good prediction of recurrence of any episode over 1, 2, 3, or 5 year follow-up intervals, with AUC's ranging from 0.77 to 0.78 (**Table 3**). The model demonstrated a somewhat higher accuracy for the prediction of depressive episodes with

**Table 1**
Demographic and clinical comparisons between the current CDS external validation sample and the prior COBY sample.

| Variable | CDS (N=258) | COBY (N=363) | Test Stat | p-value |
|---|---|---|---|---|
| Age at Study Intake (years) | 35.5 (12.0) | 12.6 (3.2) | t=29.91 | <0.0001 |
| Intake Diagnosis | | | χ2=238.10 | <0.0001 |
| Bipolar I Disorder | 44.2% | 60.1% | | |
| Bipolar II Disorder | 25.6% | 6.9% | | |
| Bipolar Disorder NOS | 0.0% | 33.1% | | |
| Major Depressive Disorder* | 30.2% | 0.0% | | |
| Age of Mood Onset (years) | 23.1 (9.2) | 9.4 (3.9) | t=22.64 | <0.0001 |
| Age at First Observed Remission (years) | 44.7 (15.4) | 15.3 (3.7) | t=30.13 | <0.0001 |
| Female | 63.2% | 47.1% | χ2=15.67 | <0.0001 |
| Socioeconomic Status | 3.4 (1.0) | 4.1 (1.2) | t=8.02 | <0.0001 |
| Global Assessment of Functioning | 41.0 (11.2) | 63.6 (14.6) | t=21.79 | <0.0001 |
| Generalized Anxiety Disorder | 5.0% | 39.7% | χ2=95.75 | <0.0001 |
| Psychosis | 41.5% | 37.5% | χ2=1.02 | 0.31 |
| Substance Use Disorder | 31.0% | 42.2% | χ2=7.99 | 0.005 |
| Family History of Bipolar Disorder | 24.8% | 58.1% | χ2=67.86 | <0.0001 |
| Family History of Depression | 53.1% | 88.7% | χ2=99.15 | <0.0001 |
| Family History of Anxiety | 22.5% | 74.1% | χ2=161.22 | <0.0001 |
| Family History of ADHD | 0.0% | 46.3% | χ2=163.69 | <0.0001 |
| Family History of Schizophrenia | 2.7% | 6.9% | χ2=5.38 | 0.02 |
| Family History of Substance Use Disorder | 43.0% | 70.0% | χ2=45.20 | <0.0001 |

This table details the sample from the current CDS external validation sample and compares it to the prior COBY sample. ADHD = Attention Deficit Hyperactivity Disorder; CDS = Collaborative Depression Study, COBY = Course and Outcome of Bipolar Youth study, NOS = Not Otherwise Specified.

* Note that all CDS participants with major depressive disorder at intake later developed bipolar disorder, thus becoming eligible for inclusion in the external validation sample.

**Table 2**
Follow-up, remission, and recurrence statistics between the current CDS external validation sample and the prior COBY sample.

| Statistic | CDS (N=258) | COBY (N=363) | Test Stat | p-value |
|---|---|---|---|---|
| Median Follow-up Duration (years) | 24.9 | 12.5 | Z=13.30 | <0.0001 |
| Median # Recurrences | 3 | 2 | Z=6.93 | <0.0001 |
| Median Recurrence Rate (per 5 years) | 0.92 | 0.80 | Z=2.34 | 0.02 |
| % of Episodes Depressive | 61.4% | 70.5% | $\chi^2$=18.80 | <0.0001 |
| % who Recurred | 90.3% | 81.0% | $\chi^2$=10.19 | 0.001 |
| Median Time to First Recurrence (months) | 9 | 18 | Log-Rank $\chi^2$=10.96 | 0.0009 |
| Median # Recovery Periods | 4 | 2 | Z=6.67 | <0.0001 |
| % of Follow-up in Recovery | 57.8% | 63.7% | Z=1.88 | 0.06 |
| Median Recovery Length (years) | 3.2 | 2.1 | Z=2.95 | 0.003 |

This table compares the course of illness over follow-up observed in the current CDS external validation sample and compares it to the prior COBY sample. ADHD = Attention Deficit Hyperactivity Disorder; CDS = Collaborative Depression Study, COBY = Course and Outcome of Bipolar Youth study.

**Table 3**
**Accuracy of prediction model in current CDS external validation sample.** This table includes the area under the curve (AUC) for the prediction models of any recurrence of a mood episode, recurrence of major depression, and recurrence of (hypo)mania at 1, 2, 3, and 5 years. The estimate for the AUC is followed by the 95% confidence interval in parentheses. CDS = Collaborative Depression Study,

| Prediction | Externally Validated AUCs (CDS Sample) | | |
|---|---|---|---|
| Horizon in Years | Any Polarity | Major Depression | Mania/ Hypomania |
| 1 | 0.779 (0.765, 0.793) | 0.815 (0.812, 0.821) | 0.722 (0.714, 0.733) |
| 2 | 0.776 (0.765, 0.792) | 0.815 (0.812, 0.821) | 0.720 (0.714, 0.729) |
| 3 | 0.774 (0.765, 0.792) | 0.814 (0.812, 0.821) | 0.719 (0.713, 0.728) |
| 5 | 0.770 (0.765, 0.777) | 0.813 (0.811, 0.816) | 0.717 (0.714, 0.723) |

AUCs just over 0.81 over 1, 2, 3, or 5 years. A somewhat lower accuracy was seen for the prediction of manic or hypomanic episodes with AUCs rounding to 0.72. Note that the risk calculator performed similarly when only validating it on the subset of CDS participants with MDD at intake (n=78), predicting recurrences (after BD onset) with all AUCs as described above >0.77.

### *3.3. Comparison between CDS external validation and COBY holdout risk calculators*

The Receiver Operator Characteristic (ROC) curves from the CDS external validation sample are contrasted to those from the COBY holdout sample in Fig. 1. A calibration plot indicated that the predicted and observed recurrence risks were consistent through the range of risk scores. The risk calculator, however, consistently underestimated risk by about 0.20 across this range, as shown in Fig. 2.

### *3.4. CDS external validation sample risk calculator test of robustness*

The robustness of the risk calculator was tested by individually removing each predictor from the model as illustrated in **Supplemental Table 2.** Removing variables recorded from the previous episode, as measured using the LIFE PSR, resulted in AUC decrements between 0.045 and 0.066. The removal of current remission length resulted in a decrement of 0.236, demonstrating that the duration of absence of mood symptoms was an extremely influential predictor of future recurrence risk. AUCs were more robust to removal of predictor variables when internally validating on the COBY holdout sample compared to this CDS

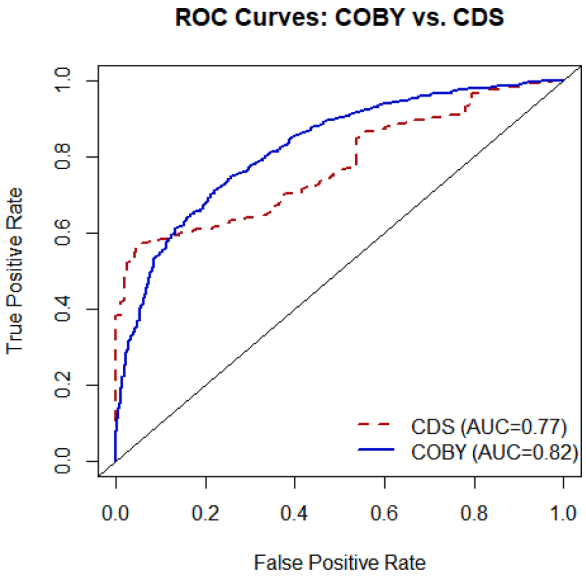


**Fig. 1. Receiver operating characteristic (ROC) curves for five-year test predictions**. The ROC curves compare the classification ability of the risk calculator in the CDS external validation sample compared to the prior COBY holdout sample. AUC = Area Under the Curve, CDS = Collaborative Depression Study, COBY = Course and Outcome of Bipolar Youth study.

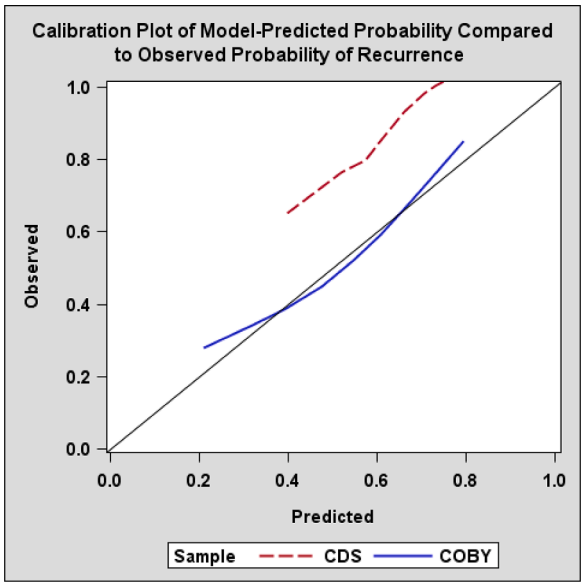


**Fig. 2. Calibration plot for five-year test predictions**. Predicted and observed recurrence-risk were consistent through the range of internally validated risk-scores, and the median predicted 5-year risk in the COBY holdout sample (0.52) closely matched the observed rate of recurrences (event rate=0.55). Further, predicted and observed 5 year recurrence risk in the prior COBY holdout sample within decile did not significantly differ (Hosmer-Lemeshow $\chi^2$=5.33, df=8, $p$=0.7), indicating no evidence of internal miscalibration. While there was a comparably linear relationship between predicted and observed 5-year recurrence risk in the CDS external validation sample, the risk calculator consistently underestimated risk by around 0.20. CDS = Collaborative Depression Study, COBY = Course and Outcome of Bipolar Youth study.

external validation sample, with two exceptions: (1) removing current age, and (2) age of mood disorder onset had less of an impact on AUC in the CDS external validation sample compared to the COBY holdout sample.

### 3.5. CDS external validation sample risk calculator sensitivity analysis

Given that the COBY sample included only early age of mood episode onset cases of BD, we conducted a sensitivity analysis to see how the risk calculator performed in the CDS external validation dataset in those with early-onset (<21 years of age, n=124) or late-onset (≥21 years of age, n=134) mood disorder. Differences in risk calculator performance by age of onset strata were small for any recurrence, with a 5-year AUC of 0.79 in the early onset CDS subsample, and 0.75 in the late onset CDS subsample. Differences were negligible between the early-onset and late-onset mood disorder groups for recurrence of major depression (AUC of 0.81 vs. 0.82) and hypomania/mania (0.72 vs. 0.72).

## 4. Discussion

This external validation study of the most recent Birmaher et al. (2020) mood episode risk calculator, which was developed in a youth and young adult sample (COBY), extends its accuracy to a much older adult sample with bipolar disorder. This CDS sample was clearly distinct from the COBY sample at intake. Participant follow-up in the CDS was also characterized by more frequent recurrence, and less time in remission, contrary to what might be expected based on the earlier age of mood disorder onset of the COBY sample, although 48% of the CDS sample had an early age of mood disorder onset. Also divergent from the COBY study, where the risk calculator was significantly more accurate for hypomanic or manic episodes, in this CDS external validation sample, the risk calculator was significantly more accurate for depressive episodes. The risk calculator also functioned similarly across all tested time frames of prediction (1, 2, 3, and 5 years), and all types of mood episode recurrences (hypomania, mania, and depressive episodes).

The observed performance of the risk calculator occurred despite several potential obstacles. The CDS data lacked a complete second-degree relative family history of BD, and included a distinctly different sampling of the population with BD compared to the COBY sample. Participants in the CDS sample came from a different time period, were older, and had a later age of mood disorder onset, at least as retrospectively estimated. The robustness of the calculator to age, age of mood disorder onset, and duration of risk prediction, opens up possibilities for use in an array of clinical contexts. While the risk calculator performed with strong discrimination, there was a consistent underestimation of risk in the CDS sample. This may be explained by some of the differences in course of illness between samples with a CDS event rate of 0.86, compared to 0.55 in COBY. Risk declined as participants aged into adulthood in COBY, whereas the CDS consisted of an entirely adult sample. Importantly, 83% of the CDS analytic sample were recruited as inpatients (Fiedorowicz et al., 2009), which is very different than the COBY sample, in which 68% of participants were recruited from outpatient clinics (Birmaher et al., 2020). Thus, recalibration of the model may be warranted when applying the risk calculator in samples that differ in important ways from the COBY sample. In our sensitivity analysis, results were similar, regardless of age of mood disorder onset.

The length of current remission was an extremely influential predictor variable in the CDS external validation sample, and its removal reduced AUC by 0.236. Remission of symptoms has indeed been shown to be a predictor of future remission for both BD, and MDD (Goldberg and Harrow, 2004). Age and age of mood disorder onset did not have as large of an impact on the performance of the risk calculator in the CDS sample compared to the COBY sample. This may be due to the large differences in both current age and age of onset of mood disorder for the CDS sample relative to the COBY sample. In an older sample with a significantly later age of mood disorder onset, the predictive effects of these variables may not have translated well from the COBY to the CDS sample.

Risk calculators integrate information from various existing and previously validated predictor variables, such as length of current remission, to provide a quantitative summary estimate of overall risk for a specific patient. Risk calculators for mood disorders remain underdeveloped and risk of mood episode recurrence has a potential niche. The risk calculator validated in this current paper is unique in that it specifically focuses on likelihood of developing a recurrence of mood episodes in BD. One of the benefits of this risk calculator is that it only requires clinical data that could be collected systematically without an extensive, structured interview, such as length of current mood remission. This risk calculator also is not dependent upon expensive or invasive procedures, such as might be found with neuroimaging (Collin et al., 2020). Clinical decisions often involve some assessment of risk-benefit ratio, which is best done with an individualized assessment of risk. For example, the guidelines on the management of blood cholesterol utilize a 10 year assessment of atherosclerotic cardiovascular disease risk to guide treatment decisions (Grundy and Stone, 2019). For comparison with our results, a large validation study of the American College of Cardiology / American Heart Association Pooled Cohort Risk Equation for atherosclerotic cardiovascular disease, the risk calculator recommended by the 2013 guidelines,(Stone et al., 2014) revealed an AUC of 0.74 in predicting 5-year risk (Rana et al., 2016). In this case, the estimates for risk of mood recurrence in the CDS external validation sample performs slightly better than this widely used cardiovascular risk calculator and on a narrower, more precise timeline. In psychiatry, guidelines for antidepressant treatment of MDD attempt to identify high risk groups for extended treatment of antidepressants using disjunctive categories without direct calculation of risk (Cleare et al., 2015; Kennedy et al., 2016). Quantitative estimates of risk, derived from a risk calculator, have the potential to integrate multiple risk factors in determining the risk that can be updated at varied points of remission.

This external validation of this risk calculator is an important advance in the field of psychiatry, in that it provides a tool to predict an individual's BD disease prognosis. The calculator's simplicity increases the feasibility and likelihood of clinical use, particularly in settings using measurement-based assessment. The validation sample was large, and was followed longitudinally for a period spanning several decades. The older age and different time period of the follow-up suggest that the calculator may be robust to patient age, and span time periods wherein treatments differed. While not the aim of this study, the validation of the risk calculator in the CDS sample of adults with BD also support a connection to the COBY sample of youth with BD. Some have found the diagnosis of BD in youth to be controversial and meet it with skepticism (Malhi et al., 2020). Similar performance of a risk calculator developed in the COBY sample in the well-established CDS sample provides support that BD can be reliably identified in youth when approached with similar rigor (Birmaher et al., 2006).

### 4.1. Limitations

The current study is not without its limitations. The CDS sample, which was recruited in the late 1970's and early 1980's, was entirely self-reported White, and the results from this sample may not generalize. The COBY sample was not exclusively, though mostly, self-reported White (82%). Further external validation in more racially diverse samples is important. While the information used for the risk calculator is readily available to clinicians (www.pediatricbipolar.pitt.edu), specific components may not be routinely collected by clinicians in their current usual practice. Should specific clinical applications be developed that utilize this calculator, this could encourage more routine collection of this accessible and relevant clinical data in practice (e.g., current remission length, age, age of mood disorder onset). The psychiatric status ratings (**Supplementary Table 1**) used as part of the LIFE should be translatable by clinicians from rating scales. The requisite predictor

variables (**Supplementary Table 2**) are not routinely collected by all clinicians although is useful to manage patients with BD. Beyond what should be routine clinical information, implementation could be accomplished through measurement-based care with routine use of validated rating scales that capture the nature, severity and duration of past episode and allow estimation of remission. Current remission length was an important predictor, and the risk calculator requires consideration of subthreshold symptoms during any such remission (Judd et al., 2016). The risk calculator accurately predicted risk of recurrence between 1 and 5 years, but does not assess more proximal risk, for example, at one month.

## Conclusions

In summary, risk of mood recurrence in BD over 1–5 years can be calculated within already accepted limits, and is consistent with methods that have been adopted by the broader medical community. Clinicians are encouraged to utilize this risk calculator to help patients with BD predict their individualized risk of mood episode recurrence. Knowledge of disease prognosis can in turn inform their treatment decisions. Additionally, research incorporating such assessments may help identify high-risk BD subgroups most likely to benefit from treatment, and could be utilized in future biological and treatment studies.

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## CRediT authorship contribution statement

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## Supplementary materials

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