

# UC San Diego

## UC San Diego Previously Published Works

### Title

28.3 PERSON-LEVEL PREDICTION OF PROGRESSION ALONG THE BIPOLAR TRAJECTORY

### Permalink

<https://escholarship.org/uc/item/1p98t8dv>

### Journal

Journal of the American Academy of Child and Adolescent Psychiatry, 58(10)

### ISSN

0890-8567

### Authors

Hafeman, Danella  
Merranko, John  
Goldstein, Benjamin I  
[et al.](#)

### Publication Date

2019-10-01

### DOI

10.1016/j.jaac.2019.07.815

### Copyright Information

This work is made available under the terms of a Creative Commons Attribution License, available at <https://creativecommons.org/licenses/by/4.0/>

Peer reviewed

history is an important predictor that gives increased precision to the diagnosis of emerging BD. Further, subtypes of BD breed true from parent to child.

### ADOL, BD, PSP

Supported by Canadian Institutes of Health Research Grant 152976  
<https://doi.org/10.1016/j.jaac.2019.07.813>

## 28.2 RISK FACTORS OF BIPOLAR DISORDERS AND MDD IN A PROSPECTIVE HIGH-RISK COHORT STUDY

Martin Preisig, MD, MPH, University Hospital of Lausanne, martin.preisig@chuv.ch; Dominique Rudaz, MSC, Pierre Marquet, MD, PhD, Jean-Michel Aubry, MD, Caroline Vandeleur, PhD

**Objectives:** By use of prospective data on the offspring of patients with unipolar and bipolar mood disorders, as well as clinical control subjects, our goals were to identify the risk factors for the onset of bipolar disorder (BD) and MDD, including parental disorders, mental illness antecedents, and personality traits and adverse life events.

**Methods:** Clinical information was collected on 163 offspring of parents with BD, 128 offspring of parents with MDD, and 158 offspring of comparison probands. Children were ages 6–17 years at study entry (mean age: 10.1 years). Offspring and their parents were interviewed directly every 3 years, with a mean duration of follow-up of 13.2 years.

**Results:** By far, the strongest predictor of the onset of manic or hypomanic episodes in offspring was a parental BD with an onset earlier than 21 years (hazard ratio = 6.7,  $p < 0.001$ ), whereas MDD episodes were the only mental health condition that independently predicted the onset of manic or hypomanic episodes. Neuroticism and life events were not associated with the onset of mania/hypomania. However, sexual abuse (hazard ratio = 3.8,  $p < 0.01$ ) and witnessing of violence (hazard ratio = 1.8,  $p < 0.01$ ) were the strongest predictors of the onset of MDD in offspring.

**Conclusions:** MDD and BD are likely to have distinct predictors of their onset. Our data confirm the importance of family history in the prediction of the onset of BD, which typically starts with an MDD episode, whereas the onset of MDD is more strongly associated with environmental factors.

### BD, RF, ADOL

Supported by Swiss National Foundation Grants 3200-040677, 32003B-105969, 32003B-118326, 3200-049746, 3200-061974, 125759, and 158776, and GlaxoSmithKline Clinical Genetics  
<https://doi.org/10.1016/j.jaac.2019.07.814>

## 28.3 PERSON-LEVEL PREDICTION OF PROGRESSION ALONG THE BIPOLAR TRAJECTORY

Danella Hafeman, MD, PhD, University of Pittsburgh, hafemand@upmc.edu; John Merranko, MA, Benjamin I. Goldstein, MD, PhD, Dara J. Sakolsky, MD, PhD, Rasim Somer Diler, MD, David Axelson, MD, Heather Meg Hower, MSW, Boris Birmaher, MD; Coby Group, Bios Group

**Objectives:** Bipolar disorder (BD) rarely comes out of the blue; rather, it is generally preceded by subthreshold mood symptoms that may portend a full-threshold bipolar I disorder/bipolar II disorder (BD-I/II), particularly in youth at familial risk. Over the past several years, we and others have used longitudinal data from familial and/or clinical high-risk groups to assess predictors of progression along the trajectory to BD-I/II. These analyses are a crucial first step but do not answer the most pertinent clinical question: What is the probability that a given individual will develop BD? Recently, we have built risk calculators (RC) using data from the Pittsburgh Bipolar Offspring (BIOS) and Course and Outcome of Bipolar Youth (COBY) studies to answer this question.

**Methods:** The BIOS RC included 412 youth (ages 8–17 years) at familial risk, 54 of whom converted to bipolar spectrum disorder (BPSD) over a median of 9.5 years. The COBY RC included 140 youth with other-specified BD (OS-BD), 75 of whom transitioned to BD-I/II over a median of 11.5 years. For both sample

groups, predictors from the literature were entered into a baseline-resetting Cox regression (using visit as the unit of analysis); discrimination was measured using the area under the curve (AUC) after 1000 bootstrap resamples.

**Results:** Both RCs showed good discrimination for predicting progression toward BD-I/II (BIOS: AUC = 0.76 [0.71, 0.82]; COBY: AUC = 0.71 [0.67, 0.74]). It is noteworthy that the COBY RC also was externally validated in the BIOS sample group (AUC = 0.75). Several similar predictors emerged as important elements of the RCs, including subthreshold mania symptoms, anxiety, and mood lability. Family history of mania also was an important predictor of progression in the COBY sample group. In the BIOS sample group, sensitivity analyses—excluding youth who: 1) developed BPSD but did not have mania or a major depressive episode throughout follow-up; and/or 2) developed BPSD before age 13 years—showed similar results, indicating that our findings were not driven by prepubertal youth and/or youth without a major mood disorder.

**Conclusions:** We have built RCs to predict person-level progression toward BD-I/II that predict with similar accuracy to RCs used in other areas of medicine (eg, heart disease, cancer). These RCs are a useful research tool (eg, to test early interventions in ultra-high-risk youth) and, if replicated, may be an important clinical measure to inform prognosis and treatment options.

### BD, RF, LONG

Supported by NIMH Grants R01-MH112544, R01-MH060952, and K23-MH110421  
<https://doi.org/10.1016/j.jaac.2019.07.815>

## 28.4 GENERALIZING THE PREDICTION OF BIPOLAR DISORDER ONSET ACROSS POPULATIONS

Anna Van Meter, PhD, Donald and Barbara Zucker School of Medicine at Hofstra University/Northwell Health, avanmeter@northwell.edu; Danella Hafeman, MD, PhD, John Merranko, MA, Eric Youngstrom, PhD; LAMS Group

**Objectives:** Bipolar spectrum disorders (BPSDs) often emerge during late adolescence; early symptoms can be hard to distinguish from typical behaviors and other disorders. Misdiagnosis and delays in treatment have consequences for both short- and long-term functioning. A recent meta-analysis showed that BPSD symptoms before an initial mood episode in BPSD provided a foundation from which a risk calculator (RC) was developed that identified offspring of BPSD who are likely to meet criteria for BPSD in the future. The goal of this presentation is to describe the process of adapting this RC, built for a familial high-risk sample group, for a new clinical high-risk population.

**Methods:** Participants (aged 6–12 years at baseline) from the Longitudinal Assessment of Manic Symptoms (LAMS) study ( $N = 685$ ) were evaluated semi-annually (6 years on average). Evaluations included a K-SADS semi-structured diagnostic interview. The majority of participants were recruited based on elevated symptoms of mania (Parent General Behavior Inventory 10-item mania scale).

**Results:** Over the follow-up period, 68 youth newly met the criteria for BPSD. The RC developed in a familial high-risk sample group did not discriminate well between youth who developed BPSD and those who did not in the LAMS sample group. We hypothesized that nonspecific predictors in the RC (eg, anxiety, psychosocial function) might be less predictive of BPSD in a clinical population. The RC was modified to include only subthreshold manic symptoms and subthreshold depressive symptoms and then trained/tested in the familial high-risk sample group and externally validated in LAMS. The modified RC performed well (area under the curves [AUCs]  $> 0.7$ ). Removing the first 2 assessments, during which participants were most symptomatic, further improved the performance of the modified RC in the LAMS sample group (AUCs  $> 0.7$ ).

**Conclusions:** It is possible to reliably estimate the probability that an individual will develop BPSD based on early symptoms. The clinical circumstances under which the assessment of early symptoms occur significantly affect prediction accuracy and have implications for the period during which the predication is valid. Integration of additional diagnostically specific factors may improve the generalizability of future RCs.

### BD, DIAG, RF

Supported by NIMH Grants R01-MH073967-06A1, R01-MH073816-06A1, R01-MH073801-06A1, and R01-MH073953-06A1  
<https://doi.org/10.1016/j.jaac.2019.07.929>