The Journal of Child Psychology and Psychiatry

Journal of Child Psychology and Psychiatry **:* (2022), pp **–** doi:10.1111/jcpp.13739

Early indicators of bipolar risk in preschool offspring of parents with bipolar disorder

Danella M. Hafeman,[1] John Merranko,[1] Heather M. Joseph,[1] Tina R. Goldstein,[1] Benjamin I. Goldstein,[2] Jessica Levenson,[1] David Axelson,[3] Kelly Monk,[1] Dara Sakolsky,[1] Satish Iyengar,[4] and Boris Birmaher[1]

[1]Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA; [2]Center for Addiction and Mental Health, University of Toronto Faculty of Medicine, Toronto, ON, Canada; [3]Nationwide Children's Hospital and Ohio State College of Medicine, Columbus, OH, USA; [4]Department of Statistics, University of Pittsburgh, Pittsburgh, PA, USA

Background: Offspring of parents with bipolar disorder (BD-I/II) are at increased risk to develop the disorder. Previous work indicates that bipolar spectrum disorder (BPSD) is often preceded by mood/anxiety symptoms. In school-age offspring of parents with BD, we previously built a risk calculator to predict BPSD onset, which generates person-level risk scores. Here, we test whether preschool symptoms predict school-age BPSD risk. **Methods:** We assessed 113 offspring of parents with BD 1–3 times during preschool years (2–5 years old) and then approximately every 2 years for a mean of 10.6 years. We used penalized (lasso) regression with linear mixed models to assess relationships between preschool mood, anxiety, and behavioral symptoms (parent-reported) and school-age predictors of BPSD onset (i.e., risk score, subthreshold manic symptoms, and mood lability), adjusting for demographics and parental symptomatology. Finally, we conducted survival analyses to assess associations between preschool symptoms and school-age onset of BPSD and mood disorder. **Results:** Of 113 preschool offspring, 33 developed new-onset mood disorder, including 19 with new-onset BPSD. Preschool irritability, sleep problems, and parental factors were lasso-selected predictors of school-age risk scores. After accounting for demographic and parental factors, preschool symptoms were no longer significant. Lasso regressions to predict mood lability and subthreshold manic symptoms yielded similar predictors (irritability, sleep problems, and parental affective lability), but preschool symptoms remained predictive even after adjusting for parental factors ($ps < .005$). Exploratory analyses indicated that preschool irritability univariately predicted new-onset BPSD ($p = .02$) and mood disorder ($p = .02$). **Conclusions:** These results provide initial prospective evidence that, as early as preschool, youth who will develop elevated risk scores, mood lability, and subthreshold manic symptoms are already showing symptomatology; these preschool symptoms also predict new-onset BPSD. While replication of findings in larger samples is warranted, results point to the need for earlier assessment of risk and development of early interventions. **Keywords:** Bipolar disorder; follow-up studies; preschool children.

Introduction

Bipolar spectrum disorder (BPSD), including BD-I, BD-II, and BD-Not Otherwise Specified, is a serious mental illness frequently associated with poor psychosocial function, substance abuse, and suicide attempts (Goldstein et al., 2009, 2012, 2013). While BPSD often onsets in adolescence and early adulthood, significant diagnostic delays mean that many individuals do not receive appropriate treatment during an important developmental period (Dagani et al., 2017). To avoid such delays in diagnosis and treatment, understanding early signs of BPSD is critical to identify children at highest risk for progression of the disorder. Previously, several symptoms have been found to predict BPSD onset, particularly in those with a family history of BD-I/II. Based on longitudinal studies of school-age youth and young adult samples, symptoms of anxiety and depression, mood lability, and subthreshold manic symptoms increase risk for BPSD onset in offspring of parents with BD-I/II, particularly in those whose parents had early onset mood disorder (Duffy, Goodday, Keown-Stoneman, & Grof, 2019; Hafeman et al., 2016; Mesman, Nolen, Keijsers, & Hillegers, 2017). However, we do not know whether symptoms manifest at even younger ages, e.g., during preschool, in youth who will later develop BPSD, and if so, which preschool symptoms are most predictive. Identification of early antecedents for disorder is critical because it opens additional avenues for intervention and may expand our understanding of BPSD from a developmental perspective.

Previous work on preschool predictors of BPSD has been limited. In the analysis of the Pittsburgh Bipolar Offspring Study (BIOS) intake data, we found that preschool offspring of parents with BD-I/II have more externalizing symptoms, dysregulation, oppositional-defiant, and generalized anxiety disorder symptoms than community controls, even after adjusting for parental comorbidities (Maoz, Goldstein, Axelson, et al., 2014). Preschool offspring of BD-I/II parents were also more likely to have anxiety, ADHD, and behavior problems than offspring of

Conflict of interest statement: See Acknowledgements for full disclosures.

healthy parents, and preschool ADHD was associated with increased risk for BPSD (Birmaher et al., 2021). In a different sample enriched for depression, preschool irritability was found to predict mania and depression during childhood, while excitability predicted later mania and mood lability (Vogel, Jackson, Barch, Tillman, & Luby, 2019). Preschool internalizing and externalizing symptoms have also been found to predict borderline personality symptoms, which include affective instability (Geselowitz et al., 2020). Based on these findings, it appears that early emotion dysregulation has some continuity through adolescence.

One challenge to studying preschool-age precursors to BPSD onset is that such studies require long duration of follow-up of a large sample to obtain enough participants with new-onset BPSD. While the BIOS preschool study is the largest of its kind, with the longest follow-up (~12 years), new-onset BPSD is still relatively infrequent ($n < 20$). To provide a complementary perspective, with increased statistical power, we can leverage previous findings to also assess preschool predictors of school-age *risk indicators for BPSD*. We have developed a tool that can be very helpful in this regard: a risk calculator. Risk calculators are frequently used in other areas of medicine, to provide a person-level assessment of risk (i.e. *risk score*) for a particular outcome, informing prognosis and treatment (Goff et al., 2014; Jin et al., 2021). Within the school-age BIOS sample, we previously built a risk calculator that predicts with good accuracy the five-year risk of developing BPSD (Hafeman et al., 2017). Integrating clinical (e.g. depression, anxiety, subthreshold manic symptoms) and demographic (e.g. parental age of onset) factors, this risk calculator generates person-level *risk scores* that can be assessed as an *intermediate outcome*. In addition, we have previously identified two proximal predictors (within 2 years) of new-onset BPSD in the school-age sample: subthreshold manic symptoms and mood lability (Hafeman et al., 2016). These *proximal symptoms* can also be assessed as *intermediate outcomes*.

In this study, we first ask which preschool dimensions (symptoms, temperament scores), previously found to differentiate at-risk and control youth in our intake paper (Maoz, Goldstein, Axelson, et al., 2014), predict school-age risk scores, mood lability, and subthreshold manic symptoms. Second, we ask, do these selected dimensions also predict new-onset BPSD and mood disorders? This *intermediate outcomes* approach allows us enough power to use sophisticated methods for predictor selection (i.e., penalized regression) and evaluate important confounds, while we are also able to triangulate results testing final models using the outcome of interest. The goal of this paper is not to develop a new risk calculator in preschool-age youth, but rather to leverage our previous risk calculator (and identification of school-age proximal symptoms) to more rigorously assess the association between preschool symptoms and later risk for BPSD.

Methods

Sample

Methods for the BIOS preschool sample have been previously described (Birmaher et al., 2010; Maoz, Goldstein, Axelson, et al., 2014). Briefly, parents with DSM-IV BD-I/II and their offspring ages 2–5 were recruited from the community primarily via advertisement (60%) and followed every 2 years. Exclusion criteria included lifetime schizophrenia, intellectual disability, autism, and mood disorders secondary to other conditions. Control parents, grouped-matched by age, sex, and neighborhood were recruited from the community via phone using random dialing. All preschool offspring from each family were included, except for children with a condition that impeded participation in the study (e.g. intellectual disability).

Procedures

The study was approved by the University of Pittsburgh Institutional Review Board. Written informed consent was obtained from parents; assent was obtained from the offspring once they turned 6 years old.

Parent (proband) diagnosis was determined using the Structured Clinical Interview-DSM-IV (SCID) in addition to items from the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version (K-SADS-PL) for ADHD, Disruptive Behavior, and Separation Anxiety Disorders (First & Gibbon, 2004; Kaufman et al., 1997). The SCID kappas were ≥0.8. Psychosocial functioning was ascertained using the Global Assessment of Functioning (GAF). Parents also completed the Beck Depression Inventory (BDI; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) and Affective Lability Scale (ALS; Harvey, Greenberg, & Serper, 1989) at each time point. Approximately half (49%; 66/134) of biological co-parents were ascertained via face-to-face assessment, as above. For biological co-parents who could not be assessed directly, as well as siblings and second-degree relatives, the Family History Research Diagnostic Criteria method (Andreasen, Endicott, Spitzer, & Winokur, 1977) was used to assess psychiatric history in first and second-degree relatives (as reported by the proband). Socioeconomic status (SES) was assessed using the Hollingshead Scale (Hollingshead, 1975).

For preschool-age offspring, only parents were interviewed about their child regarding lifetime psychiatric diagnoses using K-SADS-PL; this has previously been shown to be a valid method for diagnostic assessment in this age range (Birmaher et al., 2009; Henin et al., 2005). As previously described (Birmaher et al., 2010), language used to assess each symptom was modified to be developmentally appropriate, and symptoms had to exceed what is expected from a typically developing preschool-age child. Assessments were conducted by interviewers trained with the diagnostic instruments and were presented to a child psychiatrist/psychologist; all were blind to parental diagnoses. Parents also completed the preschool version of the Child Behavior Checklist (CBCL; Achenbach, 1991), Emotionality, Activity, Sociability (EAS) Inventory (Buss & Plomin, 1984), and Early Childhood Inventory (ECI; Sprafkin, Volpe, Gadow, Nolan, & Kelly, 2002). If participants had >1 visit between 2 and 5 years old, we used data from the last visit for the primary analysis. In addition, we conducted an exploratory analysis to assess whether symptoms at the first visit (where available) were also predictive.

Once participants turned 6 years old, offspring and parents were interviewed using the KSADS-PL to assess DSM-IV

diagnoses. BD-Not Otherwise Specified (NOS) was assessed using criteria from the Course and Outcome of Bipolar Youth Study (Birmaher et al., 2006; see Appendix S1: Methods). Pervasive developmental disorders were assessed via clinician interview using a checklist of DSM-IV symptoms. Kappas for all disorders ranged from 0.80 to 0.90. To assess subsyndromal mood symptoms, the KSADS Mania Rating Scale (KMRS) and depression items from the KSADS (KDRS) present version were used (worst week in the past month). Parents and youth also completed dimensional assessments of mood lability (Child Affective Lability Scale; CALS; Gerson et al., 1996). The Child Global Assessment Scale (CGAS) was utilized to rate psychosocial function. Clinical records were not used as part of this study.

Statistical analysis (Figure S1)

Analyses focused on assessing predictors of *risk scores* (i.e. log-transformed risk scores throughout school-age follow-up) in offspring with a parent with BD-I/II using linear mixed models (random intercept fit to account for clustering of repeated measures within subject) implemented in R. We focused particularly on preschool dimensional predictors previously found to differ between offspring of parents with BD-I/II and offspring of control parents, after adjustment for demographics and parental co-morbidity: CBCL subscales (Total, Externalizing, Somatic complaints, Sleep problems, Aggression, and Dysregulation Profile), ECI subscales (Oppositional Defiant Disorder (ODD), Generalized Anxiety, Sleep Disorder), and EAS subscales (Total, Emotionality) (Maoz, Goldstein, Axelson, et al., 2014).

Combining these factors with parental clinical characteristics (BDI score, ALS score, frequency of mood episodes, hypo/mania or depression at assessment) and demographic factors (sex, race, SES), we used lasso regression to select predictors for risk scores (shrinkage parameter selected via fivefold cross validation). We estimated the stability of Lasso predictor selections by bootstrapping the lasso procedure 1,000 times and computing the percent of iterations in which each predictor was retained (Hastie, Tibshirani, & Wainwright, 2015). To assess if prediction on risk score diminished across age, we included in the lasso regression interactions between each predictor and assessment age. In addition to risk score, we assessed mood lability (CALS) and subthreshold manic symptom (KMRS), previously found to be *proximal symptoms* that predicted bipolar onset (Hafeman et al., 2016). Because parental age of mood disorder onset is included in the risk score, we did not include this variable in the Lasso regression; for consistency, we also did not include this variable in the Lasso regressions to predict school-age mood lability and subthreshold manic symptoms.

Finally, we conducted a factor analysis using varimax (orthogonal) rotation to reduce the set of predictors selected by these lasso regression analyses (number of factors chosen via Kaiser rule and scree test) and used Cox regression (frailty models accounting for within-family clustering) to test whether these factors predicted new-onset BPSD and, more broadly, mood disorder. To test for preschool symptoms that may directly predict new-onset mood disorder or BPSD (and not intermediate outcomes), we conducted a sensitivity analysis to assess relationships between each subscale and new-onset mood disorder or BPSD.

Results

Parent characteristics

The parent sample consisted of 55 parents with BD-I and 29 with BD-II. They showed significant episodic lifetime impairment, with a mean GAF of 67.5 ± 9.3 across all assessments, and 36.7 ± 13.6 during their period of lowest functioning. At the time of assessment, 14% of offspring's parents were manic/hypomanic and 20% of offspring's parents were depressed.

Offspring demographics and DSM-IV diagnoses

Participants were 53.1% male and on average 3.7 ± 1.3 years old at intake; they were followed for a mean of 10.6 ± 4.9 years (1.1 ± 1.2 before age 6, 8.6 ± 3.6 after age 6), with a median of 7 assessments (1 before age 6, 5 after age 6) (Table 1). Over follow-up, 33 developed school-age-onset mood disorders (mean age: 13.0 ± 4.4 years old), including 19 with BPSD (mean age: 10.8 ± 4.5 years old; BD-I = 2, BD-II = 2, BD-NOS = 15). Youth diagnosed with BPSD and other mood disorders had substantial functional impairment and an elevated risk of psychiatric hospitalization, compared to those without a mood disorder diagnosis (see Appendix S2: Results).

During preschool years (age 2–5), the most common diagnoses were ADHD (20.4%) and disruptive behavior disorder (14.2%). During preschool years, those who later developed BPSD (vs. those who did not) had a marginally lower SES (z = 1.52, p = .1) and, as previously reported (Birmaher et al., 2021), higher rates of ADHD (p = .02) and ODD (p = .03).

Preschool predictors of school-age risk scores

The lasso regression predicting school-age risk scores selected ECI subscales (ODD, Sleep) and parent factors (ALS, number of total parental episodes) with good stability across bootstrap iterations (>99% of models selected these variables) (Table S1 and Table 2). Interactions between dimensions and assessment age were not selected by the lasso regression. After adjusting for age in a mixed linear regression, preschool ECI-ODD was a significant predictor of school-age risk scores (β = .24, p = .004); however, after adjustment for parental factors (ALS, number of episodes), ECI-ODD was no longer significant (β = .13, p = .19). After adjusting for age, ECI-Sleep was a marginally significant predictor of risk scores (β = .17, p = .06), but was also no longer significant after the adjustment for parental factors (β = .16, p = 0.11). Parental affective lability (ALS) was a marginally significant predictor of risk scores.

Preschool predictors of school-age proximal symptoms (Table S1 and Table 2)

Lasso regression to predict mood lability and subthreshold manic symptoms showed very similar results to risk score, which is not surprising due to large correlations between risk score and these symptoms (CALS: r = .65; KMRS: r = .63) and moderate correlations between CALS and KMRS (r = .42).

Table 1 Sample characteristics

Demographics	Full sample (N = 113)	No BPSD (n = 94)	BPSD (n = 19)	Test stat	p-Value
Intake age, mean (*SD*)	3.73 (1.26)	3.74 (1.26)	3.69 (1.25)	z = 0.10	.9235
Age at last assessment, mean (*SD*)	14.32 (5.19)	13.86 (5.52)	16.59 (1.86)	z = 1.44	.1489
White, %	82.30	82.98	78.95	FET	.7426
Male, %	46.90	48.94	36.84	FET	.4510
SES, mean (*SD*)	35.81 (14.63)	36.55 (14.71)	32.11 (14.01)	z = 1.52	.1276
Maternal Age at Offspring Birth, mean (*SD*)	28.70 (5.35)	28.51 (5.47)	29.63 (4.68)	z = 1.13	.2575
Paternal age at offspring birth, mean (*SD*)	31.32 (6.74)	31.44 (6.49)	30.70 (8.06)	z = 0.53	.5966
Psychiatric disorders between ages 2–5				Test	p-Value
Major depressive disorder, %	0	0	0	FET	–
Depression NOS, %	0.88	1.06	0	FET	~1
Attention deficit hyperactivity disorder, %	20.35	15.96	42.11	FET	**.0239**
Disruptive behavior disorders, %	14.16	10.64	31.58	FET	**.0278**
Conduct disorder, %	1.77	2.13	0	FET	~1
Oppositional defiant disorder, %	14.16	10.64	31.58	FET	**.0278**
Social phobia, %	2.65	2.13	5.26	FET	.4275
Obsessive compulsive disorder, %	3.54	3.19	5.26	FET	.5264
Post traumatic stress disorder, %	0.88	1.06	0	FET	~1
Generalized anxiety disorder, %	1.77	1.06	5.26	FET	.3093
Separation anxiety disorder, %	7.08	7.45	5.26	FET	~1
Pervasive developmental disorder, %	9.73	8.51	15.79	FET	.39

Wilcoxon nonparametric tests contrasted groups on continous variables, and Fisher's exact tests (FET) contrasted groups on categorical variables. Significant p-values (p<.05) are in bold font.

Like the risk score model, the KMRS Lasso model selected ECI-ODD and parental ALS; it also selected a sleep measure (CBCL-Sleep Problems), externalizing symptoms (CBCL-externalizing), and SES with good stability across bootstrap iterations (>97% of models selected these variables). After adjustment for demographic (SES, age) and parental factors (parental ALS), ECI-ODD (β = .31, p < .0001), CBCL-Sleep Problems (β = .27, p < .0001), and CBCL-Externalizing (β = .34, p < .0001) were significant predictors of school-age manic symptoms. Parental ALS was significant in all models for predicting manic symptoms.

Similar to the KMRS model, the CALS Lasso selections included sleep problems (CBCL-Sleep Problems), parental ALS, and SES; it also included dysregulation (CBCL-dysregulation profile). Predictor selections were stable across bootstrap iterations (>98% of models selected these variables). Adjusting for selected demographics (SES) and parental factors (ALS), CBCL-Dysregulation (β = 0.30, p = .004) and CBCL-Sleep (β = 0.29, p = .004) were both significant predictors of school-age mood lability. In these models, parental ALS was not a significant predictor of mood lability.

Preschool predictors of new-onset BPSD and mood disorders (exploratory analysis)

A factor analysis including the above selected preschool subscales (ECI: ODD, Sleep; CBCL: Externalizing, Dysregulation, Sleep) yielded two orthogonal factors: Irritability and Sleep (Table 3). The significant univariate predictors of new-onset BPSD were preschool irritability and parental ALS. In the combined model, only parental age of mood disorder onset was marginally significant (HR = 0.47, p = .06) (Table 4a). The significant univariate predictors of new-onset mood disorders were preschool irritability and parental age of mood disorder onset. In the fully adjusted model, both preschool irritability and parental age of mood disorder onset were significant predictors of new-onset mood disorder (Table 4b).

Individual preschool predictors of new-onset BPSD and mood disorders (sensitivity analysis; Table S2)

The only raw preschool subscales that individually predicted BPSD risk were CBCL: Externalizing, CBCL: Dysregulation, and ECI: Oppositional Defiant Disorder (p values < .05), all of which were selected by the lasso regressions. CBCL: Total Score, Externalizing, Sleep Problems, Aggression (a component of Externalizing), and Disregulation all individually predicted risk of any mood disorder (p values < .05).

Preschool predictors from intake (exploratory analysis; Tables S3 and S4)

Nearly half (n = 49; 43%) of our participants had >1 preschool assessments; the intake visit was at a mean age of 3.7 ± 1.3. In this sub-sample, we tested whether significant predictors, as assessed at last preschool visit, were also significant at an earlier age (i.e. first visit). Most symptoms that were significantly associated with intermediate outcomes using the last preschool visit remained significant when using the first preschool assessment (p-

Table 2 Adjusted effects of Lasso-selected predictors on intermediate outcomes

Model	Effect	Estimate	*t* Value	*p*-value
(a) Risk calculator model				
ECI-ODD: Adjusted for demographics	*ECI-ODD*	***0.2427***	***2.89***	***.004***
	Assessment age	**0.1498**	**7.12**	**<.0001**
ECI-ODD: Adjusted for demographics + Parental factors	*ECI-ODD*	*0.131*	*1.32*	*.1871*
	Assessment age	**0.1506**	**6.14**	**<.0001**
	Parental ALS total score	0.1846	1.72	.0856
	Parental episode rate >3	0.2442	1.09	.2786
ECI-sleep: Adjusted for demographics	*ECI-sleep*	*0.1664*	*1.85*	*.0648*
	Assessment age	**0.1495**	**7.1**	**<.0001**
ECI-sleep: Adjusted for demographics + Parental factors	*ECI-sleep*	*0.1582*	*1.59*	*.1127*
	Assessment age	**0.1507**	**6.14**	**<.0001**
	Parental ALS total score	**0.2171**	**2.15**	**.0318**
	Parental episode rate >3	0.3059	1.39	.1647
(b) Subthreshold manic symptoms model				
ECI-ODD: Adjusted for demographics	*ECI-ODD*	***0.3447***	***5.33***	***<.0001***
	Assessment age	0.03773	1.08	.2789
	SES	−0.1131	−1.73	.0843
ECI-ODD: Adjusted for demographics + Parental factors	*ECI-ODD*	***0.3063***	***4.31***	***<.0001***
	Assessment age	0.02998	0.72	.471
	SES	−0.07152	−0.99	.3209
	Parental ALS total score	0.1478	1.96	.0502
CBCL-externalizing: Adjusted for demographics	*CBCL – externalizing*	***0.3782***	***6.02***	***<.0001***
	Assessment age	0.04468	1.29	.1993
	SES	−0.08953	−1.4	.1619
CBCL-externalizing: Adjusted for demographics + Parental factors	*CBCL – externalizing*	***0.3444***	***5.02***	***<.0001***
	Assessment age	0.03705	0.89	.3724
	SES	−0.04849	−0.69	.4889
	Parental ALS total score	**0.1571**	**2.2**	**.0282**
CBCL-sleep: Adjusted for demographics	*CBCL – sleep*	***0.2832***	***4.38***	***<.0001***
	Assessment age	0.0332	0.95	.3424
	SES	**−0.1856**	**−2.82**	**.005**
CBCL-sleep: Adjusted for demographics + Parental factors	*CBCL – sleep*	***0.2732***	***3.95***	***<.0001***
	Assessment age	0.02951	0.71	.4788
	SES	−0.1288	−1.8	.0722
	Parental ALS total score	**0.2214**	**3.03**	**.0026**
(c) Mood lability model				
CBCL-dysregulation: Adjusted for demographics	*CBCL – dysregulation profile*	***0.3356***	***3.71***	***.0003***
	Assessment age	−0.02113	−0.27	.7857
	SES	−0.03924	−0.43	.6683
CBCL-dysregulation: Adjusted for demographics + Parental factors	*CBCL – dysregulation profile*	***0.3025***	***2.95***	***.0035***
	Assessment age	−0.02618	−0.29	.7692
	SES	−0.03301	−0.31	.7533
	Parental ALS total score	0.06136	0.59	.5553
CBCL-sleep: Adjusted for demographics	*CBCL – sleep*	***0.2512***	***2.84***	***.0048***
	Assessment age	−0.03171	−0.41	.6837
	SES	−0.1276	−1.42	.1565
CBCL-sleep: Adjusted for demographics + Parental factors	*CBCL – sleep*	***0.2877***	***2.95***	***.0036***
	Assessment age	−0.03108	−0.35	.7273
	SES	−0.09916	−0.98	.3298
	Parental ALS total score	0.1145	1.13	.2609

Preschool symptom predictors are italicized; significant findings (p<.05) are in bold font.

values < .05), with one primary exception. While ECI: Sleep was marginally associated with risk score (p = .06) when assessed at last preschool assessment, it was not predictive at first assessment (p = .97). In univariate Cox regression models, the preschool irritability factor was associated with new-onset BPSD and mood disorder at both first and last visits (p-values < .05).

Discussion

In this longitudinal study of offspring of parents with BD-I/II, recruited during preschool (ages 2–5) and followed for over a decade, we assessed demographic and dimensional predictors of risk score, proximal symptoms (mood lability, subthreshold manic symptoms), and new-onset BPSD and mood disorders. We found that the Lasso regression to predict risk

Table 3 Factor analysis loadings

	1: Irritability factor	2: Sleep factor
ECI – sleep	18	91
ECI – ODD	86	14
CBCL – sleep	28	88
CBCL – dysregulation profile	91	33
CBCL – externalizing	93	27

Items that load onto each factor are shaded.

scores, mood lability, and subthreshold manic symptoms all selected preschool measures of irritability and sleep problems, and parental affective lability. When we assessed the degree to which these variables also predicted new-onset BPSD and mood disorders, we found preschool irritability and parental age of mood disorder onset to be the most important predictors. In a sensitivity analysis, all significant predictors of BPSD were also selected by the lasso regressions for intermediate outcomes, thus supporting the utility of this approach. Interestingly, an exploratory analysis indicated that these symptoms, aside from sleep, were also predictive at an even earlier age (~3 years old).

In our sample of youth at-risk for BPSD, we found that preschool irritability was an important predictor of school-age risk indicators (i.e. risk scores, proximal risk factors) and school-age onset BPSD and mood disorders. This is consistent with findings from another sample of preschool-age children, enriched for depression, in which irritability predicted both mania and depression during adolescence (Vogel et al., 2019). Another recent longitudinal study found that preschool irritability predicted later internalizing and externalizing disorders, as well as parent-reported anxiety and depression (Sorcher et al., 2022). Thus, preschool irritability is not a specific predictor of BPSD. However, in an at-risk sample, it significantly predicts risk score, mood lability, and manic symptoms; and is associated with increased risk of a mood disorder outcome.

These current findings are somewhat consistent with what we and others have previously found as predictors of new-onset BPSD in school-age children. Regarding diagnostic predictors of new-onset BPSD, school-age youth with disruptive behavioral disorders were more likely to subsequently develop hypomania/mania (Axelson et al., 2015). Sleep problems in school-age youth (e.g. frequent awakenings) have also previously been shown to predict new-onset BPSD in this sample (Levenson et al., 2015). We and others have previously found that dimensional anxiety is an important nonspecific predictor of new-onset BPSD in school-age youth (Hafeman et al., 2016), a finding that is consistent with findings from other longitudinal at-risk studies (Duffy et al., 2019). Notably, models did not select anxiety; however, preschool CBCL-Dysregulation (which includes the anxiety/depression subscale) was selected as a predictor of school-age mood lability. Thus, these findings highlight that what we have observed in school age may be traced back even further into preschool years.

Regarding prediction of mood disorders and BPSD in the offspring, parental ALS and parental age of onset were among the strongest predictors. There are two primary explanations for this: genetic loading and environmental effects. First, these variables can be an indicator of the severity of BD-I/II in the parent, and thus the genetic loading in the offspring. Offspring of parents who have more severe manic symptoms (captured in part by the ALS) may themselves be more likely to develop BPSD, due to familial risk for disorder. Second, previous work has found that if a parent is symptomatic, the offspring is more likely to have worse outcomes, less likely to recover from a mood episode, and more likely to develop

Table 4 (a) Associations between Lasso-selected preschool predictors and (a) new-onset BPSD and (b) new-onset mood disorders

	Univariate		Fully adjusted	
Predictor	Hazard ratio (95% CI)	*p*-Value	Hazard ratio (95% CI)	*p*-Value
(a)				
Irritability factor	**1.83 (1.07, 3.12)**	**.0166**	1.69 (0.80, 3.60)	.1236
Sleep factor	1.40 (0.85, 2.29)	.1419	1.13 (0.63, 2.03)	.5731
Socioeconomic status	0.59 (0.32, 1.12)	.0777	0.73 (0.36, 1.49)	.2744
Parental ALS total score	**1.94 (0.97, 3.89)**	**.0440**	1.47 (0.69, 3.16)	.2314
Parental episode rate ≥4 per year	1.22 (0.31, 4.78)	.6117	0.87 (0.15, 5.04)	.7051
Parental mood onset age	0.60 (0.31, 1.13)	.0817	0.47 (0.19, 1.14)	.0647
(b)				
Irritability factor	**1.58 (1.01, 2.46)**	**.0250**	**2.12 (1.06, 4.27)**	**.0187**
Sleep factor	1.23 (0.82, 1.84)	.2279	1.31 (0.77, 2.25)	.2110
Socioeconomic status	0.68 (0.43, 1.08)	.0637	0.87 (0.46, 1.66)	.3948
Parental ALS total score	1.41 (0.89, 2.24)	.1092	0.86 (0.44, 1.69)	.4960
Parental episode rate ≥4 per year	1.37 (0.46, 4.04)	.3778	0.94 (0.18, 4.77)	.7039
Parental mood onset age	**0.37 (0.21, 0.64)**	**.0002**	**0.21 (0.07, 0.59)**	**.0015**

psychopathology (Barker, Copeland, Maughan, Jaffee, & Uher, 2012; Pilowsky et al., 2008). This may be due to parent–child interactions that are impaired when a parent is depressed, particularly during the sensitive period of early childhood (Fox & Gelfand, 1994; Guyon-Harris, Huth-Bocks, Lauterbach, & Janisse, 2016). Thus, based on this study, we cannot disentangle the extent to which the effect of parental factors is related to genetic vs. environmental effects.

There are several limitations of this study that should be taken into account when considering these findings. First, we only have a small number of youths with new-onset BPSD in this sample, thus yielding limited power to assess predictors of this outcome. To address this, we have conducted our statistical analyses predicting risk score and other intermediate outcomes (e.g., mood lability, subthreshold manic symptoms). Second, while the risk calculator outcome facilitates the usage of more sophisticated variable selection methods (given increased power over looking at BPSD only), it is possible that predictors of BPSD may not predict risk scores, manic symptoms, or mood lability; so, we may have missed important predictors of BPSD by only looking at those selected by the Lasso regressions for risk scores, mood lability, and subthreshold manic symptoms. However, our sensitivity analysis looking at individual scales did not yield additional predictors. Third, this sample is racially and ethnically homogeneous, reflecting the population in the surrounding area, and may not be generalizable to other populations. Fourth, our preschool predictors were parent-reports, which may be artificially elevated when parents are symptomatic (Maoz, Goldstein, Goldstein, et al., 2014). Thus, it is possible that the observed association between preschool irritability and later risk for BPSD is explained, at least in part, by parental symptomatology. We included parental symptoms (BDI, ALS) and parental mood state (depressed, hypo/manic) in our models, thus mitigating this possibility. Fifth, we did not collect data on specific indicators of mood disorder severity, such as treatment or hospitalizations for mania. Based on GAF and CGAS, a diagnosis of BD-I/II in parents (and BPSD in offspring) was associated with significant impairment, but we do not know whether this impairment was related to BPSD or co-morbidities.

In conclusion, we find that preschool externalizing behaviors, dysregulation, and sleep problems predict risk indicators and new-onset BPSD in offspring of BD-I/II parents. These findings also highlight the utility of the previously developed risk calculator and other dimensional predictors as intermediate outcomes, allowing for the use of penalized regression to narrow the most predictive variables; this would not have been possible if only assessing new-onset BPSD given the small number of participants with this outcome. Based on these findings, we would not recommend modifying treatment of underlying disorders that may be contributing to irritability, such as ADHD, anxiety, and depression. However, in the context of family history for BD-I/II (and particularly if the parent had early onset), it is important to longitudinally assess for other symptoms (e.g. mood lability, subthreshold manic symptoms) that increase risk substantially.The identification of preschool symptoms as a predictor of school-age risk also points to additional avenues for intervention, targeting both offspring and parental symptoms.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Appendix S1. Methods.
Appendix S2. Results.
Figure S1. Diagram of analyses described in the current paper.
Table S1. Lasso variable selection.
Table S2. Individual predictors of BPSD and Mood Disorder.
Table S3. First vs. Last Assessment prediction of risk score, mood lability (CALS), and subthreshold manic symptoms (KMRS).
Table S4. First vs. Last Assessment prediction of BPSD and mood disorder onset.

Acknowledgements

The authors would like to acknowledge our participants and families, and research assistants. This paper was supported by National Institute of Mental Health (NIMH) grantRO1 MH060952. D.M.H. reported consultation fees from Milken Institute Center for Strategic Philanthropy outside the submitted work. B.B. reports royalties from Random House, UpToDate, and Lippincot Williams & Wilkins outside of the submitted work. T.R.G. reports royalties from Guilford Press outside the submitted work. D.A. reports royalties from Wolters Kluwer/UpToDate outside the submitted work. The remaining authors have declared that they have no competing or potential conflicts of interest.

Correspondence

Danella M. Hafeman, 3811 O Hara St, Pittsburgh, PA 15213, USA; Email: hafemand@upmc.edu

Key points

- Previous work points to mood lability and subthreshold manic symptoms as precursors of bipolar spectrum disorder in school-age youth. We developed a risk calculator which yields a person-level estimate of risk (i.e. risk score).
- Here, we report that preschool symptoms (especially irritability) predict school-age risk scores, mood lability, and subthreshold manic symptoms in offspring of parents with bipolar disorder; and that predictors of these intermediate outcomes also predict new-onset bipolar spectrum disorder and youth.
- Findings highlight the need for earlier assessment of mood symptoms in at-risk youth, and the development and testing of early interventions to target these symptoms.

References

Achenbach, T.M. (1991). *Manual for the Child Behavior Checklist/4-18 and 1991 profile*. Burlington, VT: University of Vermont Department of Psychiatry.

Andreasen, N.C., Endicott, J., Spitzer, R.L., & Winokur, G. (1977). The family history method using diagnostic criteria. Reliability and validity. *Archives of General Psychiatry*, *34*, 1229–1235.

Axelson, D., Goldstein, B., Goldstein, T., Monk, K., Yu, H., Hickey, M.B., … & Birmaher, B. (2015). Diagnostic precursors to bipolar disorder in offspring of parents with bipolar disorder: A longitudinal study. *The American Journal of Psychiatry*, *172*, 638–646.

Barker, E.D., Copeland, W., Maughan, B., Jaffee, S.R., & Uher, R. (2012). Relative impact of maternal depression and associated risk factors on offspring psychopathology. *The British Journal of Psychiatry*, *200*, 124–129.

Beck, A.T., Ward, C.H., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An inventory for measuring depression. *Archives of General Psychiatry*, *4*, 561–571.

Birmaher, B., Axelson, D., Goldstein, B., Monk, K., Kalas, C., Obreja, M., … & Kupfer, D. (2010). Psychiatric disorders in preschool offspring of parents with bipolar disorder: The Pittsburgh Bipolar Offspring Study (BIOS). *The American Journal of Psychiatry*, *167*, 321–330.

Birmaher, B., Axelson, D., Strober, M., Gill, M.K., Valeri, S., Chiappetta, L., … & Keller, M. (2006). Clinical course of children and adolescents with bipolar spectrum disorders. *Archives of General Psychiatry*, *63*, 175–183.

Birmaher, B., Ehmann, M., Axelson, D.A., Goldstein, B.I., Monk, K., Kalas, C., … & Brent, D.A. (2009). Schedule for affective disorders and schizophrenia for school-age children (K-SADS-PL) for the assessment of preschool children – A preliminary psychometric study. *Journal of Psychiatric Research*, *43*, 680–686.

Birmaher, B., Merranko, J., Hafeman, D., Goldstein, B.I., Diler, R., Levenson, J.C., … & Sakolsky, D. (2021). A longitudinal study of psychiatric disorders in offspring of parents with bipolar disorder from preschool to adolescence. *Journal of the American Academy of Child & Adolescent Psychiatry*, *60*, 1419–1429.

Buss, A., & Plomin, R. (1984). *EAS temperament survey for children. Temperament: Early developing personality traits*. Hillsdale, NJ: Lawrence Erlbaum.

Dagani, J., Signorini, G., Nielssen, O., Bani, M., Pastore, A., Girolamo, G.D., & Large, M. (2017). Meta-analysis of the interval between the onset and management of bipolar disorder. *The Canadian Journal of Psychiatry*, *62*, 247–258.

Duffy, A., Goodday, S., Keown-Stoneman, C., & Grof, P. (2019). The emergent course of bipolar disorder: Observations over two decades from the Canadian high-risk offspring cohort. *American Journal of Psychiatry*, *176*, 720–729.

First, M.B., & Gibbon, M. (2004). The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) and the Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II). In *Comprehensive handbook of psychological assessment, Vol. 2: Personality assessment* (pp. 134–143). Hoboken, NJ: John Wiley & Sons.

Fox, C.R., & Gelfand, D.M. (1994). Maternal depressed mood and stress as related to vigilance, self-efficacy and mother-child interactions. *Early Development and Parenting*, *3*, 233–243.

Gerson, A.C., Gerring, J.P., Freund, L., Joshi, P.T., Capozzoli, J., Brady, K., & Denckla, M.B. (1996). The Children's affective lability scale: A psychometric evaluation of reliability. *Psychiatry Research*, *65*, 189–198.

Geselowitz, B., Whalen, D.J., Tillman, R., Barch, D.M., Luby, J.L., & Vogel, A. (2020). Preschool age predictors of adolescent borderline personality symptoms. *Journal of the American Academy of Child & Adolescent Psychiatry*, *59*, S260–S261.

Goff, D.C., Jr., Lloyd-Jones, D.M., Bennett, G., Coady, S., D'Agostino, R.B., Gibbons, R., … & Tomaselli, G.F. (2014). 2013 ACC/AHA guideline on the assessment of cardiovascular risk: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*, *129*(25 Suppl 2), S49–S73.

Goldstein, B.I., Strober, M., Axelson, D., Goldstein, T.R., Gill, M.K., Hower, H., … & Birmaher, B. (2013). Predictors of first-onset substance use disorders during the prospective course of bipolar spectrum disorders in adolescents. *Journal of the American Academy of Child & Adolescent Psychiatry*, *52*, 1026–1037.

Goldstein, T.R., Birmaher, B., Axelson, D., Goldstein, B.I., Gill, M.K., Esposito-Smythers, C., … & Keller, M. (2009). Psychosocial functioning among bipolar youth. *Journal of Affective Disorders*, *114*, 174–183.

Goldstein, T.R., Ha, W., Axelson, D.A., Goldstein, B.I., Liao, F., Gill, M.K., … & Birmaher, B. (2012). Predictors of prospectively examined suicide attempts among youth with bipolar disorder. *Archives of General Psychiatry*, *69*, 1113–1122.

Guyon-Harris, K., Huth-Bocks, A., Lauterbach, D., & Janisse, H. (2016). Trajectories of maternal depressive symptoms across the birth of a child: Associations with toddler emotional development. *Archives of Women's Mental Health*, *19*, 153–165.

Hafeman, D.M., Merranko, J., Axelson, D., Goldstein, B.I., Goldstein, T., Monk, K., … & Birmaher, B. (2016). Toward the definition of a bipolar Prodrome: Dimensional predictors of bipolar spectrum disorders in at-risk youths. *American Journal of Psychiatry*, *173*, 695–704.

Hafeman, D.M., Merranko, J., Goldstein, T.R., Axelson, D., Goldstein, B.I., Monk, K., … & Birmaher, B. (2017). Assessment of a person-level risk calculator to predict new-onset bipolar Spectrum disorder in youth at familial risk. *JAMA Psychiatry*, *74*, 841–847.

Harvey, P.D., Greenberg, B.R., & Serper, M.R. (1989). The affective lability scales: Development, reliability, and validity. *Journal of Clinical Psychology*, *45*, 786–793.

Hastie, T., Tibshirani, R., & Wainwright, M. (2015). *Statistical learning with sparsity*. New York: Chapman and Hall/CRC.

Henin, A., Biederman, J., Mick, E., Sachs, G.S., Hirshfeld-Becker, D.R., Siegel, R.S., … & Nierenberg, A.A. (2005). Psychopathology in the offspring of parents with bipolar disorder: A controlled study. *Biological Psychiatry*, *58*, 554–561.

Hollingshead, A.B. (1975). *Four-factor index of social status*. New Haven, CT: Yale University Department of Sociology.

Jin, J., Agarwala, N., Kundu, P., Harvey, B., Zhang, Y., Wallace, E., & Chatterjee, N. (2021). Individual and community-level risk for COVID-19 mortality in the United States. *Nature Medicine*, *27*, 264–269.

Kaufman, J., Birmaher, B., Brent, D., Rao, U., Flynn, C., Moreci, P., … & Ryan, N. (1997). Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): Initial reliability and validity data. *Journal of the American Academy of Child and Adolescent Psychiatry*, *36*, 980–988.

Levenson, J.C., Axelson, D.A., Merranko, J., Angulo, M., Goldstein, T.R., Mullin, B.C., … & Birmaher, B. (2015). Differences in sleep disturbances among offspring of parents with and without bipolar disorder: Association with conversion to bipolar disorder. *Bipolar Disorders*, *17*, 836–848.

Maoz, H., Goldstein, T., Axelson, D.A., Goldstein, B.I., Fan, J., Hickey, M.B., … & Birmaher, B. (2014). Dimensional psychopathology in preschool offspring of parents with bipolar disorder. *Journal of Child Psychology and Psychiatry*, *55*, 144–153.

Maoz, H., Goldstein, T., Goldstein, B.I., Axelson, D.A., Fan, J., Hickey, M.B., … & Birmaher, B. (2014). The effects of parental mood on reports of their Children's psychopathology. *Journal of the American Academy of Child and Adolescent Psychiatry*, *53*, 1111–1122.e1115.

Mesman, E., Nolen, W.A., Keijsers, L., & Hillegers, M.H.J. (2017). Baseline dimensional psychopathology and future mood disorder onset: Findings from the Dutch bipolar offspring study. *Acta Psychiatrica Scandinavica*, *136*, 201–209.

Pilowsky, D.J., Wickramaratne, P., Talati, A., Tang, M., Hughes, C.W., Garber, J., … & Weissman, M.M. (2008). Children of depressed mothers 1 year after the initiation of maternal treatment: Findings from the STAR*D-Child Study. *The American Journal of Psychiatry*, *165*, 1136–1147.

Sorcher, L.K., Goldstein, B.L., Finsaas, M.C., Carlson, G.A., Klein, D.N., & Dougherty, L.R. (2022). Preschool irritability predicts adolescent psychopathology and functional impairment: A 12-year prospective study. *Journal of the American Academy of Child & Adolescent Psychiatry*, *61*, 554–564.e551.

Sprafkin, J., Volpe, R.J., Gadow, K.D., Nolan, E.E., & Kelly, K. (2002). A DSM-IV-referenced screening instrument for preschool children: The Early Childhood Inventory-4. *Journal of the American Academy of Child and Adolescent Psychiatry*, *41*, 604–612.

Vogel, A.C., Jackson, J.J., Barch, D.M., Tillman, R., & Luby, J.L. (2019). Excitability and irritability in preschoolers predicts later psychopathology: The importance of positive and negative emotion dysregulation. *Development and Psychopathology*, *31*, 1067–1083.

Accepted for publication: 17 November 2022