Original Article

What differentiates children visiting outpatient mental health services with bipolar spectrum disorder from children with other psychiatric diagnoses?


Objectives: To determine the contribution of parent-reported manic symptoms, family history, stressful life events, and family environment in predicting diagnosis of bipolar spectrum disorders (BPSD) in youth presenting to an outpatient psychiatric clinic.

Methods: A total of 707 6- to 12-year-old children [621 with elevated symptoms of mania (ESM +) based on screening via the Parent General Behavior Inventory 10-item Mania Scale (PGBI-10M) and 86 without ESM (ESM–)] received a comprehensive assessment.

Results: Of the 629 with complete data, 24% (n = 148) had BPSD. Compared to those without BPSD (n = 481), children with BPSD: were older (Cohen’s $d = 0.44$) and more likely to be female (Cohen’s $d = 0.26$); had higher parent-endorsed manic symptom scores at screening (Cohen’s $d = 0.36$) and baseline (Cohen’s $d = 0.76$), more biological parents with a history of manic symptoms (Cohen’s $d = 0.48$), and greater parenting stress (Cohen’s $d = 0.19$). Discriminating variables, in order, were: baseline PGBI-10M scores, biological parent history of mania, parenting stress, and screening PGBI-10M scores. Absence of all these factors reduced risk of BPSD from 24% to 2%.

Conclusions: History of parental manic symptoms remains a robust predictor of BPSD in youth seeking outpatient care, even after accounting for parent report of manic symptoms in the child at screening. However, the risk factors identified as associated with BPSD, together had limited value in accurately identifying individual participants with BPSD, highlighting the need for careful clinical assessment.

Mary A Fristad a, Thomas W Frazier b, Eric A Youngstrom c, Katherine Mount a, Benjamin W Fields a, Christine Demeter d, Boris Birmaher e, Robert A Kowatch f, L Eugene Arnold g, David Axelson e, Mary Kay Gill e, Sarah McCue Horwitz h and Robert L Findling d

a Division of Child and Adolescent Psychiatry, Department of Psychiatry, Ohio State University, Columbus, OH. b Center for Pediatric Behavioral Health and Center for Autism, Cleveland Clinic, Cleveland, OH. c Department of Psychology, University of North Carolina at Chapel Hill, Chapel Hill, NC. d Division of Child and Adolescent Psychiatry, Department of Psychiatry, Case Western Reserve University, Cleveland, OH. e Department of Psychiatry, Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center, University of Pittsburgh, Pittsburgh, PA. f Division of Psychiatry, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH. g Department of Pediatrics and Stanford Health Policy, Stanford University School of Medicine, Stanford, CA, USA.


Key words: bipolar disorder – children – family environment – family history – high-risk – risk factors – stressful life events

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Corresponding author:
Mary A Fristad, Ph.D., ABPP
Department of Psychiatry
The Ohio State University
1670 Upham Drive, Suite 460G
Columbus
OH 43210
USA
Fax: 614-293-4949
E-mail: mary.fristad@osumc.edu
Childhood-onset bipolar spectrum disorders (BPSD) [bipolar I disorder (BP-I), bipolar II disorder (BP-II), cyclothymic disorder (CYC), and bipolar disorder not otherwise specified (BP-NOS)] are a major health concern for children and a significant challenge for clinicians to work with effectively. A family history of bipolar disorder is well established as one risk factor for developing BPSD (1–6). Offspring of two parents with bipolar disorder are at significant risk [odds ratio (OR) = 13.4] for developing BPSD, as are those having one parent with bipolar disorder (OR = 3.6) (7). Other studies have reported that approximately half the offspring of parents with bipolar disorder meet criteria for at least one psychiatric disorder, with bipolar diagnoses ranging between 14% and 50% (8, 9). Geller et al. (10) reported that one-third of her sample of children with major depressive disorder (MDD) developed BP-I; converters were six times as likely to have a family history of major affective disorder. In a 10-year follow-up, approximately half had a bipolar diagnosis, and a family history of mania predicted BP-I (11). Romero et al. (12) compared families with and without a parent with bipolar disorder and found that the majority (71%) of those with a parent with bipolar disorder had at least one child with a mood disorder (compared to 3.7% for the healthy-parent families). In addition to genetics, recent research suggests that family environment and stressful life events may also be important predictors (13).

**Family environment**

Family factors can be risk factors for an individual prone to bipolar disorder, and mood instability can impact family life (14). In adults with bipolar disorder, family climate and expressed emotion [(EE); a term that reflects high levels of criticism, hostility and/or emotional over-involvement] in relatives predict both relapse (15) and a more severe course of illness (16). Butzlaff and Hooley (15) reported that patients with high-EE relatives were at a greater risk of relapse over a 9- to 12-month period than patients with low-EE relatives. Similarly, Miklowitz et al. (16) found that distress in adults with bipolar disorder in response to their relatives' criticisms predicted depression and mania and proportion of days sick over 1 year. Kim and Miklowitz (17) reported that patients with high-EE relatives had higher levels of mania and depression at 2-year follow-up; however, high EE in relatives did not contribute to increased risk of relapse.

A child’s family environment may impact the onset of bipolar disorder (2). Families of children diagnosed with BPSD compared to healthy controls have lower Family Environment Scale scores for cohesion, expressiveness, intellectual-cultural orientation, and active-recreational orientation, and higher conflict scores (18). Furthermore, 86% of the group with BPSD had one or more first- or second-degree relatives with a mood disorder; cohesion and organization subscale scores were significantly lower in these families. Geller et al. (19) compared parent–child relations in families of children with bipolar disorder versus attention-deficit hyperactivity disorder (ADHD) versus no psychiatric condition. Families of children with bipolar disorder had greater impairment in parent–child relations and lower maternal–child warmth. Low maternal warmth contributed to a higher rate of relapse for youth with bipolar disorder (19). Poorer family functioning is also associated with higher levels of suicidality in youths with bipolar disorder (20). However, the impact of maternal warmth separate from a family history of mood instability was not examined in that report. Finally, family conflict has been demonstrated to moderate medication treatment response in youth with BPSD (21).

**Stressful life events**

Stressful life events predict both risk of relapse (22) and time to recovery (23) in adults with bipolar disorder. Stressful life events trigger depressive but not manic symptoms (24). Johnson and McMurray (25) reported that stressful life events are associated with development of bipolar disorder in children and adolescents; life stress can predict mood symptom onset in children at risk and correlates with ongoing symptoms in adolescents already diagnosed. At high stress levels, children of depressed mothers were significantly more depressed than children without depressed mothers (26). Moderate to severe interpersonal stress is more common (OR = 3.9) in offspring of parents with bipolar disorder than in comparison youth and young adults aged 13–26 (27).

In a 14-month follow-up, Reichart et al. (28) found that 33% of offspring of parents with bipolar disorder were diagnosed with a lifetime mood disorder; 4% with bipolar disorder. Within this sample, Wals et al. (29) investigated the association between person-independent and person-dependent stressful life events and first-onset or recurrence of a mood disorder. Person-dependent stressful life events were significantly associated with onset of a mood episode; first onsets were more likely than recurrences to be preceded by stressful life events.
Purpose of this study

Given that several factors—including family history of bipolar disorder, family environment and stressful life events—play important but not exclusive roles in predicting the diagnosis of BPSD in youth, this study examines the relative contribution of family history, family environment and stressful life events in predicting which youth seeking outpatient care will have a diagnosis of BPSD. The following hypotheses were tested:

(i) History of manic symptoms in biological parents will be a robust predictor of BPSD, even after accounting for current parent-reported manic symptoms in the child; and
(ii) Stressful life events and family environment each will provide a small but meaningful increase in predicting BPSD after accounting for current symptoms and family history.

Materials and methods

Procedures

Institutional Review Boards at each of the four Longitudinal Assessment of Manic Symptoms (LAMS) sites (Case Western Reserve University, Cincinnati Children's Hospital Medical Center, the Ohio State University, and the University of Pittsburgh Medical Center/Western Psychiatric Institute and Clinic) approved all protocol procedures. A two-phase study design was utilized, as described below.

Participant ascertainment

Screening. The source population consisted of all eligible patients aged between 6 and 12 years visiting nine child outpatient mental health clinics (two in Cleveland, one in Cincinnati, five in Columbus, and one in Pittsburgh) associated with universities in the LAMS study. Exclusion criteria included: (i) a prior clinic visit within the preceding year, (ii) not being accompanied by a parent or legal guardian, (iii) having a parent who did not understand or speak English, and (iv) having a sibling or other child living in their household who had already participated in LAMS screening (30).

Adults accompanying eligible children were approached and voluntarily provided written informed consent for participation in the screening portion of the study. Parents/guardians completed the Parent General Behavior Inventory 10-item Mania Scale (PGBI-10M) (31, 32) to screen for elevated symptoms of mania (ESM). Items comprising the PGBI-10M describe hypomanic, manic, and biphasic symptoms and have been reported to discriminate BPSD in youth from other diagnoses (32). Items are scored from 0 (never or hardly ever) to 3 (very often or almost constantly); total scores range from 0 to 30, with higher scores indicating greater symptoms.

Longitudinal study. Each patient whose parent/guardian rated the child ≥ 12 (ESM+) on the screening PGBI-10M was invited to participate in the longitudinal portion of the LAMS study. A smaller comparison group of patients who scored 11 or lower (ESM–) matched on age, sex, race, ethnicity, and Medicaid status was also selected. Of a total of 1124 children who screened ESM+, 621 or 55% accepted the invitation. There were no sociodemographic differences between children/families agreeing to enroll in the longitudinal study and those who did not. The mean time interval between screening and baseline assessment was 45.5 [standard deviation (SD) = 41.4] days. ESM– children were selected from the available pool to match on age (± 2 years), sex, race/ethnicity and insurance status; 86 children without ESM (ESM–) were included in the longitudinal cohort (30). It was anticipated that some, but not all children who were ESM+ would receive diagnoses of a BPSD upon completion of the baseline assessment described below.

Baseline assessment

Demographics. Information including age, sex, race, ethnicity, and health insurance status was obtained from parents/guardians.

Diagnoses. Children and their guardians were administered the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Episode (K-SADS-PL) (33) with additional depression and manic symptom items derived from the Washington University Kiddie Schedule for Affective Disorders (WASH-U K-SADS) (34, 35). Items assessing nonverbal communication, the child’s relationship with others, shared enjoyment, and social-emotional reciprocity according to DSM-IV criteria were added to the KSADS-PL to screen for pervasive developmental disorders (PDDs). The resulting instrument, the K-SADS-PL-W, is a semi-structured interview that assesses current and lifetime psychiatric diagnoses and time course of each illness. In this report, only current diagnoses at baseline assessment are presented.

Unmodified DSM-IV diagnostic criteria were used. Criteria for BP-NOS were clarified to follow those criteria used in the Course and Outcome of Risk factors: bipolar disorder in youth
Bipolar Youth (COBY) study (36) and were operationalized as follows: (i) elated mood plus two associated symptoms of mania (e.g., grandiosity, decreased need for sleep, pressured speech, racing thoughts, and increased goal-directed activity), or irritable mood plus three associated symptoms of mania; (ii) change in the participant’s level of functioning (increase or decrease); (iii) symptoms must be present for ≥ 4 hours within a 24-hour period; and (iv) the participant must have had ≥ 4 such episodes, or a total of four days of the above-noted symptom intensity in his/her lifetime. All diagnoses were reviewed and confirmed by a licensed child psychiatrist or psychologist.

Parent report of manic symptoms. The PGBI-10M, on which the parent reports on the child’s symptoms, was repeated at baseline.

Family history. The Family History Screen (FHS) (37, 38) collected information on 15 proxy psychiatric disorders and suicidal behavior in biological parents. In this study, symptoms of DSM-IV-TR defined mania were evaluated. Individuals were considered positive for a parental history of mania (PHM) if one (score = 0.5) or both (score = 1.0) parents endorsed yes for ‘elated mood’ plus three supporting symptoms (extreme or non-extreme more talkative, inflated self-esteem, decreased need for sleep, racing thoughts, distractible, restless, and excessive involvement in pleasurable activities) or yes for ‘extreme irritability’ plus four supporting symptoms. In cases where there were missing data, if enough symptoms were known to meet the above criteria, the parent was scored positively. If the parent could not meet criteria even if missing symptoms were available (e.g., if neither extreme elated mood nor extreme irritable mood was endorsed), the parent was scored negatively. If there was uncertainty regarding whether or not a parent would or would not meet criteria if missing symptoms were known, the parent was scored as unknown and that child was not included in this sample. This proxy diagnosis ensures sufficient symptoms for a diagnosis of bipolar disorder, although it does not verify sufficient duration, impairment, or episodicity. Thus, the conservative term ‘parental history of mania’ is used to describe this variable.

Family environment. The Parent Stress Survey (PSS) (39) was used to assess parental stress related to raising a psychiatrically impaired child. The PSS is a 25-item parent self-report instrument; each item has a yes or no response to document occurrence of the event, followed by a Likert-type scale, with response choices ranging from 0 (not at all stressful) to 4 (very stressful), to measure the severity of stress experienced. The total score is the sum of the 25 Likert-type items and ranges from 0 (no stress) to 100 (high stress). The questionnaire has a coefficient alpha of 0.87 (40).

Stressful life events. The Stressful Life Events Schedule (SLES) (41) collected information on occurrence, date of occurrence, duration, and perceived threat of events experienced by the youth. The SLES also allows for the determination of whether an event was independent or dependent of behaviors of the child or adolescent. The SLES has shown good test–retest reliability (κ = 0.68).

Interviewer training and inter-rater reliability

Before conducting interviews, interviewers completed formal training, rated taped or live interviews, then were observed. To prevent post-training rater drift, all interviewers rated taped administrations of the K-SADS-PL-W taped at each site throughout the course of the study. Kappas were: 0.82 for K-SADS-PL-W psychiatric diagnoses in general and 0.93 for bipolar diagnoses in particular, indicating high levels of diagnostic agreement (42).

Statistical analyses

Descriptive statistics and relative risk. Prior to examining hypotheses, descriptive statistics (means and standard deviations) and independent samples t-tests compared each of the five main predictors: (i) screening PGBI-10M, (ii) baseline PGBI-10M, (iii) PHM, (iv) PSS, and (v) SLES for participants with versus without BPSD. To provide the predictive value of each variable independent of other predictors, scores were dichotomized and relative risk estimates were computed: (i) screening PGBI-10M < or 0; (ii) baseline PGBI-10M < or 0; (iii) any versus no biological parent family history of mania (PHM); (iv) PSS < or 9; and (v) SLES < or 8.5. As the PSS and SLES do not have well-established cut scores, these scores were chosen based on median splits to provide a rough examination of predictive value, with the understanding this might underestimate predictive value. Relative risk values estimate the risk of BPSD in the absence of other factors and can be helpful for situations in which clinical data are incomplete. Categorical measures also tend to be easier for clinicians to interpret. However, artificially...
dichotomized measures may have decreased predictive power (43).

**Hypothesis testing.** To examine the hypotheses, two hierarchical logistic regressions used BPSD diagnosis of the child as the dichotomous dependent variable (criterion). In the first iteration, screening PGBI-10M scores were entered in step 1, baseline PGBI-10M scores in step 2, PHM in step 3, PSS in step 4, and SLES in step 5. The importance of PHM (Hypothesis 1) was examined by comparing increments in $R^2$ from step 2 to step 3. The second iteration of the regression switched order of input for stressful life events and family environment to examine incremental validity of each predictor in the absence of the other. Relative importance of stressful life events and family environment (Hypothesis 2) was evaluated by comparing increments in $R^2$ between step 3 and step 5 for the first and second iterations of the regression equation. Significant and meaningful increments at both steps would support the assertion that both stressful life events and family environment are important predictors of BPSD diagnosis. A significant ($p < 0.05$) and meaningful ($\Delta R^2 \geq 0.03$) increment in prediction was required to consider the hypothesis supported. Continuous measures were included in these regressions to maximize predictive accuracy for each measure.

**Results**

**Sample description**

Of 707 individuals enrolled in LAMS (621 with ESM+ and 86 ESM-), 692 had screening and baseline PGBI-10M scores as well as clinical diagnoses at baseline. Of these, 629 youth [148 with BPSD (24%), and 481 with no BPSD (76%)] had assessed history of manic symptoms for both biological parents as well as completed PSS and SLES measures. Nearly one-quarter (23.5%) of the 629 youth with complete data had a BPSD: 64 (10.2%) had BP-I, three (0.5%) had BP-II, 10 (1.6%) had CYC, and 71 (11.3%) had BP-NOS. Table 1 presents demographic characteristics for individuals with and without a diagnosis of BPSD.

Individuals with BPSD were older (Cohen's $d = 0.44$) and more likely to be female (Cohen's $d = 0.26$). Thus, additional post-hoc analyses were conducted for boys versus girls and younger (i.e., 6–8 year old) versus older (i.e., 9–12 year old) children. There were no significant differences in race, ethnicity, or insurance status (largest Cohen's $d = 0.13$).

**Risk factors**

**Descriptive and inferential statistics and relative risk.** Table 2 presents descriptive and inferential statistics and relative risk for the five predictors. As

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<th>Table 1. Demographic characteristics for individuals with and without a BPSD</th>
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<td>Age, mean (SD) at screening</td>
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For *Race* and *Insurance* status, Cohen's $d$ was calculated comparing White and all remaining races and any Medicaid and all remaining insurances.

ADHD = attention-deficit hyperactivity disorder; BPSD = bipolar spectrum disorder; SD = standard deviation.
expected, children with BPSD consistently showed higher mania symptom levels at screening and baseline. BPSD was also associated with a significantly greater proportion of biological parents with a history of mania, significantly greater parenting stress, and marginally significantly greater frequency of stressful life events. After baseline PGBI-10M scores, the next most discriminating variables were biological parent’s history of mania, then parenting stress, followed by screening PGBI-10M scores. Not surprisingly, dichotomizing the measures reduced these effects. Relative risk values demonstrate substantially increased risk from elevated symptoms of mania at screening and baseline. The value and confidence interval for the screening PGBI-10M score is larger than for the baseline PGBI-10M score due to a very small proportion of BPSD cases with low screening PGBI-10M scores (only five cases < 12; this smaller n leads to a larger standard error). Risk values were also substantial for family history and parent stress.

Logistic regression analyses. Table 3 presents results of iterative hierarchical logistic regressions predicting presence versus absence of BPSD. These regressions provided marginal support for Hypothesis 1. Specifically, PHM significantly increased prediction of child BPSD (p = 0.001); however, the increase in variance was marginal ($\Delta R^2 = 0.024$) and did not meet the a priori criteria (> 0.03) for determining a meaningful increment. Additionally, classification accuracy increased minimally (76.5% prior to and 76.9% following the addition of PHM). Results provided only weak support for Hypothesis 2. PSS scores significantly increased prediction in both iterations.
of the regression, but did not provide a meaningful increment in variance ($\Delta R^2 = 0.012$ and 0.014). SLES scores did not significantly increase prediction in either iteration of the regression (smallest $p = 0.307$). The overall classification accuracy of the logistic regression equation including predictors was 77.6%. It should be noted this is an unweighted accuracy value, as logistic regression capitalizes on the modest base rate of BPSD (24% of all cases included in the regression) by over-predicting absence of BPSD. Logistic regression does not attempt to balance sensitivity and positive predictive value (PPV). The result is excellent specificity (0.96) but very low sensitivity (0.18).

**Accounting for demographic differences.** Differences in age and sex across BPSD and no-BPSD youth (Table 1) suggested that accounting for demographic factors might improve prediction. For this reason, logistic regression analyses were repeated after dichotomizing on sex and age (6–12) to determine whether predictors might differentially influence demographic subgroups (Table 4).

Recomputed logistic regression analyses indicated that predictors have somewhat different effects across subsamples. Baseline PGBI-10M scores were significant predictors for both boys ($\Delta R^2 = 0.09, p < 0.0005$) and girls ($\Delta R^2 = 0.14, p < 0.0005$). However, in females, who comprised 31% of the sample ($n = 195$), PHM did not add to prediction of BPSD ($\Delta R^2 < 0.001, p = 0.829$) but PSS scores did ($\Delta R^2 = 0.03, p = 0.041$). Of note, the difference in $\Delta R^2$ between boys and girls for PSS was marginal (0.01 for boys, and 0.03 for girls). Findings in males paralleled those of the entire sample. PHM made a significant and meaningful contribution ($\Delta R^2 = 0.053, p < 0.001$) to the prediction of BPSD while PSS scores did not ($\Delta R^2 = 0.007, p = 0.145$).

Similarly, when younger ($n = 314$) versus older ($n = 315$) children were compared, baseline PGBI-10M scores and family history scores were significant predictors for both younger and older children (baseline PGBI-10M: younger, $\Delta R^2 = 0.09, p < 0.0005$ and older, $\Delta R^2 = 0.11, p < 0.0005$; family history, younger, $\Delta R^2 = 0.03, p = 0.008$ and older, $\Delta R^2 = 0.02, p = 0.036$). As in the full sample, parenting stress was not a significant predictor for the younger children ($\Delta R^2 < 0.01, p = 0.235$), but it approached significance for the older children ($\Delta R^2 = 0.02, p = 0.053$). However, as with the findings for boys and girls, the difference in $\Delta R^2$ between younger and older children for PSS was not clinically meaningful (0.01 for younger children, and 0.02 for older children).

**Discussion**

**Base rates and risk factors**

Approximately one-quarter of this sample seeking outpatient services, which was enriched with youth screening positive for potential manic symptoms,
had a BPSD at baseline. When all measured risk factors (i.e., high scores on screen and baseline PGBI-10M, positive parental history for mania, and high scores on parental stress and stressful life events measures) were absent, rate of diagnosis was very low (2%). As risk factors were added, the likelihood of BPSD diagnosis increased. Rates nearly doubled if two risk factors were present, either high scores on both screening and baseline PGBI-10M or a high screening score on the PGBI-10M coupled with a positive parental history for mania. However, no combination of risk factors elevated risk over 50%. Relative risk appeared to plateau as additional predictors were added. Remarkably, even repeated elevations on a measure of manic symptoms did not increase the probability of BPSD above 50% in this clinical population. This may result from considerable sharing of symptoms between BPSD and other DSM disorders and underscores the need for comprehensive diagnostic evaluation.

Stressful life events were not a robust predictor of BPSD. The one exception to this was for children whose other three risk factors were negative (i.e., low screening and baseline scores on the PGBI-10M, and a negative parental history for mania). In that case, the probability of BPSD in the child quadrupled, from 2% to 8%, but remained well below the sample base rate of 24%.

The role of screening versus baseline PGBI-10M scores

Screening PGBI-10M scores were less discriminating than baseline scores. Screening scores may be more influenced by non-specific factors such as general distress or parents’ desire to gain assistance for their child. Alternatively, perhaps baseline scores were more accurate merely because they were nearer chronologically to the diagnostic assessment. Regardless, failure of the PGBI-10M at either time to correctly classify the majority of children highlights the limitations of using paper-and-pencil measures. Such instruments will not be sufficient to ‘make a diagnosis’ in settings where the target of interest is uncommon. At present, diagnosis of BPSD can only be made by obtaining thorough clinician-filtered information to clarify persistence of manic symptoms in the often complex evaluation of BPSD in youth, and it remains a challenging endeavor fraught with low agreement (44).

Demographic differences

Several differences in risk factors between younger and older children and between boys and girls had trivial differences in the percent of variance accounted for. Only one finding, parent history of mania, resulted in a notable difference between boys and girls. A family history of mania in the biological parents accounted for a 5% increase in prediction for boys, but < 1% (nonsignificant) prediction for girls. This finding requires replication before implications are drawn, as less than a third of the sample was female and of those, less than a quarter had BPSD.

Limitations

Most notably, even with the best combination of risk factors, rates of BPSD did not exceed 50%. While this study carefully examined the a priori variables expected to aid diagnostic accuracy, further investigation of additional variables is clearly needed to develop better diagnostic guidelines. One purpose of the LAMS study is to track potential predictors and new diagnoses over time.

Another limitation, inherent to any study of BPSD in youth, is the lack of a gold standard for diagnosis. This study utilized the K-SADS supplemented by additional questions from the WASH-U K-SADS to provide a more thorough coverage of depressive and manic symptoms. While this is considered the best available method, it does not fully resolve ongoing concerns in the field about diagnosing mania in children.

Conclusions

History of parental mania is a robust predictor of BPSD in high-risk youth. Parental stress predicted BPSD for older (i.e., 9–12) but not younger (i.e., 6–8) children, and for girls more than boys. Predictor models were limited, demonstrating the need for careful clinical assessment and for the need to follow high-risk youth longitudinally to identify other key factors to develop more accurate diagnostic predictors and other guidelines.

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