The Child Behavior Checklist-Pediatric Bipolar Disorder Profile Predicts a Subsequent Diagnosis of Bipolar Disorder and Associated Impairments in ADHD Youth Growing Up: A Longitudinal Analysis

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Objective: To examine the predictive utility of the Child Behavior Checklist-Pediatric Bipolar Disorder (CBCL-PBD) profile to help identify children at risk for bipolar disorder.

Method: Subjects were ascertained from 2 identically designed longitudinal case-control family studies of subjects (males and females aged 6–18 years) with *DSM-III-R* attention-deficit/hyperactivity disorder (ADHD). Based on data from the baseline assessment, ADHD subjects without a lifetime diagnosis of bipolar disorder were stratified by the presence (CBCL-PBD positive, N = 28) or absence (CBCL-PBD negative, N = 176) of a CBCL-PBD score ≥ 210 (total of attention, aggression, and anxious/depressed subscales). Subjects were comprehensively assessed at follow-up with structured psychiatric interviews. Data were collected from April 1988 to February 2003.

Results: Over a mean follow-up period of 7.4 years, a positive CBCL-PBD score predicted subsequent diagnoses of bipolar disorder, major depressive disorder, and conduct disorder, as well as impaired psychosocial functioning and higher risk for psychiatric hospitalization.

Conclusions: This work suggests that a positive CBCL-PBD score based on elevations on the attention problems, aggressive behavior, and anxious/depressed subscales predicts subsequent pediatric bipolar disorder and associated syndrome-congruent impairments. If confirmed in other studies, the CBCL-PBD score has the potential to help identify children at high risk to develop bipolar disorder.

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The proper diagnostic approach to pediatric bipolar disorder continues to be the focus of debate.[1–11] Although the *DSM-IV* provides explicit criteria for bipolar disorder in adults, disagreement remains as to how best apply these criteria to children and adolescents.[2,12–15]

Because the empirically derived Child Behavior Checklist (CBCL)[16] is a questionnaire that does not require clinician administration, it is less likely to be affected by clinical traditions, interviewer training, or clinical interpretations. Thus, our group and others have suggested that the CBCL could offer an unbiased approach for screening complicated cases of suspected bipolar disorder.[17–20] Several groups have shown that children with a deviant profile on the CBCL's attention problems, aggressive behavior, and anxious-depressed subscales are likely to meet criteria for *DSM* bipolar I disorder in both epidemiologic and clinical samples.[16,20–24] This profile has been referred to as the CBCL-Pediatric Bipolar Disorder (CBCL-PBD) profile.[20]

Faraone et al[18] evaluated the diagnostic efficiency of the CBCL-PBD profile in youth with attention-deficit/hyperactivity disorder (ADHD). They found that the CBCL-PBD profile allowed for the determination of both lifetime and current diagnoses of bipolar disorder in ADHD youth and their siblings. In a recent set of studies, Hudziak et al[19] used a general population sample of over 21,000 twins to assess the validity of the CBCL-PBD

profile. The CBCL-PBD profile was highly heritable and had a population prevalence consistent with epidemiologic studies of bipolar disorder (~1%) of boys and girls.[25] However, since some investigators failed to find meaningful associations between the CBCL-PBD profile and a diagnosis of pediatric bipolar disorder,[26,27] additional research on the subject is needed.

One approach to further investigate the utility of the CBCL-PBD profile is to evaluate its predictive utility. Such findings may help clinicians in the community focus scarce resources toward children at very high risk for compromised outcomes. Being able to predict a subsequent diagnosis of pediatric bipolar disorder could translate into improved recognition and therapeutics in children at risk for a very serious psychiatric disorder. To date, only 1 study has investigated the long-term outcomes of youth with the CBCL-PBD phenotype. In a longitudinal high-risk study, Meyer and colleagues[28] found that the CBCL-PBD phenotype was associated with increased risk for bipolar disorder, anxiety disorders, ADHD, psychosocial impairment, and suicidal thoughts and behaviors.

The main purpose of the present work was to evaluate the predictive utility of the CBCL-PBD profile. To this end, we used data from 2 large longitudinal studies of psychiatrically and pediatrically referred males and females with ADHD without a diagnosis of bipolar disorder at baseline.[29,30] We hypothesized that the CBCL-PBD profile would predict a subsequent diagnosis of bipolar disorder in ADHD youth. Since pediatric bipolar disorder has been associated with high rates of major depressive disorder, conduct disorder, and psychiatric hospitalization,[31–33] we also predicted that the CBCL-PBD profile would be associated with these compromised outcomes.

METHOD

Subjects

Detailed study methodology has been previously described.[29,30,34,35] Briefly, subjects were derived from 2 identically designed longitudinal case-control family studies of ADHD. These studies recruited male and female subjects aged 6 to 18 years with (n = 140 males, n = 140 females) and without (n = 120 males, n = 122 females) *DSM-III-R* ADHD ascertained from pediatric and psychiatric clinics. Male subjects were assessed at baseline and at 1-, 4-, and 10-year follow-ups, while female subjects were assessed at baseline and at 5-year follow-up. Potential subjects were excluded if they had been adopted or if their nuclear family was not available for study. We also excluded potential subjects if they had major sensorimotor handicaps (paralysis, deafness, blindness), psychosis, autism, inadequate command of the English language, or a full-scale IQ less than 80. Data were collected from April 1988 to February 2003.

Parents and adult offspring provided written informed consent to participate, and parents also provided consent for offspring under the age of 18 years. Children and adolescents provided written assent to participate. The human research committee at Massachusetts General Hospital, Boston, Mass, approved this study.

Psychiatric assessments of probands younger than 18 years of age relied on the epidemiologic version of the Schedule for Affective Disorder and Schizophrenia for School-Age Children Epidemiologic Version (K-SADS-E).[36,37] Subjects 18 years of age and older were assessed with the Structured Clinical Interview for DSM-III-R[38] and DSM-IV Axis I Disorders[39] (supplemented with modules from the K-SADS-E to assess childhood diagnoses). Diagnoses for this analysis were considered positive if full criteria were met within the past year of the assessment. We interviewed the mothers of all subjects and directly interviewed subjects older than 12 years. We combined data from direct and indirect interviews by considering a diagnostic criterion positive if it was endorsed in either interview. Mothers and children were assessed by interviewers blind to all previous information about the child and family.

The interviewers had undergraduate degrees in psychology and were extensively trained. Based on 500 assessments from interviews of children and adults, the median κ coefficient for diagnoses was 0.98. The κ coefficients for individual diagnoses included ADHD (0.88), conduct disorder (1.0), major depressive disorder (1.0), mania (0.95), separation anxiety (1.0), agoraphobia (1.0), panic disorder (0.95), and substance use disorder (1.0). We considered a disorder positive if DSM diagnostic criteria were unequivocally met.

A committee of board-certified child and adult psychiatrists who were blind to the subject's ADHD status, referral source, and all other data resolved diagnostic uncertainties. Diagnoses presented for review were considered positive only when the committee determined that diagnostic criteria were met to a clinically meaningful degree. We estimated the reliability of the diagnostic review process by computing κ coefficients of agreement for clinician reviewers. For these diagnoses, the median reliability between individual clinicians and the review committee–assigned diagnoses was 0.87. The κ coefficients for individual diagnoses included ADHD (1.0), conduct disorder (1.0), major depressive disorder (1.0), mania (0.78), separation anxiety (0.89), agoraphobia (0.80), panic disorder (0.77), and substance use disorder (1.0).

All assessment personnel were blind to proband diagnosis (ADHD or control) and ascertainment site (psychiatric or pediatric). The diagnosis of major depressive disorder was made only if the depressive episode was associated with severe impairment.[40,41] Since there are many anxiety disorders measured by our structured interviews, we aggregated them into a binary measure coded positive

Table 1. Demographics of Subjects With Attention-Deficit/Hyperactivity Disorder

Demographic	CBCL-PBD Negative (N = 176)	CBCL-PBD Positive (N = 28)	Test Statistic	*P*
Age at baseline, mean ± SD, y	10.9 ± 3.1	10.4 ± 2.9	$t = 0.88$, $df = 202$	.38
Age at last assessment, mean ± SD, y	18.7 ± 4.5	17.9 ± 4.3	$t = 0.83$, $df = 202$	.41
Gender (male), N (%)	101 (57)	16 (57)	$\chi^2 = 0.00$, $df = 1$	.98
Socioeconomic status, mean ± SD	1.8 ± 0.9	2.3 ± 1.0	z = 2.62	.009
Intact family, N (%)	134 (76)	21 (75)	$\chi^2 = 0.00$, $df = 1$	.98
Psychiatric ascertainment source, N (%)	85 (48)	14 (50)	$\chi^2 = 0.03$, $df = 1$	.87

Abbreviation: CBCL-PBD = Child Behavior Checklist Pediatric Bipolar Disorder.

Table 2. One-Year Prevalence of Psychiatric Disorders at Baseline Among Subjects With Attention-Deficit/Hyperactivity Disorder

Psychiatric Disorder	CBCL-PBD Negative (N = 176), N (%)	CBCL-PBD Positive (N = 28), N (%)	Test Statistic	*P*
Subthreshold bipolar disorder	5 (3)	3 (11)	z = 1.56	.12
Major depressive disorder	20 (11)	9 (32)	z = 2.32	.02
Multiple (≥ 2) anxiety disorders	39 (22)	10 (36)	z = 1.27	.20
Oppositional defiant disorder	72 (41)	24 (86)	z = 3.90	< .001
Conduct disorder	12 (7)	8 (29)	z = 3.10	.002

Abbreviation: CBCL-PBD = Child Behavior Checklist Pediatric Bipolar Disorder.

if 2 or more anxiety disorders were endorsed and negative otherwise. Two or more anxiety disorders previously provided a reasonable trade-off between case identification and the false-positive rate when compared against an independently defined "anxiety standard" in youth with ADHD.[42] Psychoactive substance use disorder was defined as any alcohol abuse, alcohol dependence, substance abuse, or substance dependence.

Psychosocial functioning was assessed using the Global Assessment of Functioning (GAF) scale [43] and the Social Adjustment Inventory for Children and Adolescents (SAICA).[44] Socioeconomic status was measured using the 5-point Hollingshead scale.[45] At baseline, mothers completed the CBCL.[16]

Statistical Analysis

The CBCL-PBD score was defined as positive if the sum of the CBCL subscales attention problems, aggressive behavior, and anxious-depressed was greater than or equal to 210. This cutoff was previously shown to maximize the sensitivity (92%), specificity (93%), positive predictive power (27%), and negative predictive power (100%) when predicting a current diagnosis of bipolar disorder in children with ADHD.[18] We compared ADHD probands with and without a positive CBCL-PBD score on baseline demographic characteristics using *t* tests, Pearson's χ^2, or Wilcoxon rank sum tests. Subjects with a diagnosis of bipolar disorder at baseline were excluded from all analyses. The 1-year prevalences of baseline psychiatric disorders were compared using logistic regression controlling for demographic confounders. Binary outcome variables at follow-up were tested using Cox proportional hazards models, for which the failure event was a diagnosis of the disorder in the past year and the failure time was the age at assessment. Subjects who were diagnosed with a disorder in the year prior to the baseline assessment were excluded from analyses predicting that disorder at follow-up. Linear growth curves (multilevel mixed-effects linear regression) were used to test the GAF and SAICA across all assessments. All tests were 2-tailed with an α set at .05.

RESULTS

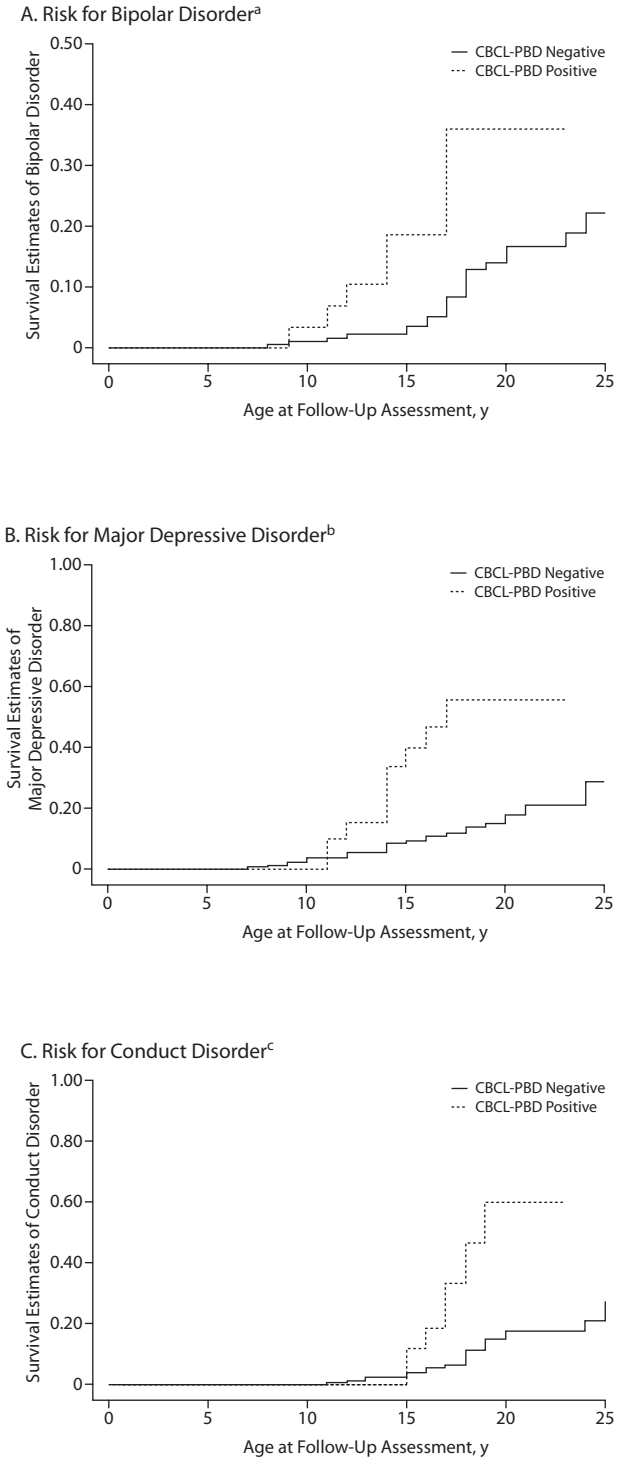
Of 280 probands with ADHD at baseline, 242 had CBCL data. Of these 242 subjects, 22 were dropped from the study because they were diagnosed with bipolar disorder at baseline. Of the remaining 220 subjects, 204 (117 males, 87 females) had follow-up data. The mean time from baseline to the last assessment was 7.4 years (SD = 3.4 years).

The ADHD subjects were stratified based on the presence or absence of a CBCL-PBD score ≥ 210 at baseline, and comparisons were made between ADHD subjects with a positive (CBCL-PBD positive, N = 28) and negative (CBCL-PBD negative, N = 176) score. Of the pool of 220 subjects at baseline with CBCL data and without a diagnosis of bipolar disorder, a higher percentage of boys had follow-up data (117/120, 97%) compared to girls (87/100, 87%, *P* = .003). Subjects assessed at follow-up (N = 204) did not significantly differ from subjects lost to follow-up (N = 16) on age at baseline (*P* = .35), socioeconomic status (*P* = .40), ascertainment source (*P* = .55), or baseline CBCL-PBD score (*P* = .47).

Sociodemographic Characteristics

There were no differences between groups on age at baseline, age at last assessment, gender, family intactness,

Figure 1. Risk for Mood and Conduct Disorders by CBCL-PBD Score



[a]Hazard ratio = 2.5, 95% CI = 1.1 to 5.7, $P = .04$.
[b]Hazard ratio = 4.2, 95% CI = 1.9 to 9.2, $P < .001$.
[c]Hazard ratio = 3.6, 95% CI = 1.4 to 9.2, $P = .006$.
Abbreviation: CBCL-PBD = Child Behavior Checklist-Pediatric Bipolar Disorder.

or ascertainment source. However, the CBCL-PBD positive group had a lower socioeconomic status (ie, higher Hollingshead score) compared to the CBCL-PBD negative group (Table 1). Therefore, we controlled for socioeconomic status in all subsequent analyses.

As shown in Table 2, at baseline, the CBCL-PBD positive group had significantly higher rates of major depressive disorder, oppositional defiant disorder, and conduct disorder compared to the CBCL-PBD negative group (Table 2).

Longitudinal Risk for Psychopathology

As shown in Figure 1, by age 25 years, ADHD subjects with a CBCL-PBD positive score had a significantly increased risk for bipolar disorder (36% vs 22%, $P = .04$), major depressive disorder (56% vs 29%, $P < .001$), and conduct disorder (60% vs 27%, $P = .006$) compared to subjects with a CBCL-PBD negative score. In contrast, the risks for developing multiple (≥ 2) anxiety disorders, oppositional defiant disorder, psychoactive substance use disorder, and smoking at follow-up were not significantly different between the 2 groups (all $P > .10$, Figure 2).

Psychosocial Functioning

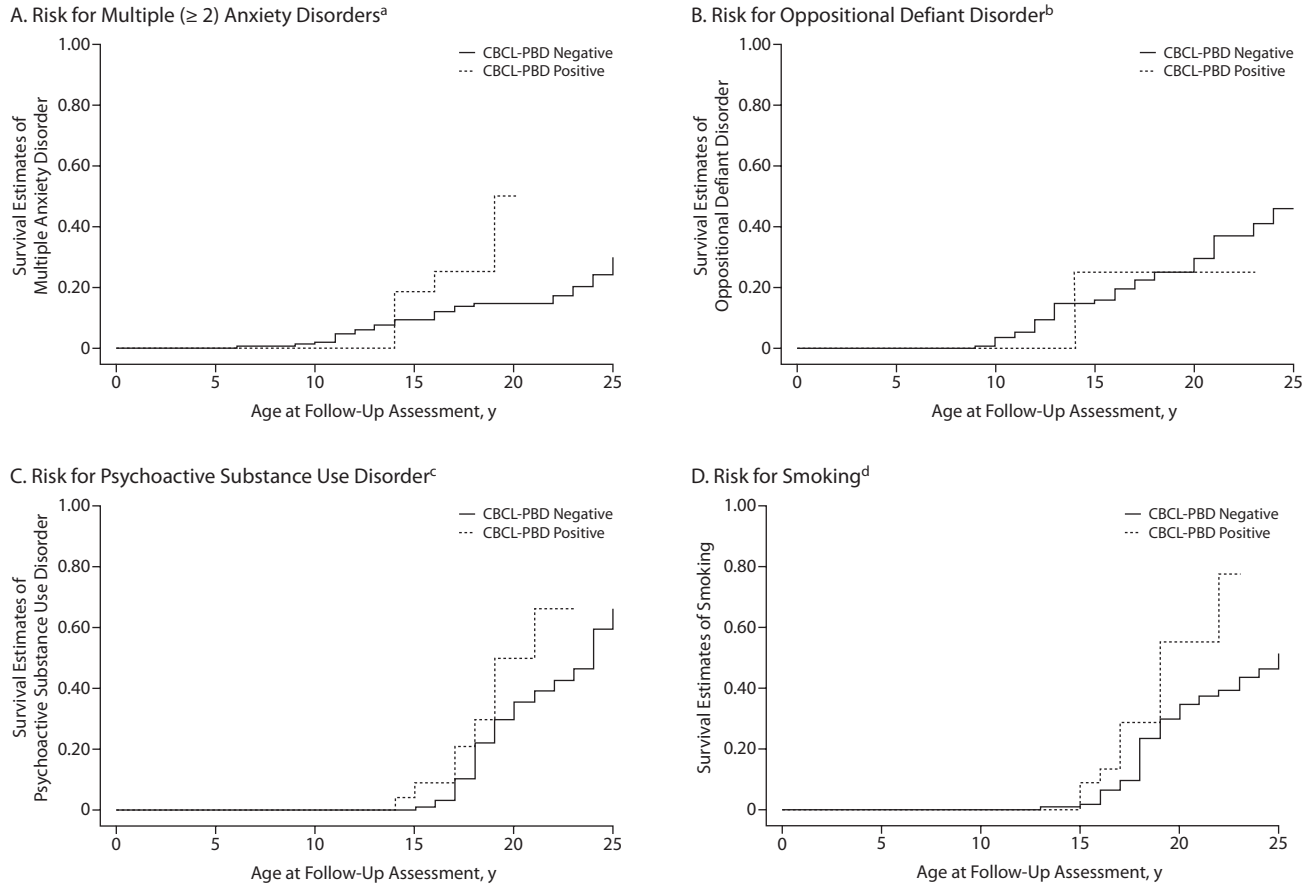
The CBCL-PBD positive group had more impaired GAF and SAICA scores compared to the CBCL-PBD negative group at baseline that persisted into follow-up assessments (both $P < .001$, Figure 3). There was no significant interaction of age and group ($P = .06$) in SAICA scores. In addition, ADHD subjects with a CBCL-PBD positive score had an increased risk for psychiatric hospitalization compared to subjects with a CBCL-PBD negative score (73% vs 13% by age 25 years, $P < .001$, Figure 4). Mood disorders were involved in nearly all hospitalizations at follow-up (18/20, 90%).

DISCUSSION

This study evaluated the prognostic utility of the CBCL-PBD profile as a predictor of a subsequent diagnosis of bipolar disorder in children with ADHD. Consistent with our study hypothesis, we found that a positive CBCL-PBD score predicted a subsequent diagnosis of bipolar disorder and syndrome-congruent outcomes including major depressive disorder and conduct disorder, as well as impaired psychosocial functioning and a higher risk for psychiatric hospitalization. These longitudinal results support the utility of the CBCL-PBD score to predict a diagnosis of bipolar disorder and syndrome congruent–associated impairments in ADHD youth.

The finding that the CBCL-PBD profile has predictive value provides further support for the utility of this profile to help identify children at high risk for bipolar disorder. This profile has been previously shown to have high diagnostic efficiency to predict current diagnoses of

Figure 2. Risk for Psychopathology by CBCL-PBD Score



[a]Hazard ratio = 2.0, 95% CI = 0.8 to 5.1, $P = .14$.
[b]Hazard ratio = 0.5, 95% CI = 0.1 to 3.8, $P = .50$.
[c]Hazard ratio = 1.6, 95% CI = 0.8 to 3.5, $P = .22$.
[d]Hazard ratio = 1.8, 95% CI = 0.9 to 3.6, $P = .12$.
Abbreviation: CBCL-PBD = Child Behavior Checklist-Pediatric Bipolar Disorder.

bipolar disorder[18] and has been replicated across multiple age groups, multiple treatment settings, and multiple cultures.[21–24,46,47]

As previously mentioned, the CBCL-PBD score also predicted subsequent major depressive disorder, conduct disorder, poor psychosocial outcomes, and psychiatric hospitalization, all of which are syndromatic features consistent with a diagnosis of pediatric bipolar disorder. For example, major depressive disorder is a syndrome-congruent expression of bipolar disorder.[31,48,49] Likewise, the finding that the CBCL-PBD score predicted subsequent diagnoses of conduct disorder is also congruent with the diagnosis of pediatric bipolar disorder. A high and bidirectional overlap between pediatric bipolar disorder and conduct disorder has been documented in studies of both children with bipolar disorder and children with conduct disorder.[32,50] Also syndrome congruent with the diagnosis of pediatric bipolar disorder is the finding that the CBCL-PBD score was predictive of compromised psychosocial outcomes and psychiatric hospitalization, adverse outcomes previously documented in studies of youth with bipolar disorder.[33,51,52] Psychiatric hospitalization was the strongest association found in our analysis, and because 90% of the hospitalizations involved mood disorders, the CBCL-PBD score may be particularly suited for identifying those children at risk for developing severely impairing mood disorders.

Although Volk and Todd[27] failed to find a cross-sectional association between the CBCL-PBD profile and structured interview-based diagnoses of pediatric bipolar disorder using data from a population-based pediatric twin sample, children with a positive CBCL-PBD score had more oppositional defiant disorder, conduct disorder, and ADHD and more frequently endorsed suicidal behaviors. This is consistent with our finding that ADHD subjects with a CBCL-PBD positive score had higher rates of

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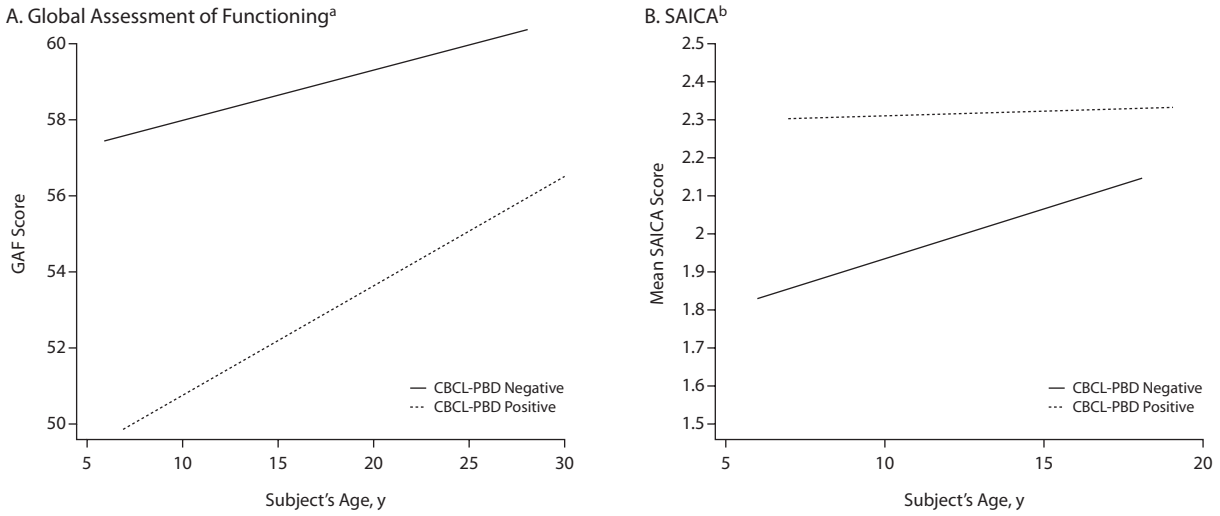
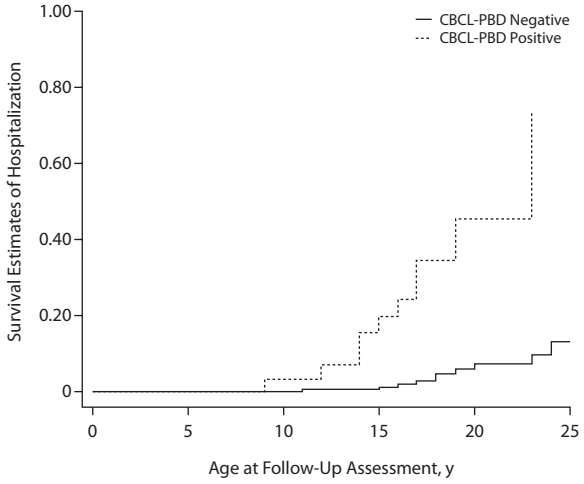
Figure 3. Psychosocial Functioning Over Time by CBCL-PBD Score



[a]CBCL-PBD coefficient = –6.1, 95% CI = –8.1 to –4.1, $P < .001$.
[b]CBCL-PBD coefficient = 0.33, 95% CI = 0.19 to 0.47, $P < .001$.
Abbreviations: CBCL-PBD = Child Behavior Checklist-Pediatric Bipolar Disorder, SAICA = Social Adjustment Inventory for Children and Adolescents.

Figure 4. Risk for Hospitalization by CBCL-PBD Score[a]



[a]Hazard ratio = 6.5, 95% CI = 2.5 to 16.9, $P < .001$.
Abbreviation: CBCL-PBD = Child Behavior Checklist-Pediatric Bipolar Disorder.

oppositional defiant disorder and conduct disorder at baseline, which is also well documented by prior studies.[53,54] Volk and Todd[27] may not have found a significant association between the CBCL-PBD profile and pediatric bipolar disorder due to the low rate of bipolar disorder in their sample. The CBCL-PBD profile in the Volk and Todd[27] study was heritable and associated with the number of dopamine transporter 9-repeat 3′ untranslated region alleles, a region recently associated with pediatric bipolar disorder.

Two other studies did not find a cross-sectional association between the CBCL-PBD profile and bipolar disorder. In the negative study by McGough et al,[55] the CBCL-PBD phenotype was associated with generalized anxiety disorder, oppositional defiant disorder, and conduct disorder. The negative study by Youngstrom et al[26] used data from a large sample derived from 6 urban community mental health centers (N = 3086). Their negative findings could have been due to their reliance on archival data and limited emphasis on operationalized diagnostic algorithms. In addition, Youngstrom and colleagues' sample was 42% black,[26] whereas 99% of our sample was white, which may have accounted for some of the differences between the studies. More work is needed to help reconcile these discrepant findings.

Although there is some disagreement among the cross-sectional studies, our study and the only other longitudinal study available both find that the CBCL-PBD phenotype predicts subsequent bipolar disorder and other adverse outcomes. Meyer et al[28] found that in childhood and adolescence, the CBCL-PBD phenotype was associated with anxiety disorders, disruptive behavior disorders, major depressive disorder/dysthymia, suicidal ideation, and suicide attempt.[28] It was not until the young adult follow-up (mean age = 21.7 years) that the CBCL-PBD phenotype was found to predict bipolar disorder.[28] Taken together with our findings, these results suggest that even in the absence of a current diagnosis of pediatric bipolar disorder, a positive CBCL-PBD profile may be indicative

of a future risk for bipolar disorder in children with a positive profile.

Because the majority of subjects who had a positive CBCL-PBD score did not develop bipolar disorder, and a positive CBCL-PBD score was also associated with subsequent major depressive disorder and conduct disorder, some may question the naming of this "bipolar disorder" profile. We use the name *CBCL-PBD* to be consistent with the previous literature[17,27,28,55–58] and due to the current findings that a positive CBCL-PBD score is a significant risk factor for bipolar disorder. However, we emphasize that while the CBCL-PBD profile could be useful to help identify children at risk for bipolar disorder, clinicians should not use the CBCL to make a diagnosis of bipolar disorder. Clearly, the diagnosis of pediatric bipolar disorder is a complicated and nontrivial enterprise. It involves careful examination of the child and parental reporting of the child's history, as well as information on family history and life charting to help clarify a diagnosis.

Unfortunately, there continues to be debate in the field about the best diagnostic definition of pediatric bipolar disorder,[7] which is influenced by clinical traditions, interview methods, and differing interpretations of the nature of a mood episode. We expect that advances in the field and the refinements to come with the *DSM-V* will improve the diagnostic process. However, for clinicians who are not skilled in diagnosing bipolar disorder, the CBCL-PBD can identify children who should be referred to an expert diagnostician. At a very minimum, the CBCL-PBD score could alert the clinician that the child is at risk for serious adverse psychopathological outcomes.

Our findings should be evaluated in light of some methodological limitations. We examined only the CBCL-PBD profile as a predictor of subsequent bipolar disorder. Other screening instruments have effectively discriminated pediatric bipolar disorder cases from noncases,[59,60] and future studies should examine their longitudinal utility. The CBCL remains an attractive tool for identifying children at risk for bipolar disorder due to its ease of administration, brevity, and reliability.[16]

In clinical practice, it may be useful to probe some items of the CBCL and rescore them according to clinical judgment. However, our CBCL scores were based solely on the mother's scoring, thereby using a standardized assessment procedure that ensures rigorous comparison to other studies using the same research methods.[16] This raises the possibility of additional variability between sites that do and do not rescore CBCL items.

Because the sample consisted of youth with ADHD, uncertainties remain as to whether our finding will generalize outside the context of ADHD. Since subjects were referred, the findings may not generalize to community samples. Since subjects were white, the findings may not generalize to other ethnic groups. Children younger than 12 years of age were not directly interviewed, which may have led to underestimates of psychopathology, especially for internalizing disorders. Although raters administering the structured diagnostic interviews were highly selected, trained, and supervised, they were not clinicians. Although our assessment methods may not elicit the same quality of information as clinician interviews, in prior work, we have shown 90% agreement between expert clinician-derived diagnoses of pediatric bipolar disorder and the structured interview diagnoses of nonclinical raters.[61] Differing diagnostic cultures could account for the different findings of studies at various institutions.

Despite these limitations, this work suggests that the CBCL-PBD score based on elevations on the attention problems, aggressive behavior, and anxious/depressed subscales is predictive of pediatric bipolar disorder and associated impairments. If confirmed in other studies, the CBCL-PBD score has the potential to be a useful screening instrument to help identify children at high risk to develop bipolar disorder.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Childhood and Adolescent Mental Health section. Please contact Karen D. Wagner, MD, PhD, at kwagner@psychiatrist.com.

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